Identifying novel hereditary prostate cancer predisposing genes in Finnish high-risk prostate cancer cohort and families

Francisco Lucena Aguilar

Physiology and Genetics
Master's thesis
Credits: 30 op

Supervisors:
Johanna Schleutker
Gudrun Wahlström
Päivi Onkamo
2.6.2025
Turku

Master's thesis

Subject: Biology, Physiology and genetics
Author: Francisco Lucena Aguilar
Title: Identifying novel hereditary prostate cancer predisposing genes in Finnish high-risk prostate cancer cohort and families
Supervisors: Johanna Schleutker, Gudrun Wahlström and Päivi Onkamo
Number of pages: 171 pages
Date: 2.6.2025

Prostate cancer (PCa) is the most common cancer in Finnish men. In hereditary prostate cancer (HPCa), PCa is characterized by at least three cases in first-degree relatives and early age at onset. Several genetic risk variants have been identified, but a large portion of its heritability remains unexplained. The aim of this study was to explain part of this missing heritability by identifying novel germline variants not previously linked to PCa.

This study investigated five novel variants not previously linked to PCa: *TP63* rs190865056, *ZBTB46* rs34785134, *PASK* rs35129131, *LETM1* rs62623389, and *IQGAP2* rs34592828, selected from the WGS data of 71 indexes of Finnish high-risk HPCa families. In HPCa high-risk families, a generalized linear mixed model (GLMM) was used to compare the prevalence of the variants in men with or without PCa considering their relatedness, and a family-based association test (FBAT) to analyze whether genetic variants are transmitted to HPCa family members more often than expected. Fisher's exact test was used to compare the variants frequencies in a positive cohort of PCa patients (TPCC sample collection) with family history of PCa and HBOC to those of a general Finnish population (FinnGen), PCa cases from a Finnish GWAS (FinnGen), and a negative subset cohort of TPCC PCa patients without family history of PCa or HBOC.

Statistically significant associations were found in the GLMM between PCa and *ZBTB46* rs34785134 and *LETM1* rs62623389 variants. In the FBAT, significant results were obtained between PCa and *ZBTB46* rs34785134 in the "absence of linkage", with a potential association indicated between PCa and *LETM1* rs62623389 variant in the "presence of linkage". Compared to the general Finnish population and the negative cohort, *PASK* rs35129131 allele and carrier frequencies were statistically significant higher in the positive cohort. These results indicate a potential association between *ZBTB46* rs34785134 and *PASK* rs35129131 variants and PCa, especially in individuals with family history of PCa and other cancers, but larger replication studies are needed to warrant these associations.

Keywords: Prostate cancer, germline variant, familial prostate cancer, hereditary prostate cancer, predisposing gene variants, *PASK*, *ZBTB46*, *LETM1*, missing heritability, risk variant

Pro gradu -tutkielma

Oppiaine: Biologia, Fysiologia ja genetiikka
Tekijä: Francisco Lucena Aguilar
Otsikko: Uusien perinnöllisten eturauhassyövän alttiusgeenien tunnistaminen suomalaisessa korkean riskin eturauhassyövän kohortissa ja suvuissa
Ohjaajat: Johanna Schleutker, Gudrun Wahlström ja Päivi Onkamo
Sivumäärä: 171 sivua
Päivämäärä: 2.6.2025

Eturauhassyöpä (PCa) on yleisin syöpä suomalaisilla miehillä. Perinnöllisessä eturauhassyövässä (HPCa) tautia esiintyy useilla lähisukulaisilla ja alkamisikä on usein varhaisempi kuin väestössä keskimäärin. Vaikka useita geneettisiä riskivariantteja on tunnistettu, suuri osa periytyvyydestä on edelleen selittämättä. Tämän tutkimuksen tavoitteena oli selittää osa tästä puuttuvasta periytyvyydestä tunnistamalla uusia ituradan variantteja, joita ei aiemmin ole yhdistetty PCa:han.

Tässä tutkimuksessa analysoitiin viittä uutta varianttia, joita ei aiemmin ole yhdistetty PCa:han: *TP63* rs190865056, *ZBTB46* rs34785134, *PASK* rs35129131, *LETM1* rs62623389 ja *IQGAP2* rs34592828, jotka valittiin 71 suomalaisen korkean riskin HPCa-suvun indeksihenkilön WGS-aineistosta. Korkean riskin PCa-perheissä käytettiin yleistettyä lineaarista sekamallia (GLMM) vertailemaan varianttien esiintyvyyttä PCa:ta sairastavien ja sairastamattomien välillä huomioiden sukulaisuussuhteet, sekä sukupohjaista assosiaatiotestiä (FBAT) analysoimaan, siirtyvätkö geneettiset variantit HPCa-perheenjäsenille odotettua useammin. Positiivisen eturauhassyöpäpotilaiden kohortin (TPCC-aineiston potilaat, joilla on PCa:n ja HBOC:n sukutaustaa) varianttien frekvenssejä vertailtiin Fisherin tarkalla testillä yleiseen suomalaiseen väestöön (FinnGen), suomalaiseen GWAS-eturauhassyöpäaineistoon (FinnGen) ja negatiiviseen kohorttiin (TPCC-aineiston potilaat, joilla ei ollut PCa:n tai HBOC:n sukutaustaa).

Tilastollisesti merkitseviä yhteyksiä havaittiin GLMM-analyysissä PCa:n ja *ZBTB46* rs34785134 sekä *LETM1* rs62623389 -varianttien välillä, ja FBAT-analyysissä PCa:n ja *ZBTB46* rs34785134 -variantin välillä tilanteessa, jossa ”kytkentää ei ole”. Lisäksi mahdollinen yhteys havaittiin PCa:n ja *LETM1* rs62623389 -variantin välillä tilanteessa, jossa ”kytkentä on olemassa”. Verrattuna yleiseen suomalaiseen väestöön ja negatiiviseen kohorttiin, *PASK* rs35129131 kantaja- ja alleelifrekvenssi oli tilastollisesti merkitsevästi korkeampi positiivisessa kohortissa, jonka potilailla on PCa:n ja HBOC:n sukutaustaa. Nämä tulokset viittaavat mahdolliseen yhteyteen *ZBTB46* rs34785134 ja *PASK* rs35129131 varianttien ja PCa:n välillä, erityisesti henkilöillä, joilla on PCa:n ja HBOC:n sukutaustaa, mutta laajempia toistotutkimuksia tarvitaan tulosten varmentamiseksi.

Avainsanat: Eturauhassyöpä, ituradan variantti, familiaalinen eturauhassyöpä, perinnöllinen eturauhassyöpä, alttiusgeenit, *PASK*, *ZBTB46*, *LETM1*, kadonnut periytyvyys, riskivariantti

CONTENTS

1. INTRODUCTION

1.1. Prostate gland

The prostate is a gland in the male reproductive system positioned beneath the urinary bladder and anterior to the rectum. It produces an alkaline fluid that contains different proteins, such as prostate-specific antigen (PSA) and β-microseminoprotein (prostate secretory protein 94), and simple sugars. Prostatic fluid is secreted into the prostatic urethra making 30 % of the final seminal liquid. This secretion is crucial for nourishing, protecting, and transporting sperm. (Tortora & Derrickson, 2017)

The prostate is made of secreting glands (70 % of the prostate tissue) that open into the urethra, and prostatic stroma (30 % of the prostate tissue) formed by smooth muscle, fibroblasts, and collagen. The epithelium lining the secreting glands consists mainly of two types of epithelial cells: tall columnar or cuboidal secretory gland cells and sparse, flat basal cells that are in contact with the basement membrane working as myoepithelial cells. Also, a small population of prostatic neuroendocrine cells in the basal cell layer regulates tissue growth, differentiation, and exocrine secretory activity (Figure 1A). Ducts connecting secreting glands and urethra are lined with tall columnar epithelium, which gradually becomes more cuboidal and eventually transitional epithelium the closer it gets to the urethra. (Lowe & Anderson, 2015)

The prostatic glands are arranged into three concentric zones around the prostatic urethra: transition, central, and peripheral zones (Figure 1B). The transition zone is the innermost layer, that occupies about 5 % of the prostate volume and contains small inner periurethral glands (mucosal glands) that open directly into the urethra. The central zone, which includes 25 % of the glandular tissue, surrounds the ejaculatory ducts and consists of many outer periurethral glands (submucosal glands). These glands open into the urethra through short ducts entering the posterolateral urethral sinuses. An abnormally enlarged prostate, benign prostatic hyperplasia, typically begins in the transition zone and can cause bladder obstruction. The peripheral zone is the outermost part of the prostate, containing 70 % of the glandular tissue. It includes the main glands that empty their secretion through long ducts to the urethral sinuses. The peripheral zone is the most affected area by chronic prostatitis and is where 70 % of adenocarcinomas occur, whereas in the central zone, adenocarcinomas rarely develop and only account for less than 1–5 % of all prostate adenocarcinomas. The prostate gland is surrounded by a fibrocollagenous capsule, which segments the gland into ill-defined lobes. (Tortora & Derrickson, 2017)

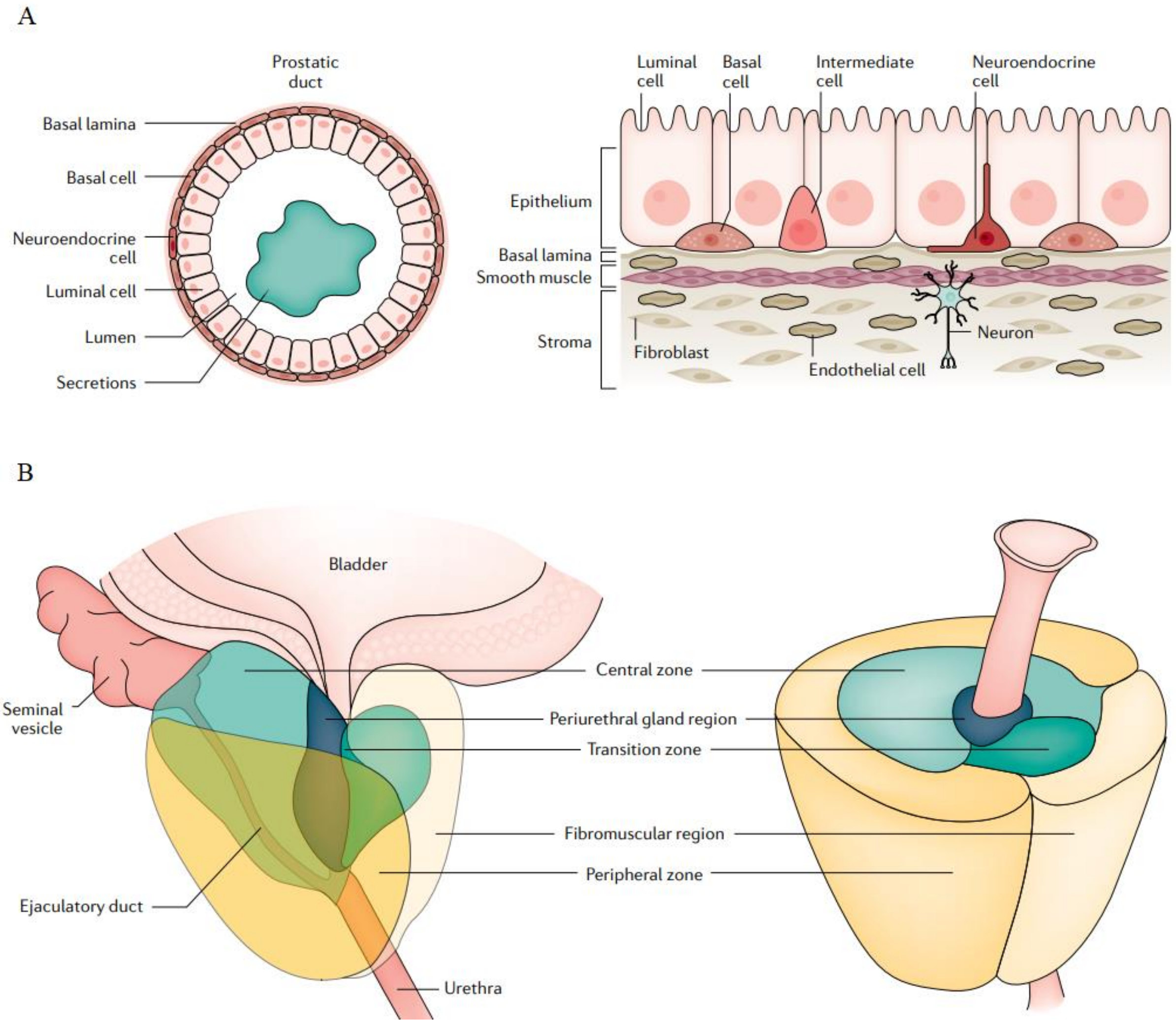


Figure 1. Histological structure and anatomy of the prostate gland. The prostatic tissue is formed by acini and ducts surrounded by stroma, which comprise a single layer of secretory cells (luminal cells) and basal cells in contact with the basement membrane (basal lamina). Prostatic neuroendocrine cells are also present in the basal cell layer. The stroma is formed by smooth muscle cells and fibroblasts (A). The prostate gland is divided into three concentric zones around the urethra: transition, central, and peripheral zones (B). Modified from Rebello et al., (2021).

1.2. Prostate cancer

1.2.1 Pathophysiology

Prostate cancer (PCa) refers to a form of cancer that occurs in the prostate gland. Malignant transformation occurs when normal cells acquire mutations that lead to uncontrolled proliferation and invasion, often due to the dysregulation of oncogenes and tumor suppressor genes. Malignant transformation in adenocarcinomas, the most common type of PCa, can be divided into different phases (Shen & Abate-Shen, 2010). First, uncontrolled localized proliferation of luminal cells gives rise to prostatic intraepithelial neoplasia (PIN), an *in situ* type of cancer, characterized by dysplastic luminal cells along the ducts. Adenocarcinomas can originate from both gland and secretory cells. Neuroendocrine cells are also involved in tumorigenesis through paracrine stimulation of adjacent cells leading to the growth, motility, and survival of prostatic cancerous cells (Amorino & Parsons, 2004). Over time, the accumulation of mutations drives the formation of localized adenocarcinoma and then invasive adenocarcinoma, where the basal cell layer is compromised, and cancerous cells penetrate surrounding tissues through the basal lamina. When cancerous cells enter the bloodstream or lymphatic system, disseminate to distant organs, and establish secondary tumors, the disease progresses to metastatic prostate cancer (mPCa) (Shen & Abate-Shen, 2010). Secondary tumors are the main cause of death in mPCa (Elmehrath et al., 2021). The most common metastatic areas are bone, distant lymph nodes, liver, and thorax (Gandaglia et al., 2014). The most affected bones belong to the axial skeleton, including the spine and the ribs, and they usually show osteoblastic lesions and osteolytic characteristics causing fractures, hypercalcemia, and pain (Coleman et al., 2020; Baldessari et al., 2023).

The development and maintenance of both normal prostate and PCa are regulated by androgens via androgen receptors (AR) (Isaacs, 2018). Continuous androgenic stimulus is essential for metabolism, differentiation, cell proliferation, apoptosis, and DNA repair. (Banerjee et al., 2018). Since PCa is highly dependent on the androgen-AR signaling pathway, AR activity can be reduced using androgen deprivation therapy (ADT), including anti-androgens, to treat PCa (Beier et al., 2023). However, these therapies are effective for a limited time before progression and resistance occurs, giving rise to primary castration-resistant prostate cancer (CRPC) or metastatic CRPC (mCRPC) (Wang et al., 2021).

1.2.2. Epidemiology and classification

PCa is the fourth most prevalent and commonly diagnosed cancer worldwide. It is the second most diagnosed cancer among men representing 15 % of all male cancers worldwide, and the most common cancer in Finnish men (Sung et al., 2021; Pitkäniemi et al., 2022). Moreover, it is the second most frequent cause of cancer mortality in men after lung cancer (Bray et al., 2023). Globally, around 10 million men have PCa and in approximately 700,000 of them, the disease has progressed to its metastatic form (GBD, 2018; Foreman et al., 2017). Additionally, autopsy studies show that latent PCa, which is only detectable through histological examination, is found in approximately 5 % of men under 30 and around in 60 % of men over 80 years old (Bell et al., 2015). The actual number of cases is likely higher than the recorded figures show due to underdiagnosis and inadequate reporting, especially in low- and middle-income countries (James et al., 2024).

PCa is a particularly clinically and genetically heterogeneous disease with different ranges of morbidity and mortality. According to the latest World Health Organization (WHO) urinary and male genital tumors classification, prostate tumors can be categorized into epithelial and mesenchymal tumors (Mohanty et al., 2022). Epithelial tumors are further divided into two families: glandular neoplasms of the prostate and (baso)squamous neoplasms of the prostate. The glandular family is composed of 6 tumor types: cystadenoma, high-grade prostatic intraepithelial neoplasia (HGPIN), intraductal carcinoma of the prostate (IDC-P), prostatic acinar adenocarcinoma (acinar PCa), prostatic ductal adenocarcinoma (ductal PCa), and treatment-related neuroendocrine prostatic carcinoma (t-NEPC), whereas the squamous family comprises three tumor types: adenosquamous carcinoma, squamous cell carcinoma, and adenoid cystic (basal cell) carcinoma of the prostate. On the other hand, the mesenchymal tumor category includes only the stromal tumor family, which contains two tumor types: prostatic stromal tumor of uncertain malignant potential and prostatic stromal sarcoma. Though urothelial carcinoma of the prostate and prostatic urethra are considered PCas, they are classified as urinary tract tumors because they originate from different types of cells and tissues than those involved in traditional PCa (Mohanty et al., 2022). Though there are many types of PCa, adenocarcinomas represent more than 95 % of them, predominantly of acinar origin (Tortora & Derrickson, 2017).

1.2.3. Diagnosis

Because PCa is initially asymptomatic, different diagnosis methods have been developed to detect PCa in the early stages. Thanks to early detection biomarkers, PCa can be diagnosed before important symptoms appear (Kohaar et al., 2019). Common symptoms due to prostate enlargement in later stages include trouble urinating, decreased force in the stream of urine, and trouble emptying the bladder completely. Other symptoms may include pain or burning sensation during urination, blood in the urine (hematuria) or blood in the semen (hematospermia), and painful ejaculation (Wein et al., 2021). The primary way to detect PCa is by a PSA test from the blood. PSA is a serine protease normally secreted into the prostatic glandular ducts, where its concentration is millions of times higher than in blood plasma. Due to neoplastic and inflammatory processes in PCa, PSA passes to the extracellular space, leading to higher PSA levels in blood serum (Lilja et al., 2008). However, several factors, such as infections or systemic inflammation can influence PSA levels (McDonald et al., 2014). A PSA level exceeding 4 ng/ml is generally considered abnormal. However, other factors should also be considered in the decision to obtain a prostate biopsy, such as digital rectal examination findings, patient age, family history, and ethnicity (Moses et al., 2023). Since PSA levels tend to rise with age, some doctors adjust the threshold to a higher cutoff (5 ng/ml) for older men and a lower cutoff (2,5 ng/ml) for younger men (Gulati et al., 2013). PSA testing increases PCa detection and reduces mortality moderately in PCa patients according to the European Randomised Study of Screening for Prostate Cancer (ERSPC) (Schröder et al., 2014). Due to early-stage diagnosis of PCa facilitated by PSA testing, curative treatment is achievable in a considerable proportion of cases. In contrast, PCa patients diagnosed clinically through evident symptoms tend to have high-grade, advanced, and often lethal tumors (Helgstrand et al., 2017).

After a positive PSA test, PCa is confirmed diagnostically with a tissue biopsy and histological evaluation, known as a 12-core systematic biopsy. In this biopsy, 12 samples are taken from different defined areas of the peripheral and transition zone (Litwin & Tan, 2017). Samples are then classified according to Gleason's grading, which evaluates the prognosis of men with PCa based on the histology of prostate biopsy and predicts how quickly the tumor is likely to grow and disseminate. Pathologists assign two grades to cancer cells on a scale of 1 (normal) to 5 (highly abnormal) based on how much the cancer cells resemble normal prostate cells. The primary grade describes the most common cell pattern observed, and the secondary grade describes the second most common pattern. The summary of both grades results in a number ranging from 2 to 10 indicating the severity of the cancer, known as the sum of scores. Scores below 6 are rarely assigned in clinical practice, making Gleason's score usually range from 6 to 10. In 2014, the International Society of Urological Pathology (ISUP) revised the Gleason grading system to improve its prognostic accuracy and clinical relevance, by restructuring the Gleason score into five grade groups (Table 1) (Srigley et al., 2016).

Table 1. The Gleason grading system, revised by the International Society of Urological Pathology (ISUP) in 2014, introduced grade groups to improve PCa classification and severity assessment.

Risk Group	Grade Group	Gleason Score
Low/Very low	Grade Group 1	Gleason Score ≤ 6
Intermediate	Grade Group 2	Gleason Score 7 (3+4)
	Grade Group 3	Gleason Score 7 (4+3)
High/Very high	Grade Group 4	Gleason Score 8
	Grade Group 5	Gleason Score 9-10

Though systematic biopsy has been the usual method for diagnosis, it sometimes misclassifies tumors or fails to detect cancer altogether (Epstein et al., 2012; Bittner et al., 2018). As a result, imaging tools have also been increasingly used to detect PCa. Multiparametric magnetic resonance imaging (mpMRI) gives an ideal 3D image of the prostate by merging diffusion-weighted (DWI), T2-weighted (T2WI), and dynamic contrast-enhanced (DCEI) images (Demirel & Davis, 2018). In contrast, computed tomography (CT) is not recommended due to poor margin definition and low resolution of the prostate soft tissue. Although it is sometimes used to detect affected lymph nodes, its resolution is insufficient to differentiate between metastatic and benign reactive nodes (Hövels et al., 2008). On the other hand, positron emission tomography (PET) is highly effective in detecting metastatic extraprostatic disease using different tracers. 18F-fludeoxyglucose (FDG) detects metastatic lesions, whereas 68Ga-prostate-specific membrane antigen (PSMA) serves to diagnosed affected lymph nodes and distant metastasis (Rowe et al., 2016; Sutherland et al., 2024).

Once the tumor is confirmed and histologically evaluated, the stage of the PCa is determined based on PSA levels, Gleason Score or Grade Groups, and TNM staging system. TNM stands for tumor, node, and metastasis and describes the size and extent of the primary tumor, the number of lymph nodes affected by the tumor, and the level of metastasis (Table 2) (Epstein et al., 2016). Generally, tumors are staged when diagnosed and before the treatment starts based on physical exams, imaging tests, endoscopy exams, and biopsies. This kind of staging is known as clinical staging and is used to decide the best treatment and assess the patient's prognosis. On the other hand, if tumor removal is the first treatment choice, preoperative results and postoperative analysis of the tumor determine pathological/surgical staging, which tends to be more precise than clinical staging (Cooke et al., 2012).

Table 2. NTM classification for PCa according to the International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma in 2014.

Classification	Definition
Tumor (T)	
Tx	Tumor cannot be evaluated (due to lack of information)
T0	No evidence of a primary tumor
T1*	Tumor was not detected during a digital rectal exam (DRE) and cannot be seen on imaging studies (tumor may be discovered during surgery for a reason other than cancer)*
T2	Tumor can be detected during a DRE but is present in the prostate only
T2a	Tumor is in half or less than one side (lobe) of the prostate
T2b	Tumor is in more than half of one prostate lobe but has not yet invaded the other lobe
T2c	Tumor is in both prostate lobes
T3	Tumor extends outside of the prostate
T3a	Tumor extends outside the prostate on one or both sides
T3b	Tumor has spread to the seminal vesicles (the glands on each side of the bladder)
T4	Tumor has spread to tissues near the prostate other than the seminal vesicles, such as the bladder or wall of the pelvis

Node (N)	
Nx	Nearby lymph nodes are not evaluated
N0	No cancer cells are found in nearby lymph nodes
N1	Cancer cells are found in nearby lymph nodes
Metastasis (M)	
M0	Cancer has not spread beyond the prostate
M1	Cancer has spread beyond the prostate
M1a	Cancer has spread to distant lymph nodes
M1b	Cancer has spread to bone
M1c	Cancer has spread to another organ or site, with or without bone disease

Tumors are considered clinically significant and require treatment if any of the following three criteria are found: TNM classification of T3 or higher, N1, M1, Gleason score ≥ 7 (especially if majority grade is 4 or higher), or PSA levels over 4 ng/ml (Mohler et al., 2019).

1.2.4. Treatment

Treatment methods are decided by tumor stage (TNM tumor classification) and grade (Gleason grading). Moreover, the patient's PSA concentration, age, comorbidities, and general health are considered when choosing the proper treatment (Hall et al., 2005; Loeb & Eastham, 2021). Low-grade and slow-growing localized PCa is monitored by active surveillance. It avoids the morbidity associated with radiotherapy, chemotherapy, and radical surgery (Bates et al., 2020). Moreover, many countries perform MRI scans as a supplementary test before enrolling patients in active surveillance. However, clinicians must identify any transition to a more advanced cancer that requires treatment through a comprehensive clinical assessment (Moore et al., 2017; Dieffenbacher et al., 2021).

In localized PCa, surgery and radiation are the main curative options for local treatment. Robot-assisted radical prostatectomy (RARP) and open radical prostatectomy (RP) are the most common surgical treatments and they demonstrate good oncological and functional outcomes (Agrawal et al., 2020; Wasim et al., 2022). Radiotherapy shows curative outcomes in 60 % of localized PCa and it is preferably chosen in surgically challenging patients or unresectable types of cancer (Harmenberg et al., 2011). Current surgical and radiotherapy treatments offer ways to treat localized PCa while aiming to preserve healthy tissue. However, the optimal approach depends on the cancer's characteristics and stage. Minimally invasive techniques and focal therapies are promising but require further development and adjustment for individualized patient care (Wasim et al., 2022).

When treating mPCa, the central therapy is the reduction of androgen levels by chemical castration using ADT (Merseburger et al., 2016). Reducing androgen levels makes prostate tumors shrink or progress more slowly, but it is not curative. In most cases, patients develop resistance to hormone therapy within 12–18 months and have a mean survival of 14–16 months. Overall survival is often worse when the resistance develops within a shorter period of time (Tannock et al., 2004; Beer et al., 2014; Moreira et al., 2017; Wenzel et al., 2021). Currently, second-generation antiandrogens in ADT (Rice et al., 2019), radiotherapy with external beam radiation therapy (ERBT) with X-ray beams and radiopharmaceuticals, such as 117Lu-PSMA-617 (Arbuznikova et al., 2024), and immunotherapy are used to treat mCRPC (Liang et al., 2023). Approximately 8–19 % of mCRPC tumors exhibit loss-of-function mutations in DNA damage repair (DDR) genes, such as *BRCA1, BRCA2, ATM*, and *CHEK2* (Robinson et al., 2015; Abida et al., 2017). Defects in DDR genes, particularly those involved in DNA double-strand break repair, can lead to a dysfunctional homologous repair pathway, resulting in increased chromosomal instability and copy number alterations (CNA), as well as sensitivity to therapies using DNA intercalators, such as platinum, poly (adenosine diphosphate-ribose) polymerase inhibitors (PARPi), or ionizing radiation (Abida et al., 2017; Pacheco-Barcia et al., 2022; Li & Heyer, 2008). Since PCa can arise from various genetic mutations and these different forms of the disease may become unresponsive to certain treatments, identifying these specific mutations in each patient is important to tailor the most effective treatment plan (Wilson & Zishiri, 2024).

1.2.5. Risk factors

PCa has a multifactorial etiology that is not yet fully understood. Older age, ethnicity, and environmental factors are the most commonly associated risk factors to its development (Patel & Klein, 2009). As with most cancers, the incidence rate increases with age. The age-standardized incidence rate (ASR) is a weighted average of age-specific rates adjusted to compensate for populations with different age distributions. PCa ASR is 1 per 100,000 for men under 50 years old, 66 per 100.000 for men between 50 and 65 years old, and 292 per 100.000 for men over 65 years old (IARC, 2022). In the United States, the incidence of PCa in the African American population is 64 % greater than in Caucasian men, with a 2.3 times higher mortality rate (Hinata & Fujisawa, 2022). On the other hand, incidence and mortality are lower in men with Asian, Pacific Islander, or Native American ancestry (National Cancer Institute, 2025). Environmental factors affecting PCa risk include diet, physical activity, and calorie intake, which are linked to other risk factors, such as obesity and metabolic syndrome, as well as exposure to different heavy metals and herbicides (Bagheri et al., 2018; Lifshitz et al., 2021; Fujita et al., 2019a; Lim et al., 2019; Pardo et al., 2020). One previous study has shown that obese patients with a high body mass index (BMI, kg/m^2) are more likely to develop advanced

PCa and have worse prognosis (Fujita et al., 2019). Moreover, individuals with a diet high in fat and choline have a higher risk for PCa (Richman et al., 2012; Niclis et al., 2015).

However, having a family history of PCa and hereditary cancers, such as hereditary breast and ovarian cancer (HBOC) and Lynch syndrome (LS), are some of the primary risk factors (Silva et al., 2009; Giri & Beebe-Dimmer, 2016; Beebe-Dimmer et al., 2020). Genetic factors contribute to the variation of PCa risk and liability, with a heritability index of 58 % (95 % CI: 52 %–63 %) (Hjelmborg et al., 2014). HBOC is a genetic syndrome associated with an increased risk for breast, ovarian, and other types of cancer, such as pancreatic cancer or melanoma, usually caused by mutations in DDR genes *BRCA1* and *BRCA2* (Yoshida, 2021). *BRCA1* mutation carriers show a PCa relative risk (RR) of around 3.75 and a cumulative risk of 8.6 % by the age of 65 (Leongamornlet et al., 2012). Similarly, individuals with *BRCA2* mutations have 8.6-fold enhanced risk and 15 % absolute risk for PCa before the age of 65 (Kote-Jarai et al., 2011). LS or hereditary nonpolyposis colorectal cancer is an autosomal dominant genetic condition produced by mutations in DNA mismatch repair (MMR) genes *MHL1, MSH2, MSH6*, and *PMS2* (Boland & Lynch, 2013). LS raises the risk for certain cancers, including colorectal, ovarian, urological, stomachal, biliary duct, and brain cancers (Curtius et al., 2022). A systematic review and meta-analysis of the risk of PCa in LS patients showed that MMR gene mutation carriers have a 3,67-fold increased risk of developing PCa (Ryan et al., 2014). Furthermore, a family history of some types of cancer, such as breast, ovarian, kidney, melanoma or cervical cancer, is associated with a higher risk of developing PCa (Brandt et al., 2012; Hemminki, 2012; Mucci et al., 2016).

PCa cases attributed to hereditary factors are estimated to range approximately between 5 %–15 % (Heidegger et al., 2019). Patients with a first-degree relative (father, brother, or son) suffering from PCa, are two to three times more likely to develop PCa (Kiciński et al., 2011). An increase in the number of affected relatives and early diagnosis are associated with a higher risk (Chen et al., 2008). Patients whose first-degree relatives had an early onset showed a RR of 3–5 to develop PCa (Kiciński et al., 2011). Although a positive family history indicates genetic susceptibility, shared environmental exposures in early life, and interactions between genes and the environment might have a small impact on the clustering of PCa within some families (Sundquist et al., 2015).

1.3 Hereditary prostate cancer

PCa can be divided based on the patterns of occurrence in families and the genetic factors involved in sporadic, familial (FPC), and hereditary prostate cancer (HPCa). Sporadic form accounts for most cases of PCa, and it means that one person in a family has developed PCa (Vietri et al., 2021). It is caused by random genetic modifications in somatic cells (somatic variants) in the prostate acquired during the person's lifetime with a typical late age of onset (Giri & Beebe-Dimmer, 2016). On the other hand, familial prostate cancer (FPC) refers to an accumulation of this type of cancer within a family. FPC is defined as families with either two first-degree relatives diagnosed with PCa at any age or one first-degree relative and two or more second-degree relatives diagnosed at any age (Ostrander et al., 2004). HPCa is a distinct subtype of familial PCa characterized by the transmission of a predisposing gene through Mendelian inheritance. In these cases, germline mutations (germline variants), present essentially in all the cells, are inherited from the parents, increasing the risk of developing PCa (Carter et al., 1992). Germline mutations, other somatic gene mutations, and environmental factors are involved in the development and progression of HPCa (Giri & Beebe-Dimmer, 2016). The broadly accepted definition of HPCa considers HPCa families with either (1) three or more affected first-degree relatives with PCa, (2) prostate cancer diagnosed in three successive generations of paternal or maternal line, or (3) two first-degree relatives both diagnosed with early-onset PCa (age ≤ 55 years) (Carter et al., 1993). Aggressive forms of the disease, early onset, and higher risk of recurrence after surgery are characteristics of HPCa (Thalgott et al., 2018). However, HPCa and sporadic PCa patients show similar disease-specific survival (Thalgott et al., 2018).

Among the major types of cancer in men, HPCa has the highest heritability (Lichtenstein et al., 2000; Hjelmborg et al., 2014; Mucci et al., 2016). Twin cohort studies performed in Nordic countries have shown that both monozygotic (identical) and heterozygotic (non-identical) twins have a higher risk of PCa when their co-twin is diagnosed with PCa, compared with the rest of the population (Hjelmborg et al., 2014). In addition, another large twin study in Nordic countries involving over 44,000 pairs of monozygotic and dizygotic twins indicated that men with an identical twin diagnosed with PCa have a 21 % likelihood of developing the disease, compared to a 6 % likelihood for those with a non-identical twin affected. Moreover, the time interval between the diagnoses of two monozygotic twins with PCa was shorter (5.7 years) than in dizygotic twins (8.8 years) (Lichtenstein et al., 2000). These studies estimated that heritable factors accounted for 42–58 % of the risk of developing PCa, highlighting the significant genetic contribution to the disease (Lichtenstein et al., 2000; Hjelmborg et al., 2014).

1.3.1 Heritability

The pattern of inheritance of HPCa depends on the gene or genes involved in its development and progression. In many pedigrees of HPCa, the pattern of inheritance is so strong that it resembles an autosomal dominant trait, like in the case of single nucleotide polymorphisms (SNPs) in *BRCA1, BRCA2*, or *HOXB13* (Xu et al., 2013; Pritchard et al., 2016). The predictive value of a specific variant in population studies is determined by a combination of its odds ratio (OR) and its frequency within the population. Both rare gene variants with high to moderate penetrance and common genetic variants with low penetrance are involved in HPCa (Al Olama et al., 2014; Rebbeck, 2017). Common variants (minor allele frequency (MAF) > 5 %) have a modest effect size (OR < 1.5) and account for 33 % of the familial risk of developing PCa (Al Olama et al., 2014). Rare variants (MAF 0.1–1%), such as those in *BRCA2* and *HOXB13*, have larger effect size (OR > 2) and may explain up to 42 % of the genetic heritability, as observed in men of African ancestry (Mancuso et al., 2016). The combined effect of multiple variants, cumulative association, in PCa has been shown in a Swedish population study, where the analyzed the cumulative association of 16 SNPs from five different chromosomal loci and family history of PCa. While individual variants had a risk ratio between 1.07 and 1.65, the combination of four or five high-risk variants created a composite risk ratio of 4.47. Both the combination of the five variants and a positive family history accounted for 46% of the population attributable risk for PCa (Zheng et al., 2008). As previously mentioned, PCa incidence is notably higher in African Americans compared to Europeans and Asians (Hinata & Fujisawa, 2022). This could suggest that while there is a strong genetic component, this difference can be influenced by environmental factors, such as diet, and screening methods disparity between populations (Lee et al., 2007; Gilligan et al., 2004). It is important to remember that individuals inherit a genetic predisposition to cancer rather than the disease itself, explaining why carriers of susceptibility genes might not develop cancer.

Genetic variants contributing to HPCa can be more prevalent or exclusive to different populations, partially explaining geographical differences in PCa incidence rates (Chang et al., 2011; Haiman et al., 2011; Cook et al., 2014; Heidegger et al., 2019). For instance, a cross-sectional study of 3,607 men with PCa from diverse ancestry revealed that individuals with Ashkenazi Jewish and European ancestry had higher rates of germline variants related to PCa compared to African American, Hispanic, or Asian individuals. Moreover, mutations in DDR genes were more commonly found in patients of Ashkenazi Jewish and European descent (Nicolosi et al., 2019). In another study, specific mutations in genes *PMS2, BRCA1, RAD51,* *RAD54L,* and *RAD54B* were detected more frequently and associated with higher rates of metastasis in African American individuals than in European American individuals when both groups had equal access to healthcare (Sartor et al., 2020; Kohaar et al., 2022). A further example is the presence of rs114798100 and rs111906923 variants in the 8q24 region exclusively in African patients (Han et al., 2016). Consequently, these differences between populations can significantly impact the effectiveness of early detection testing, diagnosis, and treatment strategies.

Individuals carrying certain germline variants have often a higher risk of early onset and more aggressive phenotypes, including high-grade diseases and progression to mCRPC (Castro et al., 2013; Castro et al. 2015a; Na et al., 2017). For instance, *HOXB13* G84E variant is associated with early-onset and more advanced forms of PCa (Trendowski et al., 2022). In the Finnish population, *HOXB13* G84E mutation carriers have an increased PCa risk, which is considerably greater if they have a family history of PCa (Laitinen et al., 2013). Moreover, patients carrying *BRCA2* mutations exhibited a 12-year PCa-specific lower survival rate (61.8 %) than patients without such mutations (94.3 %) (Akbari et al., 2014). Similarly, another study showed a powerful association between *BRCA2, ATM,* and *NBN* rare deleterious variants with aggressive and mPCa (Darst et al., 2023). This enhances the importance of germline variants in clinical risk prediction, therapeutic strategies, and clinical outcomes.

1.3.2 Susceptibility genes

Candidate gene and linkage analyses have identified rare variants with moderate effect sizes that predispose to PCa (Ewing et al., 2012; Pritchard et al., 2016). In contrast, genome-wide association studies (GWAS) have discovered common variants presenting small to modest effect sizes in PCa (Saunders et al., 2021). Family-based linkage studies are used to analyze patterns of genetic inheritance within family members to localize sections of the genome inherited along with a trait, such as a physical characteristic of a disease. For instance, linkage studies allowed the identification of various risk regions, such as the 8q24 region, and variants like the missense G84E in the *HOXB13* gene (Amundadottir et al., 2006; Ewing et al., 2012). While these studies are powerful for identifying genes related to simple Mendelian disorders, they are less effective in pinpointing those connected to complex diseases, which are affected by several genes and environmental factors, as in the case of PCa (Bush & Haines, 2010). However, they can be used to measure the statistical significance of different SNPs as linkage scores or to determine follow-up studies from the results of GWAS studies (Roeder et al., 2006;

Gudmundsson et al., 2007). Furthermore, linkage analysis coupled with whole genome sequencing (WGS) and whole exome sequencing (WES) offers a better variant selection than filtering methods that lack statistical evidence in family-based data when identifying predisposing rare variants (Ott et al., 2016). On the other hand, several large-scale GWAS have found recurrent germline SNPs and DNA copy number variation (CNV) associated with PCa (Wang et al., 2023; Wu et al., 2018) .

Concerning SNP variants, around 451 germline genetic risk variants have been identified for PCa in diverse populations using GWAS (Al Olama et al., 2014; Eeles et al., 2013; Eeles et al., 2014; Virlogeux et al., 2015; Schumacher et al., 2018; Wang et al., 2023). Germline risk-associated SNPs in non-coding regions are enriched at regulatory regions, such as enhancers and promoters, which can regulate the tumor epigenome (Cowper-Sal Iari et al., 2012; Heyn et al., 2014; Whitington et al., 2016). Changes in epigenetic mechanisms involved in DNA methylation, histone modification, or chromatin remodeling affect PCa development and progression (Cheng et al., 2010; Huang et al., 2014; Houlahan et al., 2019; Ramanand et al., 2020). For instance, individuals with deleterious germline mutations in *BRCA2* show genome-wide hypomethylation in comparison with sporadic tumors, probably explaining an enhanced aggressiveness (Taylor et al., 2017). Similarly, a study conducted in PCa patients who underwent germline WGS and methylation profiling demonstrated that 14 % of known PCa risk loci might affect cancer risk by regulating DNA methylation in tumors. Interestingly, these germline variants are in non-malignant tissue, but their regulatory function seems to be active only in a tumorigenic environment (Houlahan et al., 2019). These examples prove that germline variants can also impact tumor initiation and progression through epigenetic regulation.

Some of the risk loci identified in non-coding regions also show long-range chromatin intrachromosomal and interchromosomal interactions. For instance, PCa risk regions within the 8q24 locus containing regulatory variants physically interact with *MYC* at 8q24 (intrachromosomal interaction) and *CD96* at 3q13 (interchromosomal interaction). Furthermore, rs6983267 variant at 8q24 increases the risk of PCa in Caucasians and Africans (Zhu et al., 2017). This variant increases Wnt signaling, which participates in prostate bud growth and luminal epithelial differentiation, crucial for normal prostate development and potential PCa initiation (Kruithof-de Julio et al., 2014). The promoter motifs of transcription factor *TCF3*, which regulates Wnt signaling and functions as oncogene in PCa contributing to cell proliferation, are enriched in previously mentioned interactions (Du et al., 2015; Solberg et al., 2012; Patel & Chaudhary, 2012). These examples confirm that susceptibility variants directly impact different cell signaling pathways, such as AR, PI3K, and Wnt pathways (Du et al., 2015; Raith et al., 2023).

Regarding coding regions, germline mutations in several genes related to different DDR genes (*ATM, BRCA1, BRCA2, CHEK2, FANCA, MSH2, RAD51D*), MMR genes (*MLH1, MSH2, MSH6, NBN, PSM2*) and other cell function genes (*ANO7*, *BRP1, HOXB13, TP53*) have been associated with PCa, and are used as biomarkers (Grindedal et al., 2009; Barrow et al., 2013; Pritchard et al., 2016; Xu et al., 2013; Wilkes et al., 2017; Kote-Jarai et al., 2019; Rusak et al., 2019; Riaz et al., 2024; Jiang et al., 2024). DDR system is a complex network that includes homology-dependent combination (HR), non-homologous end joining (NHEJ), nucleotide excision repair (NER), base excision repair (BER), and MMR (Lord & Ashworth, 2012). More particularly, the MMR system is a DNA repair mechanism that recognizes and corrects base pair mismatches during DNA replication and genetic recombination (Iyer et al., 2006).

Individuals carrying germline mutations in DDR and MMR genes show higher risk to develop PCa during their lives. The most frequent DNA repair genes mutated in both somatic and germline cells in American and British PCa patients are *BRCA2, ATM*, and *CHEK2* (Pritchard et al., 2016). For instance, *BCRA2* germline variants' carriers have a 3–8.6-fold higher risk for PCa in comparison with non-carriers (Gallagher et al., 2010; Kote-Jarai et al., 2011). Interestingly, *BRCA2* germline mutations are not the major contributors to PCa predisposition or aggressive phenotype in the Finnish or Swedish population (Ikonen et al., 2003). In fact, a study done on lethal PCa patients from Finland and Sweden revealed that *CHEK2* (4.1 %) and *ATM* (3.3 %) are the most frequently mutated DNA repair genes among these populations (Rantapero et al., 2020). At the same time, the alteration of these DNA repair pathways can induce mutagenesis and genomic instability, resulting in the buildup of genomic abnormalities (Robinson et al., 2015; Mateo et al., 2015; Zhang et al., 2020). Genomic aberrations found usually in tumor tissue could also be partially explained by germline mutations in genes associated with DNA repair pathways. As an example, patients with germline *BCRA2* mutations have prostatic tumors with more copy number alterations than those with sporadic tumors (Castro et al., 2015b).

In addition to DDR gene variants, other genes like *HOXB13* and *ANO7*, present germline variants with a strong association with PCa. Germline *HOXB13* G84E variant is among the most prevalent variants in HPCa Finnish (22,4 %) and Swedish families (8,2 %) (Laitinen et al., 2013). *HOXB13* codes for a transcription factor that is part of the homeobox gene family implicated in normal prostate development. Dysregulation of the *HOXB13* gene leads to the growth of prostatic cancerous cells by a decreased inhibition of the hormone-activated androgen receptor signaling (Jung et al., 2024). Similarly, *ANO7* (anoctamin 7) codes for a transmembrane channel dependent on calcium as a possible calcium-dependent phospholipid scramblase or calcium-activated chloride channel, which is expressed in prostate tissue and whose dysfunction is associated with PCa risk (Dadaev et al., 2018; Guo et al., 2021; Jiang et al., 2024). Carriers of *ANO7* rs77559646 variant show a higher risk (OR 1.40) and association with aggressive PCa, due to the disruption of *ANO7* mRNA splicing (Kaikkonen et al., 2018; Wahlström et al., 2022).

1.4 Clinical relevance of genetic variants

Genetic variants play a crucial role in PCa susceptibility, treatment response, and clinical outcomes. Recognizing germline SNP variants associated with PCa can help understand genetic predisposition, enable early detection, and improve risk assessment. Moreover, understanding genetic variants allows the tailoring of treatment approaches, and helps predict disease progression and prognosis. Additionally, functional studies of identified variants can help to comprehend the different mechanisms underlying PCa, identify novel treatment targets, and develop new therapies.

1.4.1 Genetic testing

Several guidelines and consensuses exist concerning genetic testing for both germline and somatic variants associated with PCa (Tuffaha et al., 2024). Though there is a consensus that patients with mPCa should be offered genetic testing, there is less agreement about which patients having localized PCa should be tested (Tuffaha et al., 2024). Moreover, recommendations regarding testing methods and implementation still vary between organizations and countries. However, there is general agreement on the genes to be tested for genetic testing (Tuffaha et al., 2024). In the case of Finland, a panel containing 13 genes (*ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2*, and *TP53*) is used for HPCa (TYKS, 2025).

In the case of early-stage or localized PCa, germline variant testing is only recommended if it is presumed to affect treatment decisions, clinical trial availability, cancer risk management, and potential risk for family members to carry deleterious variants implied by family history (Tuffaha et al., 2024). Germline variant testing is often advised for individuals with regional or metastatic PCa, as well as those with high-risk of PCa, such as individuals with a family history of the disease (Tuffaha et al., 2024). Regardless of the tumor stage, it is advised for those individuals with a family history of breast cancer or a family history of early-onset breast, colorectal, or endometrial cancer (≤ 50 years), ovarian, exocrine, or pancreatic cancer (any age), PCa (≤ 60 years) or death from PCa; LS-associated cancer (particularly if < 50 years); or those of Ashkenazi Jewish descent (Tuffaha et al., 2024). Because several hereditary cancer syndromes are associated with PCa, germline testing for *BRCA1* and *BRCA2* mutations linked to HBOC, as well as for mutations in MMR genes, including *MLH1, MSH2, MSH6, and PMS2*, associated with LS, can help to assess PCa risk, predict disease nature and evaluate the threat of additional cancers (Giri & Beebe-Dimmer, 2016; Miguel-Valentin et al., 2020; Yoshida et al., 2021). In addition, genetic testing in patients with PCa can potentially benefit not only the patient but also the relatives. If a pathogenic germline mutation is detected in the patient, cascade testing or further testing in the family should be indicated (Giri et al., 2019). On the other hand, somatic testing should be performed in men with either hormone-sensitive metastatic prostate cancer or mCRPC, particularly when the patient has relatives affected by PCa, Ashkenazi Jewish ancestry, or early-onset PCa.

Regarding germline testing in men without PCa, only the guidelines of three organizations recommend it (Tuffaha et al., 2024). The Spanish Society of Medical Oncology suggest germline testing in individuals with a family history of cancer (Gonzalez del Alba et al., 2020). Similarly, the National Comprehensive Cancer Network (NCCN) recommends germline testing for those men with family history of HPCa, HBOC, or colon cancer syndromes (Schaeffer et al., 2023). The Italian Scientific Societies also recommends germline *BRCA1/2* testing for individuals with family history of pancreatic adenocarcinoma (Russo et al., 2022). In general, patients with an identified mutation in a hereditary cancer gene are recommended to be referred to genetic counselling for further assessment (Zhen et al., 2018).

Certain histopathological features can be associated with germline predisposition for PCa (Smith et al., 2014). Ductal/intraductal histology and lymphovascular invasion (LVI) are linked to a worse prognosis in PCa (Guo & Epstein, 2006; May et al., 2007). For instance, intraductal carcinoma of the prostate occurs more frequently in tumors with germline *BRCA2* mutations than in sporadic cases (Taylor et al., 2017). Analogously, a study analyzing cancer-susceptibility genes (*BRCA2, ATM, CHEK2, BRCA1, PTEN,MLH1, MSH2, MSH6, PMS2, TP53, CDH1, RAD51C,* and *RAD51D*) in PCa patients found that 48 % of the individuals carrying a germline mutation showed a ductal or intraductal histology, compared to only 12 % of the men with no germline variants. Moreover, 52 % of germline mutation carriers presented LVI in the biopsy, while only 14 % of non-carriers exhibited this characteristic (Isaacsson Velho et al., 2018). These and future discovered histopathological features associated with deleterious germline gene mutations could assist in designating individual for germline testing (Isaacsson Velho et al., 2018).

1.4.2 Early detection and risk assessment

Early detection of PCa using biomarkers improves initial disease identification, treatment efficacy, and survival rates of patients, reducing the morbidity and mortality related to advanced and mPCa (Grossman et al., 2018). There is an ongoing debate about the advantages of implementing a population-wide PCa screening program based on PSA testing. While numerous studies have shown a reduction in mortality, this comes with substantial risks of overdiagnosis and overtreatment (Walter et al., 2021). Regarding Finland, there is no national screening program for PCa (Duodecim, 2023). Because PSA testing by itself is not reliable enough at detecting PCa, additional tools such imaging and genetic testing can be used to improve personalized diagnosis (Martin et al., 2018; Kafka et al., 2021).

Using germline variants for PCa early detection has become increasingly significant in refining early diagnosis and personalized management strategies. Recent studies have shown that systematic PSA testing in men carrying specific mutations, like in *BRCA2,* detect more cases of PCa with younger onset of disease, and more clinically significant tumors (Bancroft et al., 2014). These findings suggest that genetic testing can significantly influence early detection protocols, by combining genetic and biochemical markers. This combination enables clinicians to stratify patients for early detection and more effective, individualized management, advancing past traditional PSA-based disease detection (Bancroft et al., 2014). As more germline variants are associated with PCa, such as in *BRCA2, BRCA1, ATM,* or *HOXB13*, guidelines are being updated to include these genetic factors in early detection strategies (Russo & Giri, 2022).

Knowledge of a patient’s germline variants gives important information concerning the risk of developing PCa and its prognosis. Risk scores based on an individual’s germline variants, polygenic risk scores (PRS), can be constructed by understanding polygenic disease heritability and susceptibility, as in HPCa (Raghallaigh & Eeles, 2020). PRS is calculated according to their genotype profile and relevant data from large GWAS of thousands of cases/controls. This score estimates an individual's genetic likelihood to develop the disease, helping to identify groups of people at risk. Implementing a germline variants profile alongside the patient's family history can be used to develop a risk model as part of a targeted detection strategy for high-risk individuals (Choi et al., 2020). Incorporating a genetic profile into PCa detection strategies has been shown to improve the identification of moderate to high-risk PCa, reduce the need for prostate biopsies, and identify cases with a Gleason score of 7 or higher that would have been missed by PSA-based testing when sample PSA levels were below 3 ng/ml (Grönberg et al., 2015). Germline variant profiling allows the stratification of at-risk individuals and informs clinicians and patients regarding the timing and type of diagnosis methods and treatment decisions.

1.4.3 Precision medicine

The mutation status of genes associated with PCa can influence therapeutic strategies. Incorporating PCa variants into personalized treatment enables physicians to offer more precise, effective, and individualized care to patients. By identifying the germline mutations present in a patient, specific treatments can be selected to exploit the vulnerabilities in cancerous cells associated with those mutations. For instance, AR signaling plays a crucial role in PCa initiation and progression (Lonergan & Tindall, 2011). Androgen deprivation therapy is commonly used in advanced localized and metastatic tumors (Reiss et al., 2024). However, the cancer often develops resistance and progresses to mCRPC (Coutinho et al., 2016). Reactivation of AR signaling can occur due to somatic gain-of function *AR* variants, higher expression of *AR* splice variants, and increased androgen biosynthesis in mCRPC patients (Watson et al., 2015; Ku et al., 2019). Moreover, rearrangements of the AR locus, such as tandem duplications in an upstream enhancer, can contribute to changes in the expression of AR (Viswanathan et al., 2018). Similarly, germline variants in *CYP17* and *HSD3B1*, which are involved in AR signaling, are also associated with mCRPC (Lunn et al., 1999; Yamada et al., 2001; Hearn et al., 2016). Understanding these variants can help selecting the most effective treatment strategy to regulate AR signaling. For example, patients carrying *AR* splice variants missing the ligand-binding domain but constitutively active, might benefit from treatments specifically designed to target these variants (Daniels et al., 2024).

PCa patients carrying deleterious variants in genes involved in DNA repair pathways, such as *BRCA1, BRCA2*, or *ATM*, can benefit from targeted therapies like PARP inhibitors (PARPi) and checkpoint inhibitors. PARPi are pharmacological inhibitors of the enzyme poly ADP ribose polymerase (PARP), which is involved in DNA repair mechanisms, including base excision repair (Mateo et al., 2019). Similarly, individuals with microsatellite instability–high tumors

(MSI-H), which have a high number of mutations within microsatellites, can benefit from checkpoint inhibitors (Lenis et al., 2024). Checkpoint inhibitors, such as anti-PD-1 and anti-CTLA4 antibodies, increase the immune response against cancerous cells by blocking inhibitory immune checkpoint proteins that often regulate immune tolerance (Subudhi et al., 2021). In a study with patients with MSI-H, 21.9 % had a pathogenic germline mutation in an MMR gene (*MSH2*, *MSH6*, and *PMS2*) explaining a connection between these variants and MSI-H (Abida et al., 2019). By using these therapies, the high genomic instability and impaired DNA mechanisms of cancerous cells in these germline variant carriers enables the induction of selective tumor cell cytotoxicity through the mechanism of synthetic lethality (Previtali et al., 2024).

Patients requiring radiotherapy due to relapses with localized disease or biochemical recurrence can benefit from a germline genetic profile checking the presence of risk variants for radiation toxicity and radio-resistance. This can help to decide the optimal treatment option to obtain the best results avoiding long-term side effects. A meta-analysis of four radiogenomics GWAS indicated that non-coding variants rs17599026 in 5q31.2 and rs7720298 in 5p15.2 region are associated with late radiotherapy toxicity symptoms, such as urinary frequency and reduced urine stream (Kerns et al., 2016). Variant rs17599026 lies 23bp downstream of exon 20 in the gene *KDM3B*, whose protein is highly expressed in bladder tissue, and its disruption could produce bladder dysfunction. Similarly, variant rs7720298 is located downstream of exon 30 in the gene *DNAH5*, whose protein is involved in cilia function. Cilia are found in bladder tissue, thus alterations in that gene expression might cause changes in the urinary tract (Kerns et al., 2016). Similarly, individuals with germline mutations in *BRCA1* had worse survival rates than non-carriers after radiotherapy treatment but similar survival rates when treated surgically, proving that certain variants affect radiosensitivity (Sanchez et al., 2016). Genetic profiles can be integrated into models of radiotoxicity to optimize radiation dose and decrease unwanted side effects. Given these therapeutic advancements, genetic testing for certain variants is increasingly recommended to guide precision medicine approaches in PCa management.

1.5 Uncovering novel germline variants in the Finnish population

The advancement and decreasing cost of genotyping technologies, combined with increased collaboration among institutions, have significantly enhanced the quality and scope of GWAS studies. While many common variants have been associated with PCa, few causal variants have been identified. The variants already identified explain only a small portion of heritability, leaving a significant "missing heritability" unexplained (Walsh, 2017). This "missing heritability" might be explained partly by rare and penetrant variants that act as a proxy for more common variants, phenomenon known as synthetic association, underestimating the real effect of these rare variants (Orozco et al., 2010). Synthetic association has been observed in PCa between some identified common variants and *HOXB13* G84E (Sanders et al., 2014). Moreover, other types of genetic variation, such as structural variants like copy number variants, or variants involved in epigenetic regulation, might also contribute to this "missing heritability" (Manolio et al., 2009; Kruithof-de Julio et al., 2014; Zhu et al., 2017; Dai & Liu, 2021). Additionally, many variants of uncertain significance (VUS) still lack clear clinical significance to PCa risk, making it difficult to classify them as benign or pathogenic and assess their importance (Jimenez-Sainz et al., 2021). Furthermore, the genetic heterogeneity of PCa, where cancer cells may originate from different foci and precursor cells that undergo independent malignant transformation by both germline and somatic mutations, complicates the identification of clinically relevant germline variants (Cooper et al., 2015; Yamaguchi et al., 2025).

Hereditary predisposition to PCa is likely influenced by a combination of common variants with low or moderate effect-size and rare variants with a high effect-size. Identifying rare variants would importantly help to understand the genetic basis of PCa (Wang et al., 2023). The negative/purifying selection effect makes most deleterious predisposing variants very rare in large and older populations. Isolated populations with recent bottlenecks, like the Finnish one, present enrichment of rare and low-frequency cancer-predisposing variants due to increased genetic drift. (Lim et al., 2014; Zuk et al., 2014) Therefore, the Finnish population provides a unique opportunity to detect high-risk variants that are uncommon in other populations (Lim et al., 2014; Xue et al., 2017).

1.5.1 Aims of this research

In this study, WGS data from 71 index patients of Finnish high-risk HPCa families with three or more affected cases per family is used to identify potential germline variants associated with PCa. Bioinformatically defined pathogenic variants are selected based on their high incidence in these families, their gene expression in prostatic tissue, and statistical significance in previous GWAS conducted in a Finnish PCa population (FinnGen). From this final selection, variants are prioritized if their genes had been previously linked to PCa, but the specific variants had not yet been associated with the disease.

The segregation of these variants is studied in those families whose index patients were carriers, including all the individuals diagnosed with PCa and healthy relatives who were over 50 years old. This first part of the study aims to determine whether the selected germline variants segregate with PCa within families and to validate them as potential high-risk factors for HPCa. These variants are expected to be enriched in these high-risk HPCa families and to appear significantly more often in PCa patients. Such findings would indicate that these germline variants are inherited and contribute to disease risk in these families.

Secondly, a cohort of PCa patients with a family history of PCa and HBOC from the Turku Prostate Cancer Consortium (TPCC) is created, and the frequencies of the studied variants are compared to those in PCa patients without a family history of these conditions. Further validation is done by comparing the studied variant incidence between our cohort and the general Finnish population (Finngen), as well as our cohort and a larger cohort of Finnish individuals with PCa (FinnGen). This comparison aims to identify germline variants specifically associated with hereditary forms of PCa while excluding those linked to sporadic cases. These variants are expected to have a higher frequency in the cohort of PCa patients with a family history of PCa and HBOC, than any other studied group. By distinguishing between these groups, variants that may serve as markers for HPCa risk can be pinpointed.

Finally, it is investigated whether these variants impact the clinicopathological characteristics of PCa. To do this, the age of disease onset, PSA levels, Gleason score, and TNM staging are compared between PCa patients carrying the variant and those who do not. Since the selected germline variants are considered pathogenic, patients carrying them are expected to have an earlier onset of disease, higher PSA levels, higher Gleason score, and more advanced TNM staging compared to those who do not carry the variant.

The mentioned approaches seek to identify variants located in genes previously implicated in PCa, but not previously directly associated with PCa or any other type of cancer. By performing familial studies and analyzing individuals with a history of PCa and HBOC, rare variants that might be incidental in sporadic cases are filtered out and those that are enriched and genuinely associated with HPCa can be recognized. Identifying these new variants can enhance our ability to assess genetic predisposition, enable earlier detection, and improve risk prediction. Furthermore, it allows for personalized treatment strategies and more accurate predictions of disease progression and prognosis.

2. MATERIAL AND METHODS

2.1 Study population

Familial samples

The families examined for the familial study were selected from 71 Finnish high-risk PCa index patients who had undergone WGS as part of a study on risk genes associated with hereditary prostate cancer (HPCa), conducted by Prof. Johanna Schleutker. The index patients in the WGS dataset were unrelated and had been diagnosed with high-risk PCa. In addition, the study also examined family members of these 71 index patients, including both healthy men and those with PCa. All studied individuals had consented to donate blood samples for HPCa research. These blood samples have been collected from across Finland since the early 1990s. The samples were labeled with a six-digit number, where the first three digits identified the family and the last three identified the individual's pedigree number. The families included in our familial study were those in which the index patient was heterozygous or homozygous for the studied variant. Clinical data was collected for all patients. Only family members who were ≥ 50 years old at the time of the last status update were included for analysis in the study. The last update of the family members' health status varies by family, and the corresponding year can be found in the pedigree chart (Appendix 1).

Cohort samples

Individuals included in the cohorts were selected from the consecutive RALP collection conducted by the Turku Prostate Cancer Consortium (TPCC) and PROMIC ("Prostate Metabolism, Cancer Risk, and Gut Microbiota") study led by Prof. Peter Boström (TUH). The RALP cohort consists of clinically significant PCa patients operated for radical prostatectomy, with or without pelvic lymph node dissection, using robotic-assisted laparoscopic prostatectomy (RALP). The PROMIC cohort includes individuals with clinical suspicion for PCa and indication for further PCa diagnosis based on increased PSA (> 2.5 ng/ml), a palpable prostate tumor/nodule, or imaging findings indicative of PCa. Only PROMIC participants with a PCa diagnosis defined by non-benign Gleason score were included in this study. RALP sample collection began in 2013, and as of today (8.4.2025), there are 1,564 RALP and 370 PROMIC participants, respectively.

Family history information in RALP and PROMIC datasets included whether the patient's children, siblings, parents, uncles, aunts, or grandparents have PCa or any type of cancer. In the

RALP questionnaire, a blank space allowed participants to specify the type of cancer, enabling the collection of data on all cancer types. In contrast, the PROMIC data was obtained already as an Excel table containing only information related to prostate, breast, ovarian, large intestine, rectal, bowel, colon, and bladder cancer. However, this table didn't include the number of brothers, sisters, children, aunts and uncles that a specific type of cancer. Additionally, the RALP questionnaire recorded the age at which a patient's relative was diagnosed with cancer, whereas the PROMIC data did not include this information.

The inclusion criteria for PCa patients with a family history of PCa or HBOC: (1) a first-degree relative (father, brother, or son) with PCa, or (2) two or more relatives with PCa, or (3) two or more relatives with HBOC-related cancers (prostate, breast, and ovarian cancer) (N=342). These criteria are inspired by the germline testing criteria for PCa of NCCN Guidelines Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (Version 1.2022) (Daly et al., 2021). The inclusion criteria for PCa patients without a family history of PCa or other hereditary cancer syndromes required that no first-degree relatives had been diagnosed with any type of cancer, and no second-degree relatives had been diagnosed with prostate, breast, or ovarian cancer (N=450).

RALP patients with missing questionnaires were not used in this study. Moreover, the empty questionnaires' items were considered as missing data. In the case, the type of cancer was not specified or had been answered as "?/joku", that relative was not considered for the inclusion criteria of the participant.

Clinicopathological characteristics of the analyzed patients

Clinical data from RALP patients contained preoperative/diagnostic PSA levels, biopsy Gleason score, operative Gleason score, and operative TNM classification (tumor stage, node stage, and metastasis stage). Similarly, clinical data from PROMIC patients included diagnostic PSA levels, biopsy Gleason score, clinical TNM classification (tumor stage, node stage, and metastasis stage), and radiology TNM classification (MRI tumor stage, radiological node stage, and radiological metastasis stage). TNM classification can be determined clinically or pathologically. Clinical staging uses physical examination and imaging before any final treatment is started. Pathologic stage is defined by pathologic examination of the surgical removed prostate and any lymph nodes removed during surgery. Therefore, pathologic staging is more accurate because it is not limited by estimations provided by the physical exam and imaging methods (Reese, 2016). Since the prostate gland was completely removed in RALP patients, the tumors were precisely and systematically graded and staged considering the postoperative histopathological evaluation from the pathologists (pathologic/surgical staging). In PROMIC patients, Gleason grading was defined by prostate biopsy, and TNM staging was clinically determined using MRI imaging (clinical staging).

To ensure the most comparable values in Gleason score, biopsy Gleason scores for RALP patients were selected to match the biopsy-derived scores from PROMIC patients. Since Gleason scores in PROMIC were expressed as ISUP grades, the RALP biopsy Gleason scores were converted to ISUP grades for consistency. All the genotyped RALP patients and PROMIC participants with PCa (non-benign Gleason score) were analyzed for the association between clinicopathological features and PCa (N=548). Since RALP patients without family history of PCa and HBOC were also genotyped for the *PASK* variant, the total number of individuals analyzed for that variant was 842.

2.2 SNP variant selection

The data for variant selection was obtained from the 71 Finnish high-risk PCa index patients who underwent WGS as previously described. The WGS data were processed and refined into an Excel dataset by the research group's bioinformatician. All the variants that were annotated as coding in at least one transcript were selected. For this selection, only variants with high or moderate impact on protein structure, according to the Ensembl Variant Effect Predictor (VEP), were considered. VEP is a toolset for the analysis, annotation, and evaluation of genomic variants, that provides information from different bioinformatic prediction programs, such as REVEL and CADD, to determine a variant's pathogenicity (McLaren et al., 2016). Rare Exome Variant Ensemble Learner (REVEL) is an ensemble method that predicts the pathogenicity of missense variants by combining scores from 13 individual tools: MutPred, FATHMM v2.3, VEST 3.0, PolyPhen-2, SIFT, PROVEAN, MutationAssessor, MutationTaster, LRT, GERP++, SiPhy, phyloP, and phastCons. The REVEL score ranges from 0 to 1, where higher scores indicate an increased probability of being disease-causing (Ioannidis et al., 2016). Similarly, Combined Annotation Dependent Depletion (CADD) predicts the deleteriousness of variants by integrating over 60 genomic features, such as gene model annotations, sequence context, evolutionary constraint, functional predictions, or epigenetic measurements. CADD scores range from 0 to 99, though most scores fall from 0 to 50, with higher scores suggesting a greater likelihood of deleteriousness (Rentzsch et al., 2019). For this selection, the maximum alternative allele frequency (MAF) had to be below 0.05. Additionally, variants were required to have a REVEL score above 0.6, a CADD score over 20, or be classified as likely pathogenic or pathogenic by the ClinVar (National Library of Medicine) database.

Then, the following factors were considered to select the final list: variant incidence in the 71 high-risk index patients' population, gene expression in the prostate (Human Protein Atlas 23.0, 2023), gene function (Gene cards v5.23.0, 2024), previous GWAS results in Finnish PCa cases (FinnGen Release 12, 2024), and existent literature. For the selection assessment, an Excel dataset was created by merging data from 71 high-risk index patients' variants, gene expression data from the Human Protein Atlas, and statistical values from the endpoint C3_PROSTATE_EXALLC for malignant neoplasm of the prostate from FinnGen. The variant selection was carried out based on the following criteria: (1) the variant had to be present in more than one patient, (2) the corresponding gene had a maximum normalized transcripts per million (MAX nTPM) ≥ 1 either in basal prostatic cells or prostatic glandular cells (Human Protein Atlas), and (3) the variant showed a p-value $< 1\text{x}10^{-3}$ and a positive beta coefficient in the C3_PROSTATE_EXALLC endpoint for malignant neoplasm of the prostate, excluding all cancers (controls excluding all cancers) in FinnGen. A ratio between the allele frequency in the high-risk index patients' population and the allele frequency in the general Finnish population (FinnGen) > 1 was also considered for the final selection. To reduce the number of candidate variants, variants in genes implicated in prostate cancer according to the literature but for which no specific variants have yet been associated with PCa were prioritized. Scientific peer-reviewed articles and publications were obtained from PubMed (NIH-NCBI, 2024), Web of Science (Clarivate Plc, 2024), and Scopus (Elsevier, 2024) to assist in the final selection of potential risk genes associated with PCa. The literature review was conducted between 4.9.2024–23.12.2024.

2.3 DNA extraction

DNA from high-risk PCa families and PROMIC participants had been isolated before the start of this study. While most of the DNA from RALP patients was already extracted, several samples from the latest participants were isolated from whole blood samples. DNA was isolated using Nucleon™ BACC3 Genomic DNA Extraction Kit following the manufacturer's protocol (2964876AA, Cytiva, USA). The DNA was eluted into Tris-EDTA buffer (10 mM Tris-HCl, 0,1 mM EDTA, pH 8.0) and stored at -80 ºC until utilization.

2.4 SNP genotyping

The genotyping data for the PROMIC individuals were obtained from the WES they underwent before this study. Predesigned TaqMan™ SNP Genotyping Assay (40x), human, S (4351379, ThermoFisher, USA) were used to genotype the variants of interest in the high-risk families and RALP patients: C_186512811_1 (rs190865056), C__25934487_2 (rs34785134), C__57929546_1 (rs35129131), C__25997308_2 (rs62623389), and C__25615425_3 (rs34592828). All TaqMan™ SNP Genotyping Assays have two-allele-specific TaqMan MGB probes containing distinct reporter fluorescent dyes (VIC and FAM) and a PCR primer pair to detect the specific SNP. For rs190865056, rs34785134, rs35129131, and rs62623389, VIC was used to detect wild-type (WT) sequences and FAM for the variant of interest (VOI) sequences, respectively. When genotyping rs34592828, VIC was used to detect the VOI sequences and FAM for the WT sequences. All samples' DNA concentrations were measured with NanoDrop Spectrophotometer (ThermoFisher, USA) and diluted with Tris-EDTA Buffer (10 mM Tris-HCl, 0,1 mM EDTA, pH 8.0) to obtain 10 ng/µl dilutions before genotyping. PCR amplifications were done in 96-well, thin-wall Hard-Shell PCR Plate (HSP9955, Bio-Rad, USA) in a total volume of 25 µl, containing 0,63 µl TaqMan™ SNP Genotyping Assay (20x), 12,5 µl TaqMan Genotyping Master Mix (4371355, ThermoFisher, USA), 10,87 µl ddH2O, and 1 µl of DNA sample (10 ng). DNA samples with a concentration below 10 ng/µl were directly pipetted in the PCR reaction, and ddH2O was adjusted accordingly. Index patients from the high-risk families with known genotypes from WGS were used as positive and negative controls. Positive, negative, and no-template (water) controls (NTC) were included in each 96-well plate. Real-time PCR (RT-PCR) was performed using the CFX96 Touch Real-Time PCR Detection System (Bio-Rad, USA). After enzymatic activation for 10 minutes at 95 ºC, 62 two-step cycles of 15 seconds at 95 ºC (denaturation) and 1 minute at 60 ºC (annealing/extension) were done. The fluorescence levels of FAM and VIC were automatically measured by Bio-Rad CFX Manager 3.1 (Bio-Rad, USA). Allelic discrimination results were displayed on a scatter plot, comparing the fluorescence signals of the reporter dyes (WT allele vs. VOI allele). Clustering limits for each genotype were automatically determined based on the distribution of spectral-specific plots, incorporating positive controls and sequence results from samples positioned near the lower end of the cluster boundary. Genotypes were assigned according to their respective cluster locations. Variants clustered near the NTC or exhibited an abnormal spectral pattern were reanalyzed to determine the correct genotype.

2.5 Statistical analysis

In the familial study, allele and carrier frequency differences between healthy and men with PCa were tested individually for each family using Fisher's exact test. Additionally, a pooled contingency table was used to obtain a simple overall comparison between healthy PCa individuals across all families without considering family-specific effects by using Fisher's exact test.

To account for the family structure and potential correlation within families, a binomial Generalized Linear Mixed Model (GLMM) was used. The binomial distribution was chosen because the outcome variable (health status) is binary. The analysis was performed in R using the glmer() function from the lme4 package. The binary outcome variable (PCa men vs. no PCa men) was modeled as a function of variant carrier status (carrier vs. non-carrier), with a random intercept for family to control for the potential correlation among related individuals. The model assumed a binomial distribution with a logit link. Odds ratios were calculated by exponentiating the estimate of the fixed effect (variant). Estimated marginal means (least-squares means) were calculated using the emmeans package to obtain adjusted predicted probabilities and confidence intervals for each allele count category. The adjusted predicted probabilities indicate the probability of having PCa for each allele count category, in this case having or not the variant, considering relatedness in the model. To assess whether the inclusion of the random family effect significantly improved model fit, a reduced model without the random effect was fitted using glm(), and the likelihood ratio test anova() was performed to compare the two models. This approach allowed for the evaluation of the global effect while considering the possible family structure of the data.

A Family-Based Association Test (FBAT) was also performed to provide a complementary approach by testing whether genetic variants are transmitted to PCa family members more often than expected by chance. FBAT analyses were conducted using the FBAT_v204 software (Linux, 64-bit). In the PED files, all women were assigned an "unknown" phenotype (0) to reflect that women cannot develop PCa and to avoid affecting the test results. FBAT was performed using the orthogonal mode (FBAT -o) to test whether the variant was associated with PCa in "absence of linkage", assuming no linkage and treating transmissions within nuclear families as independent under the null hypothesis. In addition, the empirical mode (FBAT -e) was applied to test whether the variant is associated with PCa in "presence of linkage", adjusting for potential within-family correlations, such as those arising from potential linkage using the PCa prevalence in Finnish men (2.24 %) as an offset parameter (μ) (Pitkäniemi et al., 2022).

Both models were run using the following settings: model = additive; test = bi-allelic; minsize = 1; min_freq = 0.000; p = 1.000; maxcmh = 1000. These parameters assume an additive model for a bi-allelic variant. The test is run using a minimum of one informative family, with no minimum allele frequency to allow for rare variants testing, default placeholder for p-value filtering, and default maximum number of strata to use in a Cochran-Mantel-Haenszel (CMH) test for not limiting most analyses.

For the cohort study, allele and carrier frequency differences between two groups of patients PCa patients with a family history vs general Finnish population (FinnGen), PCa patients with family history vs PCa cases from Finnish GWAS (FinnGen), and PCa patients with family history vs PCa patients without a family history were compared for the variants of interest using Fisher's exact test. The allele frequency for the selected variants in the general Finnish population and PCa cases from the Finnish GWAS, as well as the number of homozygous individuals for each variant in the general Finnish population were only available. Based on this, the carrier frequency in the general Finnish population was calculated using the allele frequency and the number of homozygotes. To estimate the carrier frequency among the PCa cases from the Finnish GWAS, Hardy-Weinberg equilibrium (HWE) was assumed, because genotype counts were not available.

Regarding the clinicopathological analysis, the comparison was made between patients carrying the variant of interest and those without it to examine an association between the carrier genotype and the clinicopathological nature of the PCa. Since the age of onset is a continuous variable, its normality was assessed using Shaphiro-Wilk test. As the data was not normally distributed, the non-parametric Mann-Whitney U test was used to compare differences between the two groups. In addition, the PSA level's normality was assessed using Shaphiro-Wilk test. As the data was not normally distributed, the non-parametric Mann-Whitney U test was used to compare differences between the two groups. Association between carrier status and Gleason score, T-grade, N-grade, and M-grade was examined by comparing carrier frequencies using Fisher's exact test.

The patients were also categorized into groups with more aggressive or less aggressive characteristics based on the age at onset, diagnostic PSA values, biopsy Gleason score, and TNM staging. Each characteristic was compared and analyzed individually to determine whether variant carriers tend to have an early age at onset, higher PSA levels, higher Gleason score, and more advanced TNM classification. The characteristics were considered less aggressive when the age at onset ≥ 65, PSA ≤ 20 ng/ml, Gleason score < 8 (ISUP < 4), and TNM stage < T3, or Nx/N0, or Mx/M0. Oppositely, an age at onset < 65, PSA > 20 ng/ml, Gleason score ≥ 8 (ISUP ≥ 4), and TNM stage ≥ T3, N1, or M1 were classified as more aggressive characteristics. This classification was necessary to facilitate the combined analysis of RALP and PROMIC data, as TNM staging was categorized into only two groups in PROMIC patients (<T3, T3aMRI; N0, N1; M0, M1b), whereas in RALP patients, T-class, N-class, and M-class were categorized into seven (T2, T2a, T2b, T2c, T3a, T3b, T4), three (NX, N0, N1), and five groups (MX, M0, M1, M1a, M1b) respectively. Carrier frequency differences between patients with more aggressive and less aggressive characteristics were tested individually using Fisher's exact test.

The association between variant status and aggressive forms of PCa was examined by comparing carrier frequencies between aggressive and non-aggressive PCa cases. Aggressive PCa was defined as having at least one of the following: PSA > 20 ng/ml, Gleason score ≥ 8 (ISUP ≥ 4), T stage 3 or 4, N1, or M1. The definition for aggressive PCa was decided considering the recommendations from Hurwitz and colleagues (Hurtwitz et al., 2021) but also including T3 stage cancers and cases where PSA was > 20 ng/ml. Non-aggressive PCa was defined as the cancer cases meeting all the following criteria: PSA ≤ 20 ng/mL, Gleason score 6 (ISUP 1), T stage < 3, N0, and M0. Fisher's exact test was used for the comparison of the carrier frequencies between both groups.

Statistical analysis was performed using R version 4.3.1 (2023-06-16 ucrt; R Core Team, 2023). The packages used for this thesis are: dplyr (Wickham et al., 2023), emmeans (Lenth, 2023), lme4 (Bates et al., 2015), readr (Wickham & Girlich, 2023), readxl (Wickham & Bryan, 2023), writexl (Ooms, 2024), and stats (R Core Team, 2024). All reported Fisher's exact tests are two-tailed. Statistical significance was considered when $p < 0.05$.

The different parts of this study, including the study populations and the statistical methods performed are summarized in Figure 2.

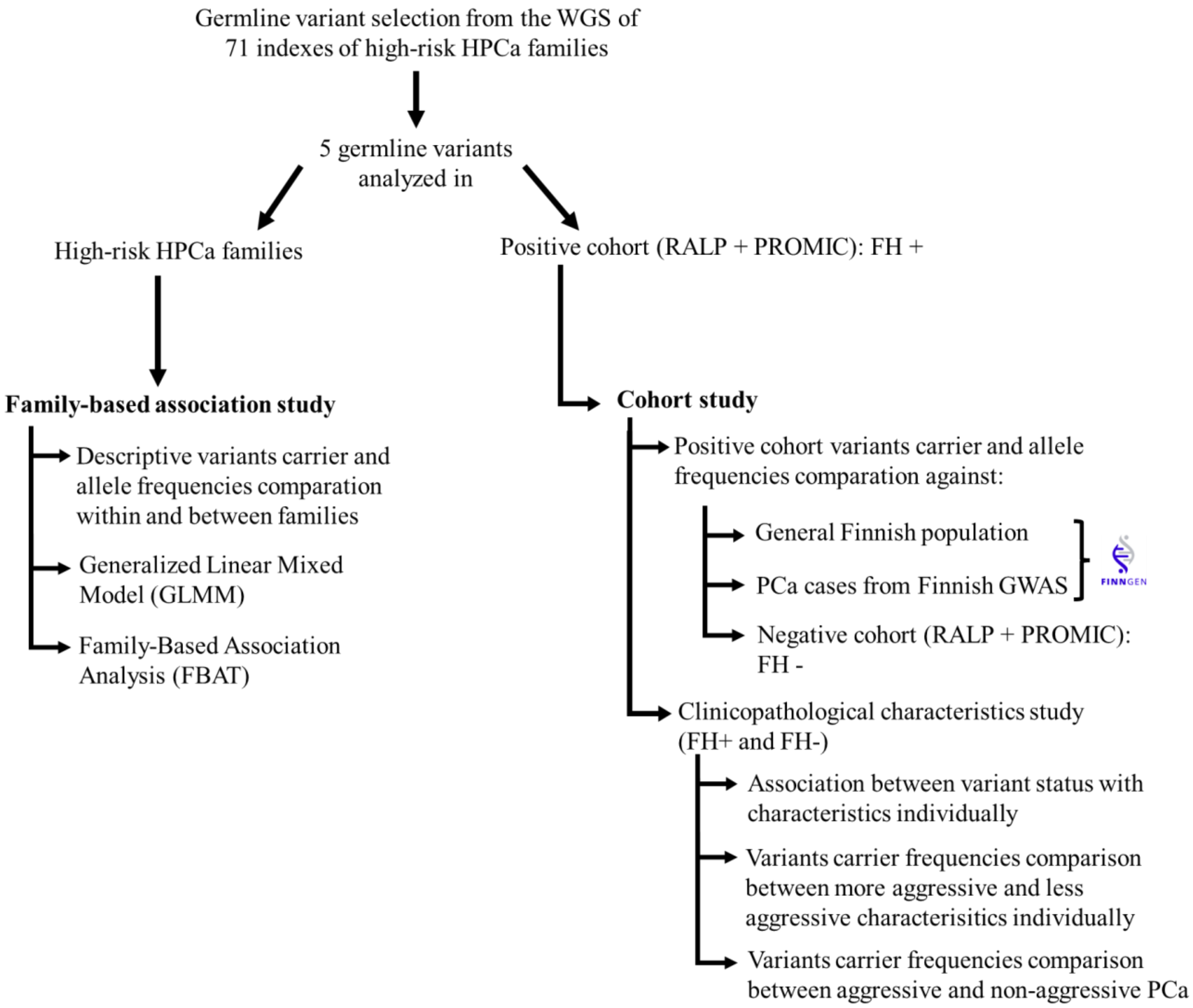


Figure 2. Schematic representation of the study, illustrating the study populations, analytical approaches, and methods applied.

2.6 Use of AI-assisted tools

OpenAI's ChatGPT-4 has been used for proofreading and language refinement in this thesis according to the University of Turku guidelines (https://utuguides.fi/tekoaly). The content, research ideas, data analysis, scientific interpretation, and conclusions are the work of the author and the research group, and AI-assisted tools were not used in their generation or development.

2.7 Ethical considerations

Individuals from high-risk families are part of research conducted by the Prostate Cancer Research Center at Tampere University, where Prof. Johanna Schleutker is affiliated. Ethical approval for this study was granted by the ethical board of Tampere University Hospital

(R03203, valid until 31.12.2025). RALP collection (TPCC) operates under Biobank permission and TYKS ethical permission (ETMK 3/1801/2013). PROMIC is a clinical trial involved in the research project "Prostate Metabolism, Cancer Risk, and Gut Microbiota" conducted by Prof. Peter Boström (TUH) (NCT06116851). All participants have provided signed informed consent for DNA analysis and further examination.

3. RESULTS

3.1 SNP variant selection

The WGS dataset from 71 Finnish high-risk prostate cancer (HPCa) index patients was analyzed to identify potential PCa-predisposing germline variants. A preliminary filtering was done by the group bioinformatician to select variants with high or moderate impact that affect protein structure, as determined by Ensembl Variant Effect Predictor (VEP). These variants also had to have a maximum alternative allele frequency (MAF) below 0.05, a REVEL score of at least 0.6, and a CADD score above 20, obtaining a dataset with 9,813 variants. Next, the potential PCa predisposing variants that appeared more than once in the high-risk HPCa index patients' cohort, had a MAX nTPM ≥ 1 in basal prostatic cells or prostatic glandular cells, and were associated or had a trend towards association with the C3_PROSTATE_EXALLC endpoint for malignant neoplasm of the prostate, excluding all cancers (controls excluding all cancers) in FinnGen, with a p-value $< 1\text{x}10^{-3}$ and a positive beta coefficient were selected. Additionally, a ratio greater than one between the allele frequency (AF) of the high-risk PCa index patients and the Finnish population (Finngen) was considered when assessing the variants for the variant selection. After filtering, the dataset was reduced to 14 variants: *HOXB13* (rs138213197), *ABI3* (rs755071175), *CDK5RAP3* (rs61758369), *CHEK2* (rs555607708), *CHEK2 (*rs17879961), *ZNF391* (rs200883853), *ZKSCAN3* (rs61744865), *LAMC2* (rs17481405), *TP63* (rs190865056), *ZBTB46* (rs34785134), *PASK* (rs35129131), *TASOR* (rs147283164), *LETM1* (rs62623389), *IQGAP2* (rs34592828) (Table 3).

To reduce the number of candidate variants, those located in genes previously associated with PCa according to the literature, but for which no specific variants have yet been associated with PCa were prioritized. To support this selection, a literature review to identify associations between the candidate genes and cancer, with a particular focus on PCa, was conducted. The selected genes and the justification for their inclusion in the filtered list based on the literature review are detailed in Appendix 2.

Table 3. The selected 14 variants from the high-risk HPCa index patients WGS dataset. Variants were filtered considering an incidence higher than one in the high-risk PCa patients (N=71), gene expression in basal prostatic cells and prostatic glandular cells MAX nTPM ≥ 1, and association with a p-value < 1x10^{-3} and a positive beta coefficient in the C3_PROSTATE_EXALLC endpoint for malignant neoplasm of the prostate, excluding all cancers (controls excluding all cancers) from Finngen. The table also includes the variant base change, variant allele frequency (AF) in Finngen, the ratio of AF between the high-risk PCa index patients and Finnish population (Finngen), and p-value and beta coefficient from the C3_PROSTATE_EXALLC endpoint. 0/0 homozygous for the reference allele, 0/1 heterozygous for the variant allele, 1/1 homozygous for the variant allele.

Gene	Genomic location	Variant	Base change	0/1	1/1	0/0	Prost. basal cells (nTPM)	Prost. glandular cells (nTPM)	AF Finngen	Ratio AF high-risk patients: Finngen	p-value	beta
HOXB13	17q21.31	rs138213197	C->T	11	0	60	0.8	209.8	8.48e-3	9.125	1.34e-194	1.488
ABI3	17q21.32	rs755071175	G->T	7	0	64	1.3	0.5	5.50e-3	8.956	6.40e-77	1.196
CDK5RAP3	17q21.31	rs61758369	A->G	6	0	65	4.6	4.7	6.58e-3	6.417	2.21e-59	0.992
CHEK2	22q12.1	rs555607708	AG->A	3	0	68	2.2	1.2	7.26e-3	2.908	4.47e-18	0.550
CHEK2	22q12.1	rs17879961	A->G	2	0	69	2.2	1.2	3.01e-2	0.468	1.72e-09	0.195
ZNF391	6p22.3	rs200883853	C->T	3	0	68	1.9	2.4	2.21e-2	0.955	9.66e-07	0.193
ZKSCAN3	6p22.3	rs61744865	A>G	2	0	69	2.1	1.7	2.07e-2	0.679	8.92e-05	0.160
LAMC2	1q25.3	rs17481405	G->A	5	0	66	25.3	1.7	3.65e-2	0.963	1.58e-04	0.120
TP63	3q28	rs190865056	T->A	4	0	67	37.8	2.1	1.42e-2	1.977	3.13e-04	0.176
ZBTB46	20q13.33	rs34785134	C->T	2	0	69	2.6	1.3	6.67e-3	2.110	3.81-e04	0.245
PASK	2q37.3	rs35129131	C->T	5	0	66	1.7	16.4	1.30e-2	2.710	4.76-e04	0.171
TASOR	3p14.2	rs147283164	C->T	2	0	69	30	31.3	2.59e-2	0.544	8.31-e04	0.123
LETM1	4p16.3	rs62623389	T->C	12	0	59	14.6	9.6	4.43e-2	1.906	8.91-e04	0.094
IQGAP2	5q13.2	rs34592828	G->A	5	0	66	99.2	90.9	4.03e-2	0.873	9.99-e04	0.096

Although each of the genes *ABI3*, *ZNF391*, and *TASOR* have been independently associated with several types of cancer, no publications were found connecting them with PCa. Moreover, *ABI3* rs755071175 variant, which is in the 17q21.32 region, is close to the 17q21.31 region containing *HOXB13* rs138213197. Many patients had both *HOXB13* and *ABI3* variants, which are quite rare and can be assumed to be in linkage disequilibrium. To check for any possible association between *ABI3* rs755071175 and PCa, the FinnGen's bioinformatician excluded all the C3_PROSTATE_EXALLC endpoint (FinnGen) *HOXB13* rs138213197 carriers from the cohort and did a regression analysis for *ABI3* rs755071175 variant with PCa endpoint as the outcome. The analysis was then repeated in the opposite direction, excluding *ABI3* rs755071175 carriers and testing *HOXB13* rs138213197. The analysis results showed that *HOXB13* rs138213197 p-value was greater when *ABI3* rs755071175 carriers were removed, but it was still genome-wide significant. On the other hand, *ABI3* rs755071175 p-value was also greater when *HOXB13* rs138213197 carriers were excluded, but it was no longer genome-wide significant. This suggested that *ABI3* rs755071175 might not represent an independent association signal and its significance comes from its proximity with *HOXB13* rs138213197. Therefore, *ABI3, ZNF391*, and *TASOR* variants were not selected for the final analysis. *HOXB13* rs138213197, *CHEK2* rs555607708, and *CHEK2* rs17879961 were also excluded, as their association with PCa has already been established (Dong et al., 2003; Seppälä et al., 2003; Ewing et al., 2012). In addition, *CDK5RAP3* rs61758369 variant and *HOXB13* rs138213197 variant are both located in 17q21.31 region. All the patients carrying *CDK5RAP3* rs61758369 also carry *HOXB13* rs138213197, indicating that there is a possible linkage explaining the statistically significant low p-value in C3_PROSTATE_EXALLC endpoint in FinnGen for *CDK5RAP3* rs61758369. Although no analysis like the one performed for the *ABI3* variant was conducted to evaluate whether the signal is independent or due to linkage disequilibrium, *CDK5RAP3* rs61758369 was excluded from the final selection due to suspected linkage with *HOXB13* rs138213197. *LAMC2* rs17481405 was also excluded due to its lower AF in the high-risk PCa index patients compared to the general Finnish population (Finngen), as well as limited literature supporting its association with PCa compared to other variants. The variant *ZKSCAN3* rs61744865 was not included in the final selection due to its lower AF in the high-risk PCa index patients in comparison to the general Finnish population (Finngen) and the unavailability of its TaqMan™ SNP Genotyping Assay from ThermoFisher. Although *IQGAP2* rs34592828 had also a lower AF in the high-risk HPCa index patients, it was included due to its high expression in basal and glandular prostatic cells. As a result, a final list with five variants to be genotyped for the family-based and cohort studies was obtained: *TP63* (rs190865056), *ZBTB46* (rs34785134), *PASK* (rs35129131), *LETM1* (rs62623389), and *IQGAP2* (rs34592828).

3.2 Samples selection

3.2.1 Familial samples selection

To analyze the association between the variants and PCa, all the families whose index patient had the corresponding variant were analyzed: families 083, 264, 364, and 407 for *TP63* rs190865056; families 045 and 241 for *ZBTB46* rs34785134; families 069, 123, 291, 433, and 451 for *PASK* rs35129131; families 001, 069, 123, 153, 236, 359, 364, 386, 393, 421, 445, and 460 for *LETM1* rs62623389; and families 062, 066, 238, 251 and 364 for *IQGAP2* rs34592828. All the family members with available blood samples or isolated DNA and who were over 50 years old by the time of the last recorded health status were selected. Selected families, family members, and their PCa status are displayed in Table 4.

Table 4. Selected families and their members for the family-based study. The health status indicates whether the individual has prostate cancer (+) or not (-). Individuals with bold numbers are the index patients for each family.

Variant	Family	Individuals
TP63 rs190865056	083	001 (+), **002** (+), 003 (-), 004 (-), 005 (-), 006 (-), 007 (-), 009 (-), 010 (+), 011 (-), 015 (-), 016 (+)
	264	001 (-), 003 (+), **004** (+), 005 (-), 006 (-), 007 (-), 008 (-), 009 (-), 010 (-), 011 (-), 012 (-), 013 (-), 014 (+), 017 (-), 019 (+)
	364	**001** (+), 002 (-), 003 (-), 005 (-), 007 (-), 008 (+), 010 (-),014 (-)
	407	001 (-), **002** (+), 003 (+), 008 (-), 011 (-), 014 (-)
ZBTB46 rs34785134	045	**001** (+), 002 (-), 003 (+), 004 (-), 006 (-), 007 (-), 008 (-), 009 (-), 010 (-), 011 (-), 012 (-), 013 (-), 014 (+)
	241	001 (-), **002** (+), 003 (+), 004 (-), 005 (-), 006 (+), 008 (-), 009 (-), 010 (-), 011 (-), 014 (-), 016 (-), 017 (-), 018 (-), 019 (-), 020 (-)
PASK rs35129131	069	**002** (+), 003 (-), 004 (-), 005 (-), 006 (-), 008 (+)
	123	**001** (+), 003 (+), 004 (+)
	291	**001** (+), 003 (+), 004 (-), 005 (+), 012 (-), 013 (-), 014 (+), 015 (-), 016 (-), 018 (-), 019 (-), 020 (-), 021 (-), 022 (-), 023 (-), 025 (-), 026 (-), 027 (-), 028 (-), 030 (-), 032 (-), 033 (-), 037 (-)
	433	**001** (+)
	451	**001** (+), 002 (+), 003 (+), 004 (+)
LETM1 rs62623389	001	001 (-), 002 (+), 003 (-), 004 (+), 008 (-), 009 (-), 011 (-), 013 (-), 014 (+), 017 (-), 018 (-), 019 (-), 020 (-), 021 (-)
	069	002 (+), 003 (-), 004 (-), 005 (-), 006 (-), 008 (+)
	123	**001** (+), 003 (+), 004 (+), 005 (+)
	153	001 (+), 003 (-), 004 (-), **005** (+), 006 (+), 007 (-), 008 (-), 010 (-)
	236	001 (+), **002** (+), 003 (-), 004 (-), 005 (+), 006 (+), 007 (-), 008 (-), 009 (-), 010 (-), 011 (-), 012 (-), 013 (-), 014 (-), 015 (-), 016 (-), 018 (-)
	359	**001** (+), 002 (+), 003 (-), 004 (-), 005 (+), 006 (-), 010 (+), 013 (-), 014 (-), 016 (-)
	364	**001** (+), 002 (-), 003 (-), 008 (+), 010 (-), 014 (-)
	386	**001** (+), 002 (+), 003 (+), 004 (-), 005 (-), 006 (+), 008 (-)
	393	**001** (+), 002 (+), 003 (-), 005 (-), 010 (-), 015 (-)
	421	**001** (+), 002 (+), 003 (+), 004 (-), 005 (-)
	445	**001** (+), 002 (+), 003 (+)
	460	**001 (**+), 002 (-), 003 (-), 009 (-)
IQGAP2 rs34592828	062	**001** (+), 002 (-), 003 (+), 004 (+), 005 (-), 006 (-), 007 (+),008 (-), 009 (-), 010 (+), 011 (-), 012 (-), 013 (-), 014 (-), 015 (-), 016 (-), 017 (-), 018 (+), 019 (-), 020 (-), 021 (-), 022 (-), 023 (-), 024 (-), 025 (-), 026 (-), 027 (-), 030 (-), 032 (-), 033 (-), 034 (-), 035 (-), 036 (-), 037 (-), 038 (-), 040 (-), 042 (-), 043 (-)
	066	**001** (+), 002 (+), 003 (-), 004 (-), 005 (-), 006 (+), 007 (-), 008 (-), 009 (-), 010 (-), 011 (-), 012 (-), 013 (-), 014 (-), 015 (-), 016 (-), 017 (-),

	018 (-), 019 (-), 020 (-), 021 (-), 022 (-), 023 (-), 024 (-), 025 (-), 026 (+)
238	**001** (+), 002 (+), 003 (+), 004 (-), 005 (-), 006 (+), 007 (-), 008 (-), 009 (-), 010 (-), 011 (-), 012 (-), 014 (-), 015 (-), 016 (-), 017 (-), 018 (-), 019 (-), 020 (-), 022 (-), 023 (-), 024 (-), 025 (+), 027 (-), 028 (-), 030 (+)
251	001 (-), **002** (+), 003 (-), 004 (-), 005 (-), 006 (-), 007 (-), 008 (+), 009 (-), 010 (-), 012 (-), 013 (-), 014 (-), 015 (-), 016 (-), 017 (-), 018 (-), 019 (-), 020 (-), 021 (-), 022 (-), 023 (+), 024 (+)
364	**001 (**+), 002 (-), 003 (-), 005 (-), 007 (-), 008 (+), 010 (-),014 (-)

3.2.1 Cohort samples selection

To be able to associate the studied variants specifically with PCa cases that also present a family history of the disease, PCa individuals with family history of PCa and hereditary breast and ovarian cancer syndrome (HBOC) from the 1527 RALP and 370 PROMIC participants were selected to create a positive cohort. Conversely, those ones without family history of PCa or HBOC were used to generate a negative cohort. The family history-positive (FH+) cohort consisted of 342 participants (294 RALP and 48 PROMIC), whereas the family history-negative cohort had 450 individuals (295 RALP and 155 PROMIC).

3.3 Genotyping

Before the actual genotyping, TaqMan™ SNP Genotyping Assays were validated by genotyping index patients from the 71 high-risk HPCa families with previously known genotypes. The patients used as positive and negative controls are listed in Table 5.

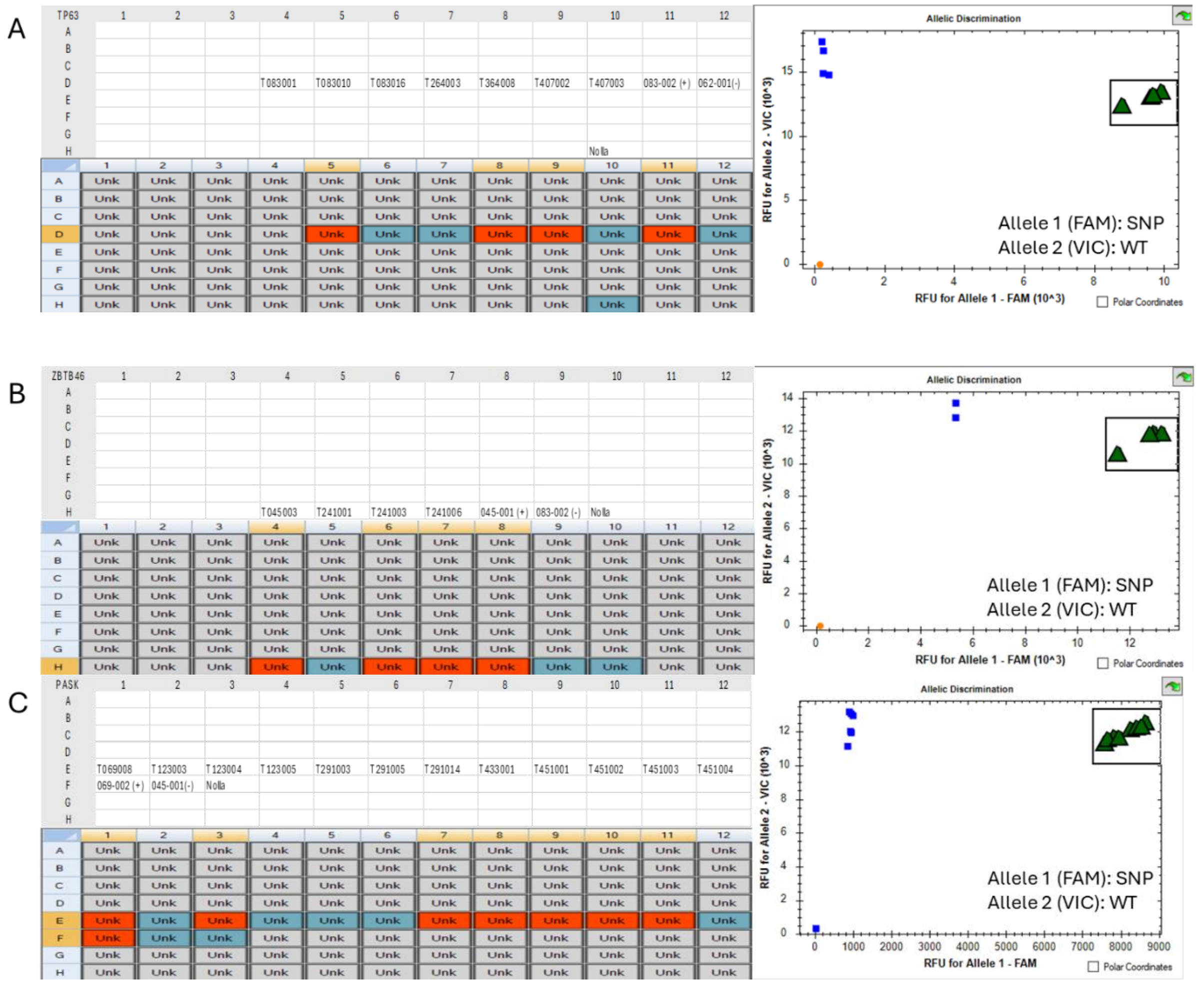
Table 5. High-risk HPCa families' index patients used as positive and negative controls for TaqMan™ SNP Genotyping Assays validation.

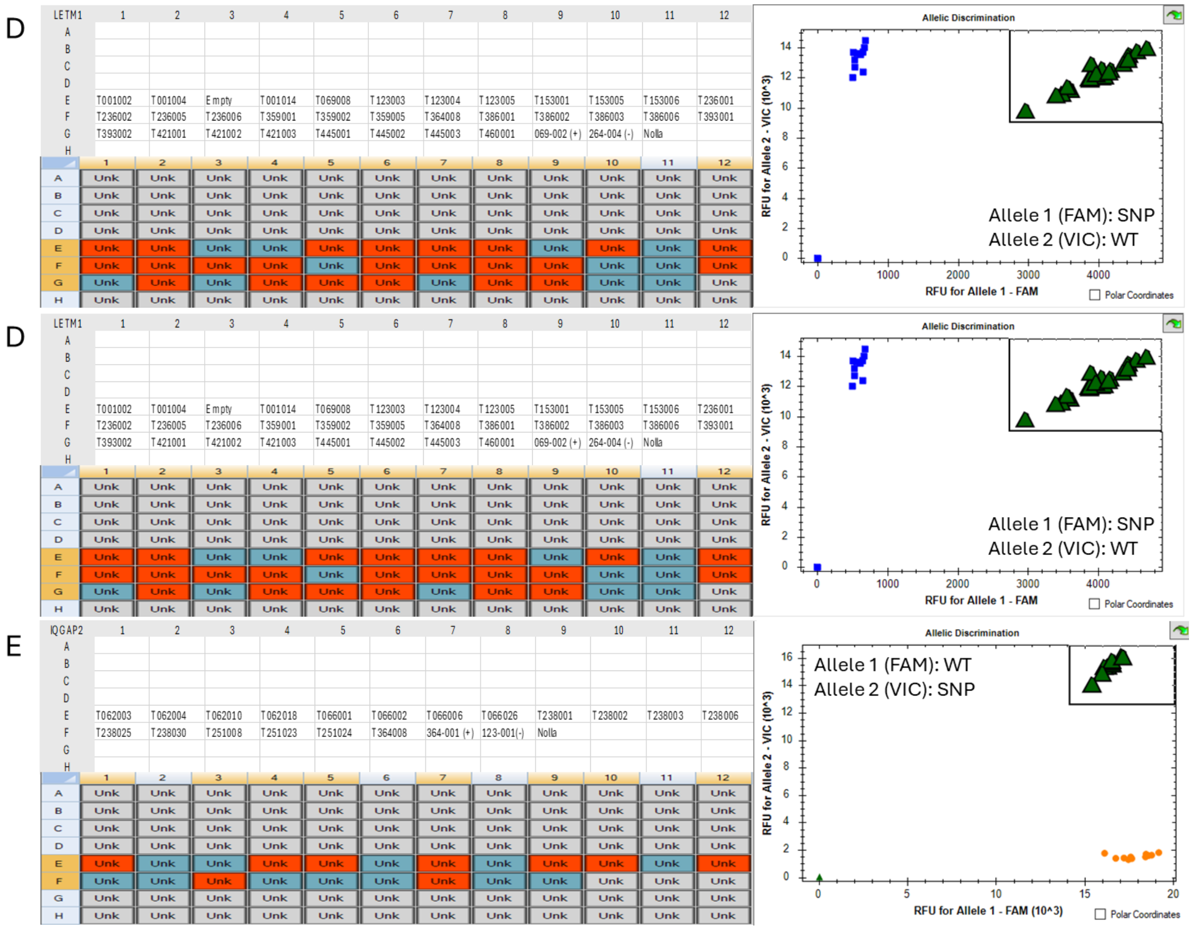
Variant	Positive control	Negative control
TP63 rs190865056	083-002, 264-004, 364-001	062-001, 066-001, 045-001
ZBTB46 rs34785134	045-001, 241-002	083-002, 264-004, 364-001
PASK rs35129131	069-002, 123-001, 291-001	045-001, 241-002, 083-002
LETM1 rs62623389	001-002, 069-002, 123-001	291-001, 045-001, 241-002
IQGAP2 rs34592828	062-001, 066-001, 238-001	001-002, 069-002, 123-001

All TaqMan™ SNP Genotyping Assays correctly genotyped the samples. The allelic discrimination scatter plot showed genotype clusters that matched the known genotypes of all controls (Appendix 3).

3.3.1 High-risk PCa families genotyping

All the families' members whose index patient carried one or more of the studied variants were genotyped for their respective variants using the pertinent TaqMan™ SNP Genotyping Assay. In the allelic discrimination plots, individuals showing a signal only from VIC were homozygous for the reference allele in *TP63* rs190865056, *ZBTB46* rs34785134, *PASK* rs35129131, and *LETM1* rs62623389. Conversely, individuals with a signal only from FAM were homozygous for the reference allele in *IQGAP2* rs34592828 tests. If signals were detected from both VIC and FAM, individuals were heterozygous for the studied variant. For *TP63* rs190865056, *ZBTB46* rs34785134, *PASK* rs35129131, and *LETM1* rs62623389 genotyping, a signal only from FAM indicated a homozygous genotype for the studied variant. In contrast, a signal only from VIC indicated a homozygous genotype for the studied variant in *IQGAP2* rs34592828. First, relatives diagnosed with PCa, excluding the index patients, were genotyped (Figure 3). Next, all the relatives without PCa were genotyped (Figure 4). All the PCa and non-affected individuals were genotyped successfully, and their genotypes are displayed in Table 6 and 7.



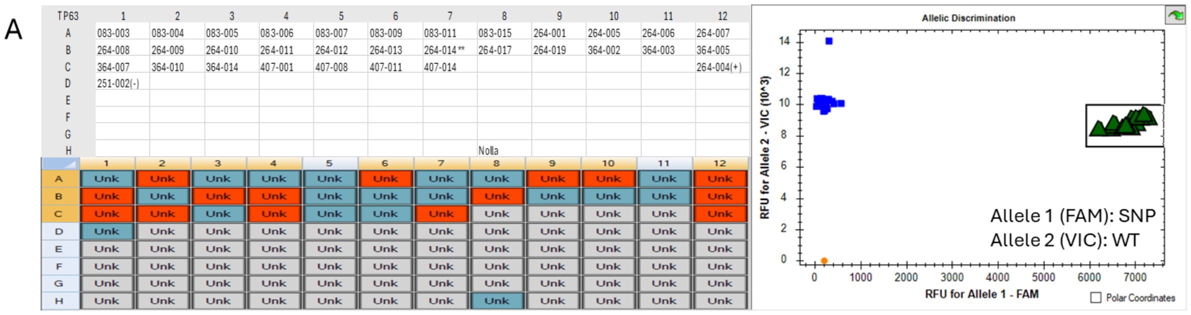


LETM1	1	2	3	4	5	6	7	8	9	10	11	12
A												
B												
C												
D												
E	T001002	T001004	Empty	T001014	T069008	T123003	T123004	T123005	T153001	T153005	T153006	T236001
F	T236002	T236005	T236006	T359001	T359002	T359005	T364008	T386001	T386002	T386003	T386006	T393001
G	T393002	T421001	T421002	T421003	T445001	T445002	T445003	T460001	069-002 (+)	264-004 (-)	Nolla	
H												

LETM1	1	2	3	4	5	6	7	8	9	10	11	12
A												
B												
C												
D												
E	T001002	T001004	Empty	T001014	T069008	T123003	T123004	T123005	T153001	T153005	T153006	T236001
F	T236002	T236005	T236006	T359001	T359002	T359005	T364008	T386001	T386002	T386003	T386006	T393001
G	T393002	T421001	T421002	T421003	T445001	T445002	T445003	T460001	069-002 (+)	264-004 (-)	Nolla	
H												

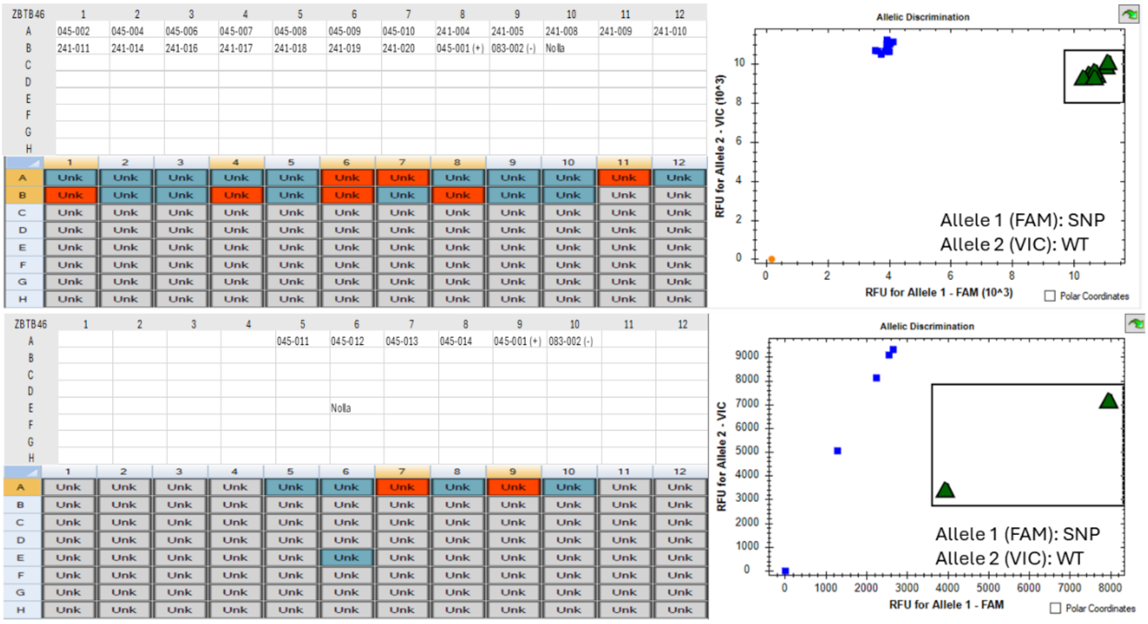
IQGAP2	1	2	3	4	5	6	7	8	9	10	11	12
A												
B												
C												
D												
E	T062003	T062004	T062010	T062018	T066001	T066002	T066006	T066026	T238001	T238002	T238003	T238006
F	T238025	T238030	T251008	T251023	T251024	T364008	364-001 (+)	123-001(-)	Nolla			
G												
H												

Figure 3. Plate maps and allelic discrimination scatter plots of the high-risk families' prostate cancer (PCa) individuals using TaqMan™ SNP Genotyping Assays. Individuals were genotyped for *TP63* rs190865056 (A), *ZBTB46* rs34785134 (B), *PASK* rs35129131 (C), *LETM1* rs62623389 (D), and *IQGAP2* rs34592828 (E). The orange boxes indicate the samples that are heterozygous for the studied variant in the plate map. The black rectangles in the allelic discrimination plot indicate the samples that are heterozygous for the tested variant. Nolla no-templated control, SNP variant allele, WT reference allele.



TP63	1	2	3	4	5	6	7	8	9	10	11	12
A	083-003	083-004	083-005	083-006	083-007	083-009	083-011	083-015	264-001	264-005	264-006	264-007
B	264-008	264-009	264-010	264-011	264-012	264-013	264-014 **	264-017	264-019	364-002	364-003	364-005
C	364-007	364-010	364-014	407-001	407-008	407-011	407-014					264-004(+)
D	251-002(-)											
E												
F												
G												
H								Nolla				

B



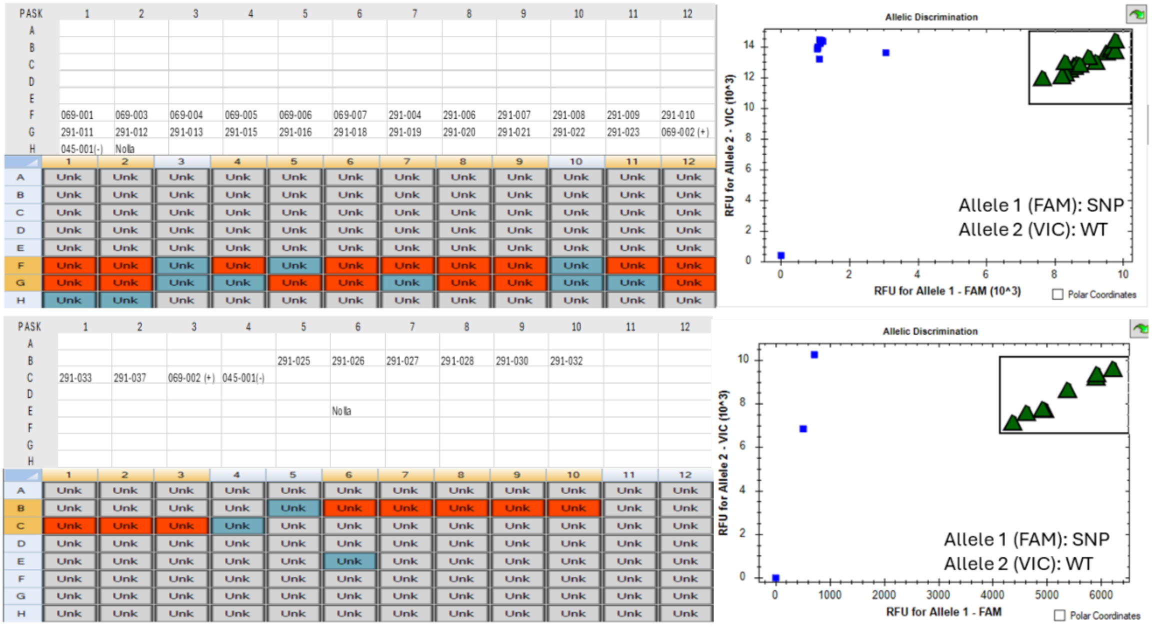
ZBTB46	1	2	3	4	5	6	7	8	9	10	11	12
A	045-002	045-004	045-006	045-007	045-008	045-009	045-010	241-004	241-005	241-008	241-009	241-010
B	241-011	241-014	241-016	241-017	241-018	241-019	241-020	045-001 (+)	083-002 (-)	Nolla		
C												
D												
E												
F												
G												
H												

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk

ZBTB46	1	2	3	4	5	6	7	8	9	10	11	12
A					045-011	045-012	045-013	045-014	045-001 (+)	083-002 (-)		
B												
C												
D												
E						Nolla						
F												
G												
H												

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk

C

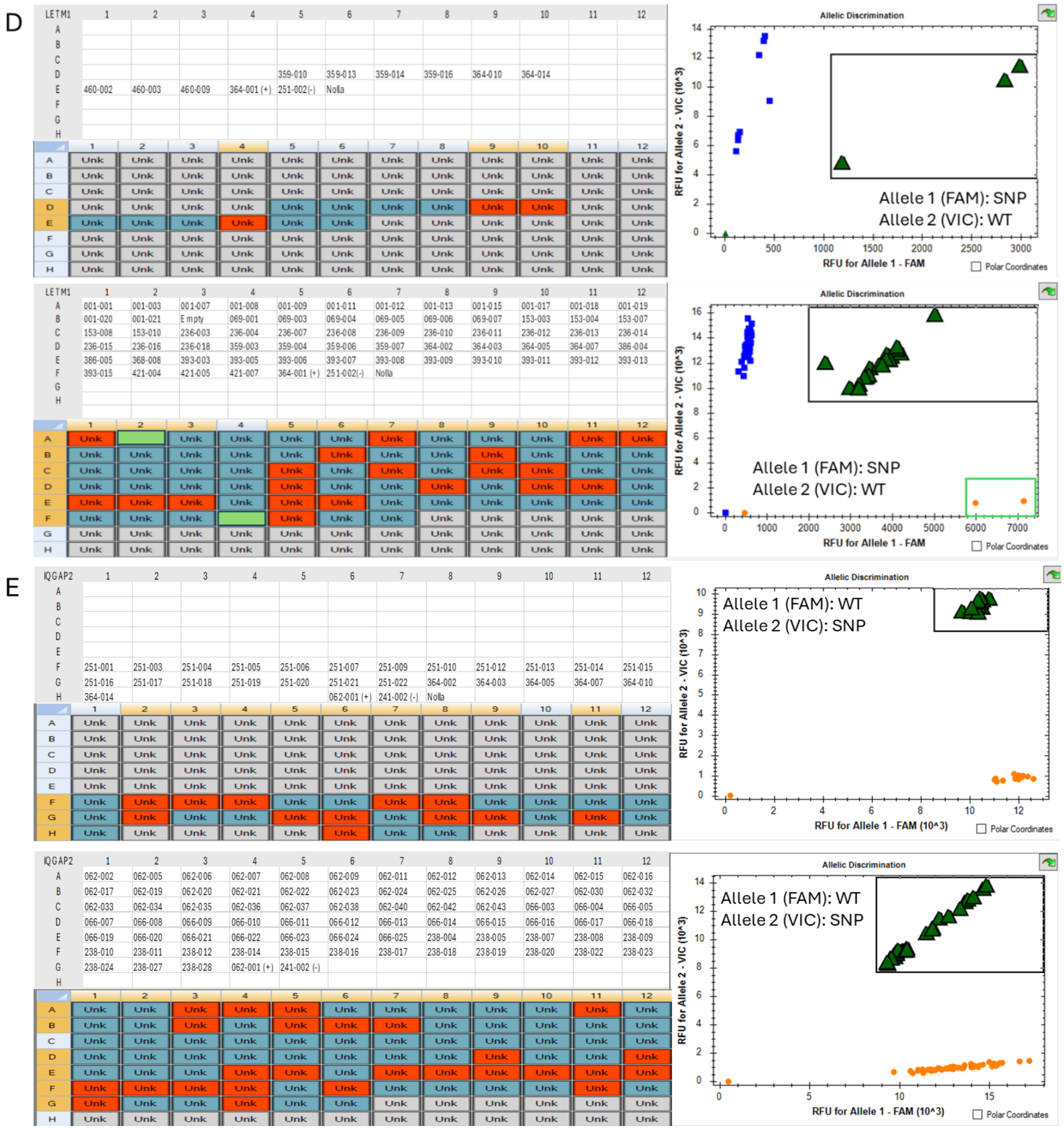


PASK	1	2	3	4	5	6	7	8	9	10	11	12
A												
B												
C												
D												
E												
F	069-001	069-003	069-004	069-005	069-006	069-007	291-004	291-006	291-007	291-008	291-009	291-010
G	291-011	291-012	291-013	291-015	291-016	291-018	291-019	291-020	291-021	291-022	291-023	069-002 (+)
H	045-001(-)	Nolla										

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk

PASK	1	2	3	4	5	6	7	8	9	10	11	12
A												
B					291-025	291-026	291-027	291-028	291-030	291-032		
C	291-033	291-037	069-002 (+)	045-001(-)								
D												
E						Nolla						
F												
G												
H												

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk



LETM1	1	2	3	4	5	6	7	8	9	10	11	12
A												
B												
C												
D					359-010	359-013	359-014	359-016	364-010	364-014		
E	460-002	460-003	460-009	364-001 (+)	251-002(-)	Nolla						
F												
G												
H												

LETM1	1	2	3	4	5	6	7	8	9	10	11	12
A	001-001	001-003	001-007	001-008	001-009	001-011	001-012	001-013	001-015	001-017	001-018	001-019
B	001-020	001-021	Empty	069-001	069-003	069-004	069-005	069-006	069-007	153-003	153-004	153-007
C	153-008	153-010	236-003	236-004	236-007	236-008	236-009	236-010	236-011	236-012	236-013	236-014
D	236-015	236-016	236-018	359-003	359-004	359-006	359-007	364-002	364-003	364-005	364-007	386-004
E	386-005	368-008	393-003	393-005	393-006	393-007	393-008	393-009	393-010	393-011	393-012	393-013
F	393-015	421-004	421-005	421-007	364-001 (+)	251-002(-)	Nolla					
G												
H												

IQGAP2	1	2	3	4	5	6	7	8	9	10	11	12
A												
B												
C												
D												
E												
F	251-001	251-003	251-004	251-005	251-006	251-007	251-009	251-010	251-012	251-013	251-014	251-015
G	251-016	251-017	251-018	251-019	251-020	251-021	251-022	364-002	364-003	364-005	364-007	364-010
H	364-014					062-001 (+)	241-002 (-)	Nolla				

IQGAP2	1	2	3	4	5	6	7	8	9	10	11	12
A	062-002	062-005	062-006	062-007	062-008	062-009	062-011	062-012	062-013	062-014	062-015	062-016
B	062-017	062-019	062-020	062-021	062-022	062-023	062-024	062-025	062-026	062-027	062-030	062-032
C	062-033	062-034	062-035	062-036	062-037	062-038	062-040	062-042	062-043	066-003	066-004	066-005
D	066-007	066-008	066-009	066-010	066-011	066-012	066-013	066-014	066-015	066-016	066-017	066-018
E	066-019	066-020	066-021	066-022	066-023	066-024	066-025	238-004	238-005	238-007	238-008	238-009
F	238-010	238-011	238-012	238-014	238-015	238-016	238-017	238-018	238-019	238-020	238-022	238-023
G	238-024	238-027	238-028	062-001 (+)	241-002 (-)							
H												

Figure 4. Plate maps and allelic discrimination scatter plots of the high-risk families' individuals without PCa using TaqMan™ SNP Genotyping Assays. Individuals were genotyped for *TP63* rs190865056 (A), *ZBTB46* rs34785134 (B), *PASK* rs35129131 (C), *LETM1* rs62623389 (D), and *IQGAP2* rs34592828 (E). In the plate map, orange boxes indicate heterozygous individuals, while green boxes represent those homozygous for the studied variant. In the allelic discrimination plot, the black rectangle highlights the heterozygous samples, and the green rectangle indicates the homozygous ones for the tested variant. Nolla no-template control, SNP variant allele, WT reference allele.

Table 6. Genotypes of the studied variants in the high-risk families' participants with prostate cancer (PCa). 0/0 homozygous for the reference allele, 0/1 heterozygous for the studied variant.

Variant	**Family**	**Genotype 0/0**	**Genotype 0/1**
TP63 rs190865056	083	016	002, 010
	264	003, 014, 019	004
	364	-	001, 008
	407	003	002
ZBTB46 rs34785134	045	014	001, 003
	241	-	002, 003, 006
PASK rs35129131	069	-	002, 008
	123	003	001, 004
	291	003, 005	001, 014
	433	-	001
	451	004	001, 002, 003
LETM1 rs62623389	001	014	002, 004
	069	-	002, 008
	123	-	001, 003, 004, 005
	153	001, 006	005
	236	-	001, 002, 005, 006
	359	002, 010	001, 005
	364	-	001, 008
	386	003, 006	001, 002
	393	002	001
	421	002	001, 003
	445	003	001, 002
	460	-	001
IQGAP2 rs34592828	062	004, 010, 018	001, 003, 007
	066	002, 026	001, 006
	238	003, 030	001, 002, 006
	251	023, 024	002, 008
	364	008	001

Table 7. Genotypes of the studied variants in the high-risk families' participants without prostate cancer (PCa). 0/0 homozygous for the reference allele, 0/1 heterozygous for the studied variant.

Variant	**Family**	**Genotype 0/0**	**Genotype 0/1**
TP63 rs190865056	083	003, 005,006, 007, 011, 015	004, 009
	264	006, 009, 012, 013	001, 005, 007, 008, 010, 011, 017
	364	002, 003, 014	010
	407	001, 008, 011	014
ZBTB46 rs34785134	045	002, 004, 006, 007, 008, 011, 012	010, 013
	241	001, 004, 005, 010, 014, 016, 018, 020	009, 011, 017, 019
PASK rs35129131	069	004, 006	003, 005
	123	-	-
	291	013, 015, 019, 022, 023, 025	004, 012, 016, 018, 020, 021, 026, 027, 030, 032, 033, 037
	433	-	-
	451	-	-
LETM1 rs62623389	001	008, 008, 011, 013, 017, 020, 021	001, 003*, 018, 019
	069	003, 005, 006	004
	123	-	-
	153	003, 004, 007, 008, 010	-
	236	003, 004, 008, 010, 013, 014	007, 009, 011, 012
	359	003, 006, 013, 014, 016	004
	364	003	002, 010, 014
	386	004	005
	393	005, 010, 015	003
	421	004, 005	-
	445	-	-
	460	002, 003, 009	-
IQGAP2 rs34592828	062	002, 005, 009, 011, 012, 013, 014, 016, 017, 019, 021, 025, 026, 027, 030, 032, 033, 034, 035, 036, 037, 038, 040, 042, 043	006, 008, 015, 020, 022, 023, 024
	066	003, 004, 005, 007, 008, 009, 010, 011, 012, 013,	015, 018, 022, 023, 025

		014, 016, 017, 019, 020, 021, 024	
	238	015, 017, 018, 019, 020, 023, 027, 028	004, 005, 007, 008, 009, 010, 011, 012, 014, 016, 022, 024
		001, 006, 007, 016, 022	003, 004, 005, 009, 010
	251	010, 014	002, 003
	364		

* Homozygous for the studied variant (1/1)

3.3.2 RALP patients genotyping

RALP patients with a family history of PCa and HBOC (FH+) were genotyped for all the variants of the final list using the pertinent TaqMan™ SNP Genotyping Assays (Appendix 4). Additionally, RALP patients without a family history of PCa or HBOC (FH-) were genotyped only for the *PASK* rs35129131 variant (Appendix 5). This was done because the *PASK* rs35129131 variant's allele frequency showed a tendency to be higher in the FH+ cohort compared to the normal Finnish population (FinnGen), and PCa cases from C3_PROSTATE_EXALLC endpoint from FinnGen (section 3.5.1). In cases where no signal was obtained in the RT-PCR, new dilutions were prepared from the original DNA, and the samples were run again, successfully obtaining the genotype. Seven and eight RALP FH+ patients were observed to be heterozygous for *TP63* rs190865056 and *ZBTB46* rs34785134 variants respectively. 16 RALP FH+ patients were heterozygous for *PASK* rs35129131, whereas one patient was homozygous. Also, there was one RALP FH+ patient homozygous for *LETM1* rs62623389 and 27 heterozygous. 24 RALP FH+ patients were heterozygous for *IQGAP2* rs34592828. Interestingly, three RALP FH+ patients carried both *PASK* and *IQGAP2* variants, and two patients carried both *ZBTB46* and *IQGAP2* variants. Moreover, each of the next combinations were identified in a single distinct patient: *PASK* and *TP63* variants, *PASK* and *LETM1* variants, *ZBTB46* and *LETM1* variants, and *TP63* and *LETM1* variants. RALP FH+ patients' genotypes for *TP63* rs190865056, *ZBTB46* rs34785134, *PASK* rs35129131, *LETM1* rs62623389, and *IQGAP2* rs34592828 are shown in Appendix 6. On the other hand, six RALP FH- patients were found to be heterozygous for *PASK* rs35129131. No homozygous cases for the *PASK* variant were found in the FH- cohort. RALP FH- patients' genotype for *PASK* rs35129131 are displayed in Appendix 7.

3.4 Family-based study

3.4.1 Descriptive and model-based familial analysis

To find an association between the five different variants and PCa within families, the carrier and allele frequencies between PCa men (PCa+) and those without PCa (PCa-) were compared for each family separately using Fisher's exact test. When analyzing carrier frequencies across the different families, all the PCa men were found to carry the *TP63* rs190865056 variant in the family 364 (2/2), the *ZBTB46* rs34785134 variant in the family 241 (3/3), the *PASK* rs35129131 variant in the families 069 (2/2) and 433 (1/1), and the *LETM1* rs62623389 variant in the families 069 (2/2), 123 (4/4), 236 (4/4), 364 (2/2) and 460 (1/1). Interestingly, half of the PCa individuals carried the *IQGAP2* rs34592828 variant in all the analyzed families. When comparing carrier frequencies between affected and unaffected individuals, no statistically significant differences were observed (Table 8). In addition, allele frequencies were compared to account for cases where individuals were homozygous for the variant. Similarly, no statistically significant differences were observed between family members with and without PCa for any variant in any family (Table 9).

Table 8. The distribution of individuals within each family based on their PCa status and the presence or absence of the variant (carrier-based). The carrier frequencies between PCa relatives (PCa+) and unaffected relatives (PCa-) were compared independently for each family using Fisher's exact test. CI confidence interval, OR odds ratio, Var. variant, WT reference allele.

Variant	**Family**	**PCa+ Var.**	**PCa+ WT**	**PCa- Var.**	**PCa- WT**	**P-value**	**OR (95 % CI)**
TP63	083	2	2	0	1	1	Inf (0.02–Inf)
rs190865056	264	1	3	3	0	0.14	0 (0.00–2.70)
	364	2	0	0	2	0.33	Inf (0.22–Inf)
	407	1	1	1	2	1	1.73 (0.01–233.8)
ZBTB46	045	2	1	0	3	0.4	Inf (0.20–Inf)
rs34785134	241	3	0	1	3	0.14	Inf (0.37–Inf)
PASK	069	2	0	0	0	1	0 (0–Inf)
rs35129131	123	2	2	0	0	1	0 (0–Inf)
	291	2	2	4	2	1	0.54 (0.02–13.01)
	433	1	0	0	0	1	0 (0–Inf)
	451	3	1	0	0	1	0 (0–Inf)
LETM1	001	2	1	3	0	1	0 (0.00–39.00)
rs62623389	069	2	0	0	0	1	0 (0–Inf)
	123	4	0	0	0	1	0 (0–Inf)

	153	1	2	0	2	1	Inf (0.02–Inf)
	236	4	0	3	3	0.2	Inf (0.29–Inf)
	359	2	2	0	1	1	Inf (0.02–Inf)
	364	2	0	2	1	1	Inf (0.02–Inf)
	386	2	2	1	1	1	1 (8.5e-3–1.2e+2)
	393	1	1	0	1	1	Inf (0.02–Inf)
	421	2	1	0	2	0.4	Inf (0.12–Inf)
	445	2	1	0	0	1	0 (0–Inf)
	460	1	0	0	1	1	Inf (0.03–Inf)
IQGAP2	062	3	3	4	11	0.31	2.61 (0.24–29.39)
rs34592828	066	2	2	3	7	0.58	2.19 (0.11–45.42)
	238	3	3	9	3	0.34	0.35 (0.03–4.17)
	251	2	2	5	3	1	0.63 (0.03–13.19)
	364	1	1	2	1	1	0.58 (0.004–78.09)

Table 9. The distribution of individuals within each family based on their PCa status and the presence or absence of the variant (allele-based). The allele frequencies between PCa relatives (PCa+) and unaffected relatives (PCa-) were compared independently for each family using Fisher's exact test. CI confidence interval, OR odds ratio, Var. variant, WT reference allele.

Variant	**Family**	**PCa+ Var**	**PCa+ WT**	**PCa+ Var %**	**PCa- Var**	**PCa- WT**	**PCa- Var %**	**Tot. Var**	**Tot. WT**	**Tot Var %**	**P-value**	**OR (95 % CI)**
TP63	083	2	6	25	0	2	0	0	8	0	1	Inf (0.04–Inf)
rs190865056	264	1	7	12.5	3	3	0.5	4	10	28.5	0.24	0.17 (0.002–3.06)
	364	2	2	50	0	4	0	2	6	25	0.43	Inf (0.20–Inf)
	407	1	3	25	1	5	16.7	2	8	20	1	1.58 (0.02–156.4)
ZBTB46	045	2	4	33.3	0	6	0	2	10	16.7	0.45	Inf (0.19–Inf)
rs34785134	241	3	3	50	1	7	12.5	4	10	28.6	0.24	5.99 (0.33–417.2)
PASK	069	2	2	50	0	0	0	2	2	50	1	0 (0–Inf)
rs35129131	123	2	6	25	0	0	0	2	6	25	1	0 (0–Inf)
	291	2	6	25	4	8	33.3	6	14	30	1	0.68 (0.05–6.84)
	433	1	1	50	0	0	0	1	1	50	1	0 (0–Inf)
	451	3	5	37.5	0	0	0	3	5	37.5	1	0 (0–Inf)

LETM1 rs62623389	001	2	4	33.3	4	2	66.6	6	6	50	0.56	0.28 (0.01–4.30)
	069	2	2	50	0	0	0	2	2	50	1	0 (0–Inf)
	123	4	4	50	0	0	0	4	4	50	1	0 (0–Inf)
	153	1	5	16.6	0	4	0	1	9	10	1	Inf (0.02–-Inf)
	236	4	4	50	3	9	25	7	13	35	0.36	2.83 (0.31–30.18)
	359	2	6	25	0	2	0	2	8	20	1	Inf (0.04–Inf)
	364	2	2	50	2	4	33.3	4	6	40	1	1.86 (0.08–48.96)
	386	2	6	25	1	3	25	3	9	25	1	1 (0.04–78.38)
	393	1	3	25	0	2	0	1	5	16.7	1	Inf (0.01–Inf)
	421	2	4	33.3	0	4	0	2	8	20	0.47	Inf (0.12–Inf)
	445	2	4	33.3	0	0	0	2	4	33.3	1	0 (0–Inf)
	460	1	1	50	0	2	0	1	3	25	1	Inf (0.03–Inf)
IQGAP2 rs34592828	062	3	9	20	4	26	13.3	7	35	16.7	0.39	2.12 (0.26–15.44)
	066	2	6	25	3	17	15	5	23	17.9	0.61	1.84 (0.12–20.72)
	238	3	9	20	9	15	37.5	12	24	33.3	0.71	0.56 (0.08–3.13)
	251	2	6	25	5	11	31.3	7	17	29.2	1	0.74 (0.05–6.55)
	364	1	3	25	2	4	33.3	3	7	30	1	0.69 (0.01–20.30)

Pooled contingency tables were also created by summing all the PCa+ and PCa- men from different families genotyped for the same variant. This approach allowed the assessment of associations between the specific variants and PCa across families by analyzing all the families genotyped for the same variant collectively. Fisher’s exact test was used to compare both carrier and allele frequencies between PCa+ and PCa- individuals. In the carrier frequency comparison, *ZBTB46* rs34785134 (P=0.029; OR=19.7; CI95% 1–1617.3) was found significantly more often in PCa individuals compared to those without it. However, the wide confidence interval might reflect a low precision of the estimate due to a small sample size. In addition, *LETM1* rs62623389 (P=0.049; OR=3.25; CI95% 0.93–12.05) was observed to be borderline significantly more often in PCa individuals. Nonetheless, the CI barely crosses 1, indicating unreliability, probably again due to a small sample size (Table 10). On the other hand, comparison of allele frequencies didn't show any significant difference between the two groups (Table 11).

Table 10. Carrier frequency comparison in the individuals pooled from all the families analyzed for the same variant based on their PCa status. The values between brackets are the number of carriers per total amount of the group individuals. The carrier frequencies between PCa relatives (PCa+) and unaffected relatives (PCa-) were compared for each variant using Fisher's exact test. CI confidence interval, OR odds ratio, Var. variant allele, WT reference allele.

Variant	**PCa+ Var.**	**PCa+ WT**	**PCa- Var.**	**PCa- WT**	**P-value**	**OR (95 % CI)**
TP63 rs190865056	0.5 (6/12)	0.5 (6/12)	0.44 (4/9)	0.56 (5/9)	1	1.23 (0.16–9.89)
ZBTB46 rs34785134	0.83 (5/6)	0.17 (1/6)	0.14 (1/7)	0.86 (6/7)	0.029	19.7 (1–1617.3)
PASK rs35129131	0.67 (10/15)	0.33 (5/15)	0.67 (4/6)	0.33 (2/6)	1	1 (0.07–10.32)
LETM1 rs62623389	0.71 (25/35)	0.29 (10/35)	0.43 (9/21)	0.57 (12/21)	0.049	3.25 (0.93–12.05)
IQGAP2 rs34592828	0.5 (11/22)	0.5 (11/22)	0.48 (23/48)	0.52 (25/48)	1	1.09 (0.35–3.37)

Table 11. Allele frequency comparison in the individuals pooled from all the families analyzed for the same variant based on their PCa status. The values between brackets are the number of alleles per total amount of alleles in the individuals of the group. The allele frequencies between PCa relatives (PCa+) and unaffected relatives (PCa-) were compared for each variant using Fisher's exact test. CI confidence interval, OR odds ratio, Var. variant allele, WT reference allele

Variant	**PCa+ Var.**	**PCa+ WT**	**PCa- Var.**	**PCa- WT**	**P-value**	**OR (95 % CI)**
TP63 rs190865056	0.25 (6/24)	0.75 (18/24)	0.22 (4/18)	0.78 (14/18)	1	1.16 (0.22–6.75)
ZBTB46 rs34785134	0.42 (5/12)	0.58 (7/12)	0.07 (1/14)	0.93 (13/14)	0.065	8.50 (0.74–470.6)
PASK rs35129131	0.33 (10/30)	0.67 (10/30)	0.33 (4/12)	0.67 (8/12)	0.47	1.96 (0.37–11.98)
LETM1 rs62623389	0.36 (25/70)	0.64 (45/70)	0.24 (10/42)	0.76 (32/42)	0.21	1.77 (0.70–4.73)
IQGAP2 rs34592828	0.25 (11/44)	0.75 (33/44)	0.24 (23/95)	0.76 (73/95)	1	1.06 (0.41–2.58)

Pooling individuals across families assumes independence between individuals across the families, ignores relatedness, and doesn't consider family-specific effects. To assess the association between the variant and PCa accounting for within-family correlations, a binomial generalized linear mixed model (GLMM) was used, incorporating family as a random effect to correct for family structure. The fixed effect for variant *TP63* rs190865056 was not statistically significant (β=0.223, OR=1.25, SE=0.885, P=0.801), suggesting no evidence of association between variant carriage and PCa status. The least-squares means showed a slightly higher predicted probability of PCa for individuals with the variant (60 %) compared to those without it (54.5 %). Moreover, the random effect for family had zero variance, indicating no between-family variation. A likelihood ratio test (Anova) comparing the full model to a reduced model without the random effect indicated that the inclusion of the family didn't improve the model fit (P=0.80) (Table 12).

Table 12. Fixed effects and random effects table for the generalized linear mixed model (GLMM) for *TP63* rs190865056. The odds ratio for PCa in carriers of the variant was calculated by exponentiating the estimate of the fixed effect (variant) (A). Predicted probabilities for reference (0) and variant allele (1) by least-squares means. These probabilities are the estimated values of the outcome (PCa) for each allele group. The confidence intervals show the range where the true probabilities are potentially being. The p-values indicate whether the predicted probabilities differ from 50 % (B). The random effect significance was tested by comparing the full model to a reduced model without the random effect using a likelihood ratio test (Anova) (C). CI confidence interval, Dev. deviance, Df degrees of freedom, OR odds ratio, Res. residual, SE standard error, SD standard deviation, Z parameter estimated. Significance: <0.001 (***); <0.01 (**); <0.05(*).

A)

Fixed Effects	**Estimate (β)**	**SE**	**Z**	**P-value**
Intercept	0.182	0.606	0.301	0.763
Variant *TP63*	0.223 (OR=1.25)	0.885	0.252	0.801
Random Effects	**Variance**	**SD**		
Family	0	0		

B)

Fixed Effects	**Estimated % PCa**	**SE**	**CI 95%**	**Z**	**P-value**
0	54.5	0.150	0.27–0.80	0.301	0.763
1	60	0.155	0.30–0.84	0.628	0.530

C)

	Df	**Dev.**	**Resid. Df**	**Resid. Dev.**	**P-value**
NULL			20	28.68	
Variant	1	0.064	19	28.62	0.80

The fixed effect for variant *ZBTB46* rs34785134 was statistically significant (β=3.401, OR=29.99, SE=1.538, P=0.027), suggesting an association between variant carriage and PCa status. Carriers of the variant had about 30 times higher odds of having PCa compared to non-carriers. The predicted probability of having PCa increased from 14.3 % for individuals without the variant to 83.3 % for those carrying the variant. Also, the random effect for family had zero variance, meaning a minimal between-family variation. The full model and reduced model comparison confirmed that family as the random effect improved model fit (P=0.009), and thus, considering within-family correlation was needed in the analysis (Table 13).

Table 13. Fixed effects and random effects table for the generalized linear mixed model (GLMM) for *ZBTB46* rs34785134. The odds ratio for PCa in carriers of the variant was calculated by exponentiating the estimate of the fixed effect (variant) (A). Predicted probabilities for reference (0) and variant allele (1) by least-squares means. These probabilities are the estimated values of the outcome (PCa) for each allele group. The confidence intervals show the range where the true probabilities are potentially being. The p-values indicate whether the predicted probabilities differ from 50 % (B). The random effect significance was tested by comparing the full model to a reduced model without the random effect using a likelihood ratio test (Anova) (C). CI confidence interval, Dev. deviance, Df degrees of freedom, OR odds ratio, Res. residual, SE standard error, SD standard deviation, Z parameter estimated. Significance: <0.001 (***); <0.01 (**); <0.05(*).

A)

Fixed Effects	**Estimate (β)**	**SE**	**Z**	**P-value**
Intercept	-1.792	1.080	-1.659	0.0971
Variant *ZBTB46*	3.401 (OR=29.99)	1.538	2.211	0.0270*
Random Effects	**Variance**	**SD**		
Family	0	0		

B)

Fixed Effects	**Estimated % PCa**	**SE**	**CI 95%**	**Z**	**P-value**
0	14.3	0.132	0.02–0.58	0.581	0.097
1	83.3	0.152	0.37–0.98	0.977	0.142

C)

	Df	**Dev.**	**Resid. Df**	**Resid. Dev.**	**P-value**
NULL			12	17.95	
Variant	1	6.80	11	11.15	0.009**

In the case of the *PASK* rs35129131 variant, the fixed effect was not statistically significant (β=-0.675, OD=0.78, SE=1.365, P=0.621), indicating no evidence of association between variant carriage and PCa status. However, the least-squares means showed high predicted probabilities of PCa for both allele groups (99.9 %). These results may reflect an imbalance in the data, where most individuals had PCa and there were not enough unaffected individuals to provide contrast. Furthermore, the random effect for family had a high variance (39.82) suggesting that differences between families might explain variation in PCa status. However, the inclusion of family as random effect didn't improve the model fit for this variant (P=1) (Table 14).

Table 14. Fixed effects and random effects table for the generalized linear mixed model (GLMM) for *PASK* rs35129131. The odds ratio for PCa in carriers of the variant was calculated by exponentiating the estimate of the fixed effect (variant) (A). Predicted probabilities for reference (0) and variant allele (1) by least-squares means. These probabilities are the estimated values of the outcome (PCa) for each allele group. The confidence intervals show the range where the true probabilities are potentially being. The p-values indicate whether the predicted probabilities differ from 50 % (B). The random effect significance was tested by comparing the full model to a reduced model without the random effect using a likelihood ratio test (Anova) (C). CI confidence interval, Dev. deviance, Df degrees of freedom, OR odds ratio, Res. residual, SE standard error, SD standard deviation, Z parameter estimated. Significance: <0.001 (***); <0.01 (**); <0.05(*).

A)

Fixed Effects	**Estimate (β)**	**SE**	**Z**	**P-value**
Intercept	7.321	5.343	1.370	0.171
Variant *PASK*	-0.675 (OR=0.78)	1.365	-0.495	0.621
Random Effects	**Variance**	**SD**		
Family	39.82	6.31		

B)

Fixed Effects	**Estimated % PCa**	**SE**	**CI 95%**	**Z**	**P-value**
0	99.9	0.003	0.04–1	1.370	0.171
1	99.9	0.007	0.03–1	1.303	0.193

C)

	Df	**Dev.**	**Resid. Df**	**Resid. Dev.**	**P-value**
NULL			20	25.127	
Variant	1	0	19	25.127	1

The *LETM1* rs62623389 variant's fixed effect was statistically significant (β=1.301, OR=3.67, SE=0.638, P=0.038), indicating an association between variant carriage and PCa status. Carriers of the variant had 3.67 times higher chances of having PCa compared to non-carriers. The predicted probability of having PCa increased from 43.4 % for individuals without the variant to 74.2 % for those with the variant. Moreover, the random effect for family had a close to zero variance, meaning a minimal between-family variation. The full model and reduced model comparison confirmed that family as the random effect improved model fit (P=0.022), and therefore, considering within-family correlation was necessary in the analysis (Table 15).

Table 15. Fixed effects and random effects table for the generalized linear mixed model (GLMM) for *LETM1* rs62623389. The odds ratio for PCa in carriers of the variant was calculated by exponentiating the estimate of the fixed effect (variant) (A). Predicted probabilities for reference (0) and variant allele (1) by least-squares means. These probabilities are the estimated values of the outcome (PCa) for each allele group. The confidence intervals show the range where the true probabilities are potentially being. The p-values indicate whether the predicted probabilities differ from 50 % (B). The random effect significance was tested by comparing the full model to a reduced model without the random effect using a likelihood ratio test (Anova) (C). CI confidence interval, Dev. deviance, Df degrees of freedom, OR odds ratio, Res. residual, SE standard error, SD standard deviation, Z parameter estimated. Significance: <0.001 (***); <0.01 (**); <0.05(*).

A)

Fixed Effects	**Estimate (β)**	**SE**	**Z**	**P-value**
Intercept	-0.264	0.431	-0.613	0.540
Variant *LETM1*	1.301 (OR=3.67)	0.638	2.072	0.038*
Random Effects	**Variance**	**SD**		
Family	0.05	0.22		

B)

Fixed Effects	**Estimated % PCa**	**SE**	**CI 95%**	**Z**	**P-value**
0	43.4	0.106	0.25–0.64	-0.613	0.540
1	74.2	0.090	0.53–0.88	0.879	0.025

C)

	Df	**Dev.**	**Resid. Df**	**Resid. Dev.**	**P-value**
NULL			56	76.03	
Variant	1	5.24	55	70.79	0.022*

The fixed effect for variant *IQGAP2* rs34592828 was not statistically significant (β=0.083, OR=1.08, SE=0.515, P=0.871), suggesting no evidence of association between variant carriage and PCa status. The least-squares means showed a higher predicted probability of PCa for individuals with the variant (26.2 %) compared to those without it (16.2 %). Moreover, the random effect for family had a variance of zero, indicating a minimal variation between families. In addition, the likelihood ratio test between the full and reduced model showed that the inclusion of family didn’t improve the model fit (P=0.871) (Table 16).

Table 16. Fixed effects and random effects table for the generalized linear mixed model (GLMM) for *IQGAP2* rs34592828. The odds ratio for PCa in carriers of the variant was calculated by exponentiating the estimate of the fixed effect (variant) (A). Predicted probabilities for reference (0) and variant allele (1) by least-squares means. These probabilities are the estimated values of the outcome (PCa) for each allele group. The confidence intervals show the range where the true probabilities are potentially being. The p-values indicate whether the predicted probabilities differ from 50 % (B). The random effect significance was tested by comparing the full model to a reduced model without the random effect using a likelihood ratio test (Anova). CI confidence interval, Dev. deviance, Df degrees of freedom, OR odds ratio, Res. residual, SE standard error, SD standard deviation, Z parameter estimated. Significance: <0.001 (***); <0.01 (**); <0.05(*).

A)

Fixed Effects	**Estimate (B)**	**SE**	**Z**	**P-value**
Intercept	-1.821	0.361	-2.269	0.023
Variant *IQGAP2*	0.083 (OR 1.08)	0.515	0.162	0.871
Random Effects	**Variance**	**SD**		
Family	0	0		

B)

Fixed Effects	**Estimated % PCa**	**SE**	**CI 95%**	**Z**	**P-value**
0	30.6	0.077	0.18–0.47	-2.269	0.023
1	32.4	0.080	0.19–0.50	-2.012	0.044

C)

	Df	**Dev.**	**Resid. Df**	**Resid. Dev.**	**P-value**
NULL			69	87.15	
Variant	1	0.026	68	87.12	0.871

3.4.2 Family-Based Association Testing (FBAT)

Although GLMM was used to determine the association between the variants and PCa status considering family as a random effect to account for within-family correlation, a Family-Based Association Test (FBAT) was also performed to provide a complementary approach by testing whether genetic variants are transmitted to PCa family members more often than expected by chance. FBAT was performed using the orthogonal mode (FBAT -o) to test whether the variant was associated with PCa, assuming "absence of linkage" and treating transmissions within nuclear families as independent under the null hypothesis. Moreover, the empirical mode (FBAT -e) was applied to test whether the variant is associated with PCa in "presence of linkage", by adjusting for potential within-family correlations, such as those arising from potential linkage, using the PCa prevalence in Finland (2.24 %) as an offset parameter (μ) (Pitkäniemi et al., 2022).

The *ZBTB46* rs34785134 variant showed a significant association in the orthogonal model (P=0.013), indicating a potential association with PCa assuming independence of transmissions within nuclear families. However, no significant association was observed in the empirical model, which adjusts for potential within-family correlation, suggesting that the association signal might not be strong within the family data. On the other hand, the *LETM1* rs62623389 variant had a stronger signal in the empirical model, close to being statistically significant (P=0.062), which may indicate a more consistent segregation of this variant in affected family members considering familial correlation (Table 17).

Table 17. FBAT for the five studied variants using orthogonal model to test association to PCa, assuming "no linkage" and treating transmissions within nuclear families as independent under the null hypothesis (A). FBAT for the five studied variants using empirical model and PCa prevalence in Finland (2.24 %) as an offset to test association with PCa in "presence of linkage", adjusting for potential within-family correlations, such as those arising from potential linkage (B). Settings for both models: model additive; test bi-allelic; minsize 1; min_freq 0.000; p 1.000; maxcmh 1000. AF allele frequency, Fam# number of informative nuclear families, S-E(S) observed number of transmissions minus expected number of transmissions if there is no association. Var(S) variance of the expected transmission, Z standardized test statistic. Significance: <0.001 (***); <0.01 (**); <0.05(*).

A) Orthogonal FBAT

Variant	**AF**	**Fam#**	**S-E(S)**	**Var(S)**	**Offset**	**Z**	**P-value**
TP63 rs190865056	0.193	5	0.576	0.707	0.370	0.685	0.493
ZBTB46 rs34785134	0.117	5	1.634	0.435	0.387	2.477	0.013*
PASK rs35129131	0.314	4	-0.767	0.361	0.661	-1.275	0.202
LETM1 rs62623389	0.205	10	1.810	1.815	0.495	1.343	0.179
IQGAP2 rs34592828	0.175	9	0.138	1.783	0.405	0.786	0.917

B) Empirical FBAT

Variant	**AF**	**Fam#**	**S-E(S)**	**Var(S)**	**Z**	**P-value**
TP63 rs190865056	0.193	2	1.444	1.197	1.320	0.187
ZBTB46 rs34785134	0.117	2	1.357	0.985	1.368	0.171
PASK rs35129131	0.314	2	-0.300	0.994	-0.381	0.703
LETM1 rs62623389	0.205	8	2.660	2.026	1.869	0.062
IQGAP2 rs34592828	0.175	5	1.106	1.404	0.933	0.350

3.5 Cohort study

3.5.1 Comparative analysis of variant frequencies

In addition to the family-based analysis, a cohort study was done to investigate whether the variants were linked to familial PCa using RALP and PROMIC individuals with a family history of PCa and HBOC as a positive cohort. Carrier frequencies and allele frequencies for these variants were compared between the positive cohort and the general Finnish population (FinnGen), and between the positive cohort and the PCa cases from the C3_PROSTATE_EXALLC endpoint (FinnGen) using Fisher's exact test. The carrier and allele frequencies of *ZBTB46* rs34785134 and *PASK* rs35129131 were higher in the positive cohort compared to both the general Finnish population and the PCa cases from the C3_PROSTATE_EXALLC endpoint (Table 18). Interestingly, *PASK* rs35129131 showed a statistically significant difference in both carrier frequency (P=0.024, OR=1.86, CI95% 1.05–3.06) and allele frequency (P=0.011, OR=1.93, CI95% 1.12–3.12) between the positive cohort and the general Finnish population. Additionally, this variant showed a trend toward statistical significance when comparing allele frequencies between the positive cohort and FinnGen PCa cases (P=0.089) (Table 19).

Table 18. Carrier and allele frequencies of the positive cohort (PCa patients with family history of PCa and HBOC), general Finnish population (FinnGen), and malignant PCa cases from the C3_PROSTATE _EXALLC endpoint (FinnGen). The number of carriers and alleles in relation to the total number of individuals and alleles respectively are shown between brackets.

A) Carrier frequencies

Variant	Cohort	Finnish population (FinnGen)	Malignant PCa (FinnGen)
TP63 rs190865056	0.0205 (7/342)	0.0278	0.0298
ZBTB46 rs34785134	0.0234 (8/342)	0.0129	0.0216
PASK rs35129131	0.0468 (16/342)	0.0258	0.0318
LETM1 rs62623389	0.0789 (27/342)	0.0860	0.0918
IQGAP2 rs34592828	0.0702 (22/342)	0.0784	0.0842

B) Allele frequencies

Variant	Cohort	Finnish population (FinnGen)	Malignant PCa (FinnGen)
TP63 rs190865056	0.0102 (7/684)	0.014	0.015
ZBTB46 rs34785134	0.0117 (8/684)	0.0065	0.0078
PASK rs35129131	0.0249 (17/684)	0.013	0.016
LETM1 rs62623389	0.0409 (28/684)	0.044	0.047
IQGAP2 rs34592828	0.0351 (24/684)	0.040	0.043

Table 19. Carrier (CF) and allele frequency (AF) comparisons between the positive cohort (PCa patients with family history of PCa and HBOC), and both general Finnish population (FinnGen) and malignant PCa cases from the C3_PROSTATE_EXALLC endpoint (FinnGen) using Fisher´s exact test. Significance: <0.001 (***); <0.01 (**); <0.05(*).

Variant	**Cohort vs Finnish population (CF)**		**Cohort vs Finnish population (AF)**		**Cohort vs Malignant PCa (CF)**		**Cohort vs Malignant PCa (AF)**	
	P-value	OR (CI 95 %)	P-value	OR (CI 95 %)	P-value	OR (CI 95 %)	P-value	OR (CI 95 %)
TP63 rs190865056	0.51	0.73 (0.29–1.52)	0.51	0.73 (0.29–1.51)	0.42	0.68 (0.27–1.42)	0.42	0.68 (0.27–1.42)
ZBTB46 rs34785134	0.091	1.83 (0.78–3.64)	0.093	1.81 (0.78–3.59)	0.71	1.08 (0.46–2.18)	0.27	1.50 (0.64–3.0)
PASK rs35129131	0.024*	1.86 (1.05–3.06)	0.011*	1.93 (1.12–3.12)	0.12	1.49 (0.84–2.48)	0.089	1.57 (0.90–2.55)
LETM1 rs62623389	0.70	0.91 (0.59–1.35)	0.78	0.93 (0.61–1.35)	0.45	0.85 (0.55–1.26)	0.52	0.87 (0.57–1.27)
IQGAP2 rs34592828	0.69	0.89 (0.56–1.34)	0.62	0.87 (0.56–1.31)	0.43	0.82 (0.52–1.25)	0.34	0.81 (0.51–1.22)

Based on the statistically significant differences in *PASK* rs35129131 allele frequencies between groups, carrier and allele frequencies of this variant were later compared between our positive cohort and a negative cohort consisting of PCa individuals without a family history of PCa and HBOC using Fisher's exact test. The carrier frequency of *PASK* rs35129131 in the positive cohort (0.047) was notably higher than in the negative cohort (0.020). Similarly, PASK rs35129131 allele frequency was higher in the positive cohort (0.025) compared to the negative cohort (0.010). When analyzing carrier frequencies, a statistically significant difference was observed, suggesting a potentially increased likelihood of carrying the variant among individuals with a family history of the disease compared to those without (P=0.040, OR=2.40, CI95% 0.98–6.25). However, since the confidence interval included 1, the result indicated a borderline effect. Nevertheless, the allele frequency comparison also showed a statistically significant difference between the two groups, indicating that the variant is carried more frequently among PCa patients with a family history of the disease (P=0.027, OR=2.54, CI 1.06–6.52) (Table 20).

Table 20. *PASK* rs35129131 carrier and allele frequency comparisons between the positive cohort (PCa patients with family history of PCa and HBOC (+)), and the negative cohort (PCa patients without family history of PCa and HBOC (-)) using Fisher's exact test. AF allele frequency, CF carrier frequency, CI confidence interval, OR odds ratio, Var. variant allele, WT reference allele. Significance: <0.001 (***); <0.01 (**); <0.05(*).

A) Carrier frequency comparison

	Variant	**WT**	**Total**	**CF**	**P-value**	**OR (CI 95 %)**
Cohort (+)	16	326	342	0.047	0.040*	2.40 (0.98–6.25)
Cohort (-)	9	441	450	0.020		

B) Allele frequency comparison

	Variant	**WT**	**Total**	**AF**	**P-value**	**OR (CI 95 %)**
Cohort (+)	17	667	684	0.025	0.027*	2.54 (1.06–6.52)
Cohort (-)	9	891	900	0.010		

3.5.2 Association between variant status and clinicopathological features

As a secondary analysis, it was investigated whether carrying the different variants was associated with several clinicopathological characteristics of the patient. This was performed by comparing RALP and PROMIC participants' clinicopathological features based on their carrier status for each variant independently using Fisher's exact test. The patients were also categorized into groups with more aggressive or less aggressive characteristics based on the age at onset, PSA values, biopsy Gleason score, and TNM staging. Each characteristic was compared and analyzed individually to determine whether variant carriers tend to have an early age at onset, higher PSA levels, higher Gleason score, and more advanced TNM classification. Patients were classified as having less aggressive characteristics if they had an age at onset ≥ 65, PSA ≤ 20 ng/ml, Gleason score < 8 (ISUP < 4), and TNM stage < T3, N0, or M0. Oppositely, patients with an age at onset < 65, PSA > 20 ng/ml, Gleason score ≥ 8 (ISUP ≥ 4), and TNM stage ≥ T3, N1, or M1 were classified as having more aggressive characteristics.

Concerning the age of onset, participants carrying any studied variant had an earlier age of disease onset, especially those ones carrying the *ZBTB46* rs34785134 (61.5 years), compared with those without the studied variants (65–65.5 years). However, a statistically significant association was not found between any of the studied variants and age of onset. Moreover, the studied variants were not statistically more frequent in those PCa patients with an age of disease onset < 65 years (Table 21).

Table 21. Comparison of the mean age of PCa onset between variant carriers and variant non-carriers using Mann-Whitney U test. Also, comparison of the variants' carrier frequency between variant carriers and non-variant carriers with age of onset < 65 and ≥65 using Fisher´s exact test. The number of carriers in relation to the total number of individuals per group is shown between brackets. CI confidence interval, OR odds ratio, Var. variant allele. Significance: <0.001 (***); <0.01 (**); <0.05(*).

Variant	**Mean age onset**		**P-value**	**< 65 yo age onset**		**≥65 yo age onset**		**P-value**	**OR (CI 95 %)**
	0/0	0/1		0/0	0/1	0/0	0/1		
TP63 rs190865056	65.5	63.8	0.43	0.97 (215/222)	0.03 (7/222)	0.97 (281/290)	0.03 (9/290)	1	0.98 (0.32–3.17)
ZBTB46 rs34785134	65.5	61.5	0.21	0.98 (217/222)	0.02 (5/222)	0.98 (284/290)	0.02 (6/290)	1	0.92 (0.23–3.85)
PASK rs35129131	65	63.8	0.21	0.96 (310/324)	0.04 (14/324)	0.97 (388/399)	0.03 (11/399)	0.31	0.63 (0.25–1.51)
LETM1 rs62623389	65.5	64.8	0.49	0.91 (203/222)	0.09 (19/322)	0.94 (272/290)	0.06 (18/290)	0.39	0.71 (0.34–1.46)
IQGAP2 rs34592828	65.5	64.3	0.49	0.93 (206/222)	0.07 (16/222)	0.93 (270/290)	0.07 (20/290)	1	0.95 (0.46–2.02)

When comparing mean preoperative PSA levels between variant carriers and non-variant carriers, the individuals carrying the *TP63* rs190865056, *LETM1* rs62623389, and *IQGAP2* rs34592828 variant showed higher mean PSA levels than the non-carriers. However, no statistically significant association was found between PSA levels and any of the studied variants. Furthermore, the carrier frequencies of the studied variants were not significantly different among PCa patients with PSA levels > 20 ng/ml compared to those with ≤ 20 ng/ml levels (Table 22).

Table 22. Comparison of the mean PSA levels between variant carriers and non-variant carriers using Mann-Whitney U test. Also, comparison of the variants' carrier frequency between variant carriers and non-variant carriers with PSA levels s 20 ng/ml and > 20 ng/ml using Fisher´s exact test. The number of carriers in relation to the total number of individuals per group is shown between brackets. CI confidence interval, OR odds ratio, Var. variant allele. Significance: <0.001 (***); <0.01 (**); <0.05(*).

Variant	**Mean PSA (ng/ml)**		**P-value**	**≤ 4 ng/ml**		**> 4 ng/ml**		**P-value**	**OR (CI 95%)**
	0/0	0/1		0/0	0/1	0/0	0/1		
TP63 rs190865056	9.04	11.60	0.43	0.98 (61/62)	0.02 (1/62)	0.97 (458/473)	0.03 (15/473)	1	0.50 (0.02–3.37)
ZBTB46 rs34785134	9.14	8.22	0.20	1 (62/62)	0 (0/62)	0.97 (460/473)	0.03 (13/473)	0.38	0 (0.0–2.50)
PASK rs35129131	9.86	7.93	0.39	0.95 (80/84)	0.05 (4/84)	0.97 (722/745)	0.03 (2/745)	0.34	1.57 (0.38–4.75)
LETM1 rs62623389	8.95	11.2	0.49	0.90 (56/62)	0.10 (6/62)	0.93 (440/473)	0.07 (33/473)	0.44	1.43 (0.47–3.66)
IQGAP2 rs34592828	9.08	9.58	0.49	0.98 (61/62)	0.02 (1/62)	0.92 (437/473)	0.08 (36/473)	0.11	0.20 (0.0–1.23)

Regarding histological findings, the median Gleason score ISUP was the same for both variant carriers and non-variant carriers (Gleason score=2), except for individuals carrying *TP63* rs190865056, who had a median Gleason score of 2.5. However, no statistically significant association was found between any of the analyzed variants and Gleason score. Additionally, the carrier frequencies of the studied variants were not significantly different among PCa patients with Gleason score ISUP ≥ 4 compared to those with a score < 4 (Table 23).

Table 23. Comparison of Gleason Score biopsy (ISUP) medians between variant carriers and non-variant carriers using Fisher´s exact test . Also, comparison of the variants' carrier frequency between variant carriers and non-variant carriers with ISUP < 4 and ≥ 4 1 using Fisher´s exact test. The number of carriers in relation to the total number of individuals per group is shown between brackets. CI confidence interval, OR odds ratio, Var. variant allele. Significance: <0.001 (***); <0.01 (**); <0.05(*).

Variant	**Median Gleason Score ISUP (1–5)**		**P-value**	**Gleason Score ISUP < 4**		**Gleason Score ISUP ≥ 4**		**P-value**	**OR (CI 95 %)**
	0/0	0/1		0/0	0/1	0/0	0/1		
TP63 rs190865056	2	2.5	0.20	0.98 (331/339)	0.02 (8/339)	0.95 (78/82)	0.05 (4/82)	0.26	2.11 (0.45–8.15)
ZBTB46 rs34785134	2	2	0.50	0.97 (329/339)	0.02 (10/339)	0.98 (80/82)	0.02 (2/82)	1	0.82 (0.09–3.97)
PASK rs35129131	2	2	0.34	0.96 (502/524)	0.04 (22/524)	0.98 (167/170)	0.02 (3/170)	0.16	0.41 (0.08–1.39)
LETM1 rs62623389	2	2	0.53	0.93 (315/339)	0.07 (24/339)	0.89 (73/82)	0.11 (9/82)	0.25	1.62 (0.63–3.79)
IQGAP2 rs34592828	2	2	0.32	0.92 (313/339)	0.08 (26/339)	0.89 (78/82)	0.11 (4/82)	0.48	0.62 (0.15–1.86)

TNM-classification was also analyzed to assess its association with the studied variants. The carrier frequencies of the studied variants were not significantly different among PCa patients with cancer ≥ T3 compared to those with < T3. Moreover, no significant difference in the variants' carrier frequencies were observed between PCa patients with cancer N1 compared to those with Nx/N0. Likewise, the carrier frequencies of the variants were not significantly different among PCa patients with cancer M1 compared to those with Mx/M0 (Table 24).

Table 24. Comparison of carrier frequencies between variant carriers and non-variant carriers with T-grade < T3 and ≥ T3, N-grade N0 and N1, and M-grade M0 and M1 using Fisher´s exact test. The number of carriers in relation to the total number of individuals per group is shown between brackets. CI confidence interval, OR odds ratio, Var. variant allele. Significance: <0.001 (***); <0.01 (**); <0.05(*).

Variant	**T-grade < T3**		**T-grade ≥ T3**		**P-value**	**OR (CI 95 %)**
	0/0	0/1	0/0	0/1		
TP63 rs190865056	0.96 (201/209)	0.04 (8/209)	0.98 (120/123)	0.02 (3/123)	0.65	0.42 (0.01–4.33)
ZBTB46 rs34785134	0.96 (201/209)	0.04 (8/209)	0.97 (119/123)	0.03 (4/123)	1	0.85 (0.18–3.24)
PASK rs35129131	0.96 (308/320)	0.04 (12/320)	0.97 (224/231)	0.03 (7/231)	0.81	0.80 (0.26–2.25)
LETM1 rs62623389	0.93 (194/209)	0.07 (15/209)	0.90 (111/123)	0.10 (12/123)	0.41	1.40 (0.58–3.33)
IQGAP2 rs34592828	0.92 (193/209)	0.08 (16/209)	0.94 (115/123)	0.06 (8/123)	0.83	0.84 (0.30–2.16)

Variant	**N-grade N0**		**N-grade N1**		**P-value**	**OR (CI 95 %)**
	0/0	0/1	0/0	0/1		
TP63 rs190865056	0.97 (420/434)	0.03 (14/434)	0.96 (25/26)	0.04 (1/26)	0.59	1.20 (0.03–8.52)
ZBTB46 rs34785134	0.97 (421/434)	0.03 (13/434)	1 (26/26)	0 (0/26)	1	0 (0.0–5.66)
PASK rs35129131	0.96 (601/623)	0.04 (22/623)	1 (57/57)	0 (0/57)	0.24	0 (0.0–1.99)
LETM1 rs62623389	0.93 (404/434)	0.07 (30/434)	0.88 (23/26)	0.12 (3/26)	0.42	1.76 (0.32–6.33)
IQGAP2 rs34592828	0.94 (408/434)	0.06 (26/434)	0.88 (23/26)	0.12 (3/26)	0.22	2.04 (0.37–7.46)

Variant	**M-grade M0**		**M-grade M1**		**P-value**	**OR (CI 95 %)**
	0/0	0/1	0/0	0/1		
TP63 rs190865056	0.97 (464/478)	0.03 (14/478)	0.8 (4/5)	0.2 (1/5)	0.15	8.19 (0.16–90.24)
ZBTB46 rs34785134	0.97 (465/478)	0.03 (13/478)	1 (5/5)	0 (0/5)	1	0 (0.0–42.72)
PASK rs35129131	0.96 (683/708)	0.04 (25/708)	1 (7/7)	0 (0/7)	1	0 (0.0–19.99)
LETM1 rs62623389	0.93 (443/478)	0.07 (35/478)	0.8 (4/5)	0.2 (1/5)	0.32	3.15 (0.06–32.98)
IQGAP2 rs34592828	0.94 (448/478)	0.06 (30/478)	0.8 (4/5)	0.2 (1/5)	0.28	3.72 (0.07–39.12)

Finally, it was examined whether the variants were carried more commonly in the cases of aggressive PCa in comparison with non-aggressive PCa cases. Aggressive PCa was defined as the cases having at least one of the following characteristics: PSA > 20 ng/mL, ISUP grade ≥ 4, T stage 3 or 4, N1, or M1. On the other hand, non-aggressive PCa was defined as the cases meeting all the following criteria: PSA ≤ 20 ng/mL, ISUP grade 1, T stage < 3, N0, and M0. The carrier frequencies of the studied variants did not differ significantly between patients with aggressive PCa and those with non-aggressive PCa (Table 25).

Table 25. Comparison of carrier frequencies of the studied variants between individuals with aggressive PCa (PSA > 20 ng/ml, or ISUP ≥ 4, or T3/T4, or N1, or M1) and non-aggressive PCa (PSA ≤ 20 ng/mL, and ISUP 1, and not T3/T4, and not, and not M1) using Fisher´s exact test. The number of carriers in relation to the total number of individuals per group is shown between brackets. CI confidence interval, OR odds ratio, Var. variant allele. Significance: <0.001 (***); <0.01 (**); <0.05(*).

Variant	**Non-aggressive**		**Aggressive**		**P-value**	**OR (CI 95 %)**
	0/0	0/1	0/0	0/1		
TP63 rs190865056	0.93 (52/56)	0.07 (4/56)	0.98 (165/169)	0.02 (4/169)	0.11	0.32 (0.06–1.76)
ZBTB46 rs34785134	0.93 (52/56)	0.07 (4/56)	0.97 (164/169)	0.03 (5/169)	0.23	0.39 (0.08–2.08)
PASK rs35129131	0.95 (77/81)	0.05 (4/81)	0.97 (324/333)	0.03 (9/333)	0.29	0.54 (0.14–2.44)
LETM1 rs62623389	0.93 (52/56)	0.07 (4/56)	0.91 (154/169)	0.09 (15/169)	0.79	1.26 (0.38–5.47)
IQGAP2 rs34592828	0.95 (53/56)	0.05 (3/56)	0.94 (159/169)	0.06 (10/169)	1	1.11 (0.27–6.51)

4. DISCUSSION

Prostate cancer (PCa) has a high genetic factor estimated to account for 42–58 % of the risk of developing PCa (Lichtenstein et al., 2000; Hjelmborg et al., 2014). Though 451 germline genetic risk variants have been identified for PCa in diverse populations using GWAS (Al Olama et al., 2014; Eeles et al., 2013; Schumacher et al., 2018; Wang et al., 2023), many variants pathogenicity remain unclear or only explain small portion of the heritability (Saunders et al., 2014; Walsh, 2017). Moreover, the genetic heterogeneity of PCa complicates the identification of clinically relevant variants (Cooper et al., 2015).

Studies in the Finnish population bring the opportunity to detect rare high-risk variants due to the population's enrichment of rare and low-frequency cancer-predisposing variants (Lim et al., 2014; Xue et al., 2017). This enrichment is caused by genetic thrift in an isolated population with recent bottlenecks (Lim et al., 2014; Zuk et al., 2014). The aim of this study was to identify novel predisposing variants in the Finnish population, particularly in genes that have been previously associated with PCa but for which no specific predisposing variants have yet been identified. To accomplish this, a whole-genome sequencing (WGS) dataset from high-risk HPCa families' indexes was screened to select candidate variants. These variants were then further investigated using a combination of family-based and cohort-based analyses, allowing us to evaluate their segregation with affected families and their frequency in larger affected populations.

4.1 Variant selection from high-risk PCa families WGS dataset

Families with a high number of PCa cases are more likely to contain individuals carrying deleterious variants among their members. Moreover, WGS provides deeper genomic profiling, enabling the detection of variants in both coding and non-coding regions (Nakagawa & Fujita, 2018). Therefore, the starting point of this study was to find the most pathogenic or likely pathogenic variants from the WGS data of index individuals from 71 high-risk HPCa families. The previously performed filtering step by the group's informatician included variants with high or moderate impact on protein structure according to the Ensembl Variant Effect Predictor (VEP), using bioinformatic prediction programs, such as REVEL or CADD, which are widely used to determine variant's pathogenicity (Ioannidis et al., 2016; McLaren et al., 2016; Rentzsch et al., 2019). Additionally, the variant's maximum alternative allele frequency (MAF) was required to be below 0.05. This threshold was chosen because variants with MAF below 0.05 are more likely to be found deleterious and have a greater effect size, since low frequency and rare variants typically require higher odds ratios to be detected (Manolio et al., 2009).

In the second filtering step, those variants present in more than one index patient, located in genes expressed in basal prostatic cells or prostatic glandular cells, and showed a near statistically significant association in the C3_PROSTATE_EXALLC endpoint in the FinnGen GWAS were selected. Selecting recurrent variants present in index patients helps prioritize clinically relevant variants, while filtering by gene expression ensures biological relevance in prostate tissue. Moreover, focusing on variants with low p-values and positive beta coefficients in C3_PROSTATE_EXALLC endpoint supports the selection of statistically supported variants with increased disease risk.

After obtaining a list of 14 candidate variants, a literature review was conducted to prioritize those located in genes previously associated with PCa, but for which no specific variants have yet been associated with the disease. After the final filtering step, five variants were selected for further analyses: *TP63* (rs190865056), *ZBTB46* (rs34785134), *PASK* (rs35129131), *LETM1* (rs62623389), and *IQGAP2* (rs34592828).

The transcription factor Tumor Protein P63 (TP63) is a p53 family protein that acts as a transcriptional activator or repressor, determined by the isoform expressed (Osterburg & Dötsch, 2022). It is crucial in the development of epithelial and derived glandular tissue (Candi et al., 2014). Abnormal expression of *TP63* has been observed in various cancers, including triple-negative breast and non-small cell lung cancer (Coated et al., 2016; Shen et al., 2023). Its silencing has been shown to improve anti-PD-1 cancer immunotherapy efficacy by promoting the infiltration and retention of cancer-killing T cells into the tumor (Jiang et al., 2024). In PCa, *TP63* is downregulated in prostate adenocarcinoma, where it regulates enhancer methylation levels in prostate basal cells (Sultanov et al., 2024). Additionally, *TP63* and *FOXO1* function as suppressors of PCa lineage plasticity (Wei et al., 2024). The variant *TP63* rs190865056 is located in the 3q28 chromosomal region. There are no previous studies suggesting that this region is a possible susceptibility locus for PCa. However, variants in 3q28 region have been found to be linked to various types of cancer, such as bladder and lung cancer (Stern et al., 2009; Lehmann et al., 2010; Hosgood III et al., 2012). For instance, the functional germline rs1464938 variant, located in the promoter of *FGF12* (fibroblast growth factor 12), is associated with a higher risk to develop bladder transitional cell carcinoma (Wu et al., 2020). Moreover, the germline variants rs4396880, which is associated with an enhanced expression of *TP63* in lung tissue, and rs3856776, which is associated with inhibition of *P3H2* (prolyl 3-hydroxylase 2) translation, are both associated with an increased risk of lung cancer (Wen et al., 2019)

Zinc Finger and BTB Domain Containing 46 (ZBTB46) is a transcriptional factor, part of the BTB-ZF (broad complex, tramtrack, bric-à-brac, and zinc finger) family of transcriptional repressors, known as a classical marker of dendritic cells (Satpathy et al., 2012; Meredith et al., 2012). Activation of *ZBTB46* has been associated with survival and proliferation of cancerous cells in acute myeloid leukemia cell lines, whereas its inactivation in endothelial cells and dendritic cells, induced angiogenesis and myeloid lineage skewing in cancer broadly (Liu et al., 2020; Kabir et al., 2024). *ZBTB46* also contributes to the progression of PCa, especially in the most aggressive types. Androgen receptor inhibition leads to *ZBTB46* activation, inducing metastasis (Chen et al., 2017). Moreover, *ZBTB46* activation contributes to neuroendocrine differentiation and castration-resistant PCa through interactions with other factors, such as *FOXA2*, *HIFA*, and *PCK1*, increasing cancer cell migration and lineage plasticity (Liu et al., 2017; Liu et al., 2024; Wen et al., 2022). The variant *ZBTB46* rs34785134 is in the 20q13.33 region. The region 20q13 has been previously reported as a susceptibility locus for PCa in linkage analysis (Berry et al., 2000; Bock et al., 2001; Zheng et al., 2001). In addition, this region is often amplified and coupled to the regulation of androgen receptor (*AR*) in prostate tumors, which is closely linked to the development of metastatic PCa (Labbé et al., 2014). Moreover, two transcription factors encoded in this region, *SNAI1* (snail family transcriptional repressor 1) and *CEBPB* (CCAAT enhancer binding protein beta) are involved in epithelial-mesenchymal transition, cell survival, and Ras-mediated tumorigenesis (Zhu et al., 2002; Kudo-Saito et al., 2009; Emadi Baygi et al., 2010). Interestingly, genomic amplification of the 20q13.33 region in colorectal tumors is also associated with the tumorigenesis of the disease (Bui et al., 2020). For instance, the germline rs6066825 variant in *PREX1* (phosphatidylinositol-3,4,5-trisphosphate dependent Rac exchange factor 1) gene, which is involved in cell migration and invasion, is associated with colorectal cancer (Schumacher et al., 2015). Also, germline variants rs6017452 and rs7271519 in *STK4* (serine/threonine kinase 4) gene, and rs2273535 and rs8173 in *AURKA* (aurora kinase a) gene at the 20q13 region, are involved in hormone receptor status in breast cancer, influencing disease aggressiveness and patient survival (Shi et al., 2011).

Per-Arnt-Sim (PAS) Domain Containing Serine/Threonine Kinase (PASK) is a nutrient-responsive kinase involved in lipid and glucose metabolism, mitochondrial respiration, and gene expression (Grose & Rutter., 2010; Cardon & Rutter, 2012; Cardon et al., 2012; DeMille & Grose, 2013). *PASK* overexpression has been associated with low risk and better prognosis in ovarian cancer (Zhu et al., 2023). Moreover, *PASK* was identified as one of nine differentially expressed genes significantly associated with overall survival, clinical features, immune cell function in the tumor microenvironment, tumor mutation burden, and cancer-related pathways in stomach adenocarcinoma (Ye at al., 2020). Additionally, *PASK* was observed to be overexpressed in PCa patients according to urinary exosomal mRNA (Yu et al., 2024). The variant *PASK* rs35129131 is located in the 2q37.3 chromosomal region. This region has also been previously reported as a susceptibility locus for PCa in linkage analysis (Suarez et al., 2000; Pierce et al., 2007; Cropp et al., 2011). The *ANO7,* which is also in the 2q37.3 region, is a gene involved in the regulation of genes associated with PCa, such as *KLK3*, *PAP* and *KLK2* (Walker et al., 1999; Kiessling et al., 2005). For instance, *ANO7* rs77559646 is associated with increased PCa risk and aggressiveness (Kaikkonen et al., 2018; Wahlström et al., 2022). Moreover, *ANO7* variants rs74804606 and rs60985508 are also associated with PCa risk in men with African ancestry (Chen et al., 2023; Jiang et al., 2024).

Leucine Zipper AND EF-Hand Containing Transmembrane 1 (LETM1) is in the inner mitochondrial membrane and is crucial for maintaining mitochondrial morphology and keeping cellular viability. It functions as a calcium or potassium/proton antiport in mitochondria (Waldeck-Weiermair et al., 2011). *LETM1* has been associated with tumor progression and prognosis in thyroid, bladder, breast, and esophageal cancer (Li et al., 2015; Lee et al., 2016; Huang et al., 2017; Yang et al., 2018). Moreover, its expression is correlated with cancer stemness genes and poor prognosis in colorectal adenocarcinoma (Piao et al., 2019). In PCa, *LETM1* expression is associated with genes involved in epithelial-mesenchymal transition, cell cycle regulation, PI3K/Akt signaling, and cell stemness, which are biological processes implicated in tumor progression (Piao et al., 2020). The *LETM1* rs62623389 variant is in the 4p16.3 region, a locus that has not previously been associated with PCa susceptibility, and where no germline variants have been linked to the disease. However, somatic copy number loss of 4p16.3 has been identified in prostate tumors from African American patients (Castro et al., 2009). Similarly, loss of 4p16.3 has been found in other types of cancer, such as colon, breast, and bladder cancer (Shivapurkar et al., 1999; Sibley et al., 2000; Shivapurkar et al., 2001). For instance, rs798766 variant in *TACC3* (transforming acidic coiled-coil containing protein 3) gene, which is in the 4p16.3 region, is associated with urinary bladder cancer (Kiemeney et al., 2010).

IQ Motif Containing GTPase Activating protein (IQGAP2) is a scaffold protein that interacts with both Rho GTPase and calcium/calmodulin signals, participating in cytoskeleton regulation (Ghaleb et al., 2015). *IQGAP2* downregulation and loss is associated with ovarian cancer, hepatocellular carcinoma, and gastric cancer (White et al., 2010; Deng et al., 2015; Xu et al., 2020). Conversely, *IQGAP2* overexpression is associated with poor prognosis and immune changes in diffuse large B-cell lymphoma (Tang et al., 2021). Additionally, *IQGAP2* functions as a tumor suppressor in PCa by up-regulating E-cadherin, halting epithelial-mesenchymal transition, and inhibiting cancer cell invasion (Xie et al., 2012). Similarly, *IQGAP2* downregulation is associated with PCa recurrence and metastasis (Xie et al., 2019). The *IQGAP2* rs34592828 variant is in the 5q13.2 region, which is close to the 5q11-12 region, previously identified as a PCa susceptibility locus by linkage analysis (Xu et al., 2005; Christensen et al., 2010). However, there is no known germline variants associated with PCa in

5q13.2 region. Interestingly, somatic deletion of 5q13 is associated with aggressive PCa (Möller et al., 2020).

Although these genes have previously been associated with PCa, no studies have yet identified specific variants that may contribute to increased risk of developing or progressing the disease. This study is one of the first to explore such variants for further analysis in both family-based and cohort studies.

4.2 Variant association with PCa in high-risk families

HPCa high-risk families were used to find an association between the selected variants and the disease. High-risk cancer families have been previously used to assess the association between genetic variants and an increased risk of cancer, such as in breast and PCa (Johnson et al., 2014; Laitinen et al., 2016; Muranen et al., 2016). For this, those families whose index cases tested positive for the variant in the WGS were selected to ensure that more relatives would carry the same variant as well. This approach resulted in a different set of families been studied for each variant analysis. However, there were several families analyzed for more than one variant. Families 066 and 123 were analyzed for *PASK* and *LETM1* variants, and family 364 for *TP63*, *LETM1* and *IQGAP2* variants.

First, carrier and allele frequencies were compared between affected and unaffected men within families separately. No statistically significant difference was found, probably due to the small number of participants in each family. To increase statistical power, the affected and unaffected participants were summed across all the families genotyped for the same variant. Pooled contingency tables were created, which allowed us to have a larger population size for the comparisons. When comparing carrier and allele frequencies between affected and unaffected participants across families, statistically significant higher carrier frequency for *ZBTB46* rs34785134 and borderline significant higher carrier frequency *LETM1* rs62623389 in individuals with PCa were observed. However, the wide 95 % confidence interval in the *ZBTB46* rs34785134 comparison, and the 95 % confidence interval crossing 1 in the *LETM1* rs62623389 comparison, suggest low precision and low reliability, probably due to a small sample size. On the other hand, there were not significant differences for any variant between both groups when comparing allele frequencies.

Because pooling individuals across families doesn't consider relatedness among participants from the same families, a binomial generalized linear mixed model (GLMM) was used, where family was incorporated as random effect to correct for family structure. GLMM is commonly performed in family-based and longitudinal studies to adjust for potential relatedness among samples (Zhan et al., 2021). Associations between PCa status and carriage of the *ZBTB46* rs34785134 and *LETM1* rs62623389 variant were found using this model. Carriers of the *ZBTB46* rs34785134 variant had 29.99 times higher odds of having PCa compared to non-carriers, whereas *LETM1* rs62623389 variant carrier had 3.67 times higher odds. To evaluate the contribution of the random effect, the full model containing family as a random effect to a reduced model without the random effect were compared using a likelihood ratio test for every variant. This allowed us to determine whether adding the random effect, the family, improved the model fit. Statistically significant p-values for the *ZBTB46* rs34785134 and *LETM1* rs62623389 model indicated that including family structure improved model fit for this variant, supporting the use of the GLMM over a simpler generalized linear model, at least for the analysis of these two variants.

A Family-Based Association Test (FBAT) was also performed to evaluate whether these variants were transmitted to PCa family members more frequently than expected by chance. FBAT examines both linkage and association by using not only parent-offspring trios, but any pedigree structure, such as extended pedigrees, multiple siblings, or missing parental data (Lasky-Su et al., 2011). The test compares the observed genotype distribution among individuals with a particular phenotype, in our study PCa status, to the expected genotype distribution under the null hypothesis. Null hypotheses tested are either “no association no linkage”, meaning the variant is not associated with PCa, treating transmissions within nuclear families as independent; or “no association in the presence of linkage”, meaning the variant is not associated with PCa, adjusting for potential within-family correlations, such as those arising from potential linkage, using the disease prevalence (Lazzeroni & Lange, 1998; Rabinowitz & Laird, 2000). By focusing on within-family transmission, FBAT is powerful against population stratification and minimizes the possibility of the control group not being representative of the case group (Lasky-Su et al., 2011).

To test for “association in the absence of linkage”, the FBAT orthogonal test, which minimizes the variance of the test statistic by optimally setting an offset (μ) for the trait, was used (Lunetta et al., 2000). The orthogonal test results indicated a statistically significant association between the *ZBTB46* rs34785134 and PCa status. Additionally, the FBAT empirical test was applied to evaluate “association in presence of linkage”. The empirical test generates test statistics using the empirical variance that accounts for genotype correlations among siblings and among nuclear families inside a pedigree (Lake et al., 2001). For a single dichotomous trait, the theory of score test recommends using the disease prevalence as the offset of the test (Laird et al., 2000). In our analysis, the offset was set according to the prevalence of PCa in Finnish men (Pitkäniemi et al., 2024). The results in the empirical test showed a trend towards association for the *LETM1* rs62623389 variant, suggesting that the variant might be co-inherited with the disease. Because definitive knowledge that linkage actually exists for a variant is generally lacking, orthogonal test results should be considered more reliable in this study. However, it is relevant to mention that the FBAT manual used for this study recommends a minimum number of 10 descriptive families for robust testing, and except for the *LETM1* rs62623389 variant in the orthogonal test, this threshold was not met in this study. Nevertheless, results from both GLMM and FBAT support potential association between *ZBTB46* rs34785134 and *LETM1* rs62623389 variants and PCa status, underlining the importance of accounting for relatedness and family structure in genetic association studies, as well as using familial data to detect heritability and transmission of variants. Moreover, *ZBTB46* rs34785134 is located within the 20q13 region, which has previously been proposed as a PCa susceptibility locus (Berry et al., 2000; Bock et al., 2001; Zheng et al., 2001). Since no specific germline variants have yet been identified in this region, *ZBTB46* rs34785134 could partly explain the linkage signals observed in previous analyses.

4.3 Variant association with PCa in cohort with family history of PCa and HBOC

Several previous studies have studied the association between family history, germline variants, and cancer risk in different types of cancer, including PCa (Muranen et al., 2016; Weigl et al., 2018; Kurian et al., 2021; Rumpf et al., 2024). In this study, it was evaluated whether the selected variants were associated with forms of PCa that have hereditary component. To do this, a cohort formed by PCa patients with family history of PCa and HBOC was created. Family history of PCa and HBOC related cancers (breast, ovarian and prostate cancer) are among the most important risk factors for PCa (Giri & Beebe-Dimmer, 2016; Ren et al., 2019; Beebe-Dimmer et al., 2020).

The variants' carrier and allele frequencies in this cohort were compared to those of the general Finnish population (FinnGen) and PCa cases from a Finnish GWAS (FinnGen). The *PASK* rs35129131 variant was statistically significantly more frequent in the positive cohort compared to the general Finnish population, and it also showed a trend toward a difference when compared to PCa cases from Finnish GWAS (FinnGen). Since the PCa cases from a Finnish GWAS include all PCa patients, not just sporadic ones, a negative cohort formed by PCa patients without family history of PCa and HBOC, was created and compared to the positive cohort. Interestingly, the allele frequency of *PASK* rs35129131 was statistically significantly more common in the positive cohort compared to the negative cohort. These findings indicate that *PASK* rs35129131 is carried more commonly by affected individuals in comparison with unaffected individuals and it is carried more frequently in PCa individuals with family history of PCa and HBOC compared to those without it, implying that this variant may be associated with hereditary susceptibility to PCa. Since *PASK* rs35129131 is genomically close to *ANO7*, a gene associated with PCa (Kaikkonen et al., 2018; Wahlström et al., 2022), it would be important to examine the genotypes for PCa predisposing *ANO7* variants in these same cohorts, to determine whether the observed results are due to an independent effect of this novel variant or are driven by linkage disequilibrium with known *ANO7* variants.

4.4 Association between variants and clinicopathological characteristics in PCa

In this study, the possible effects of these variants on the clinicopathological features of PCa were also evaluated. Certain germline variants are known to be associated with more aggressive PCa phenotypes (Castro et al., 2013; Castro et al. 2015a; Na et al., 2017). For example, the *HOXB13* G84E variant is associated with a higher risk of early age at onset and more aggressive phenotypes, such as high-grade PCa and progression to metastatic forms (Trendowski et al., 2022). Therefore, it was investigated whether there is any association between the selected variants individually and the following clinicopathological features: the age at onset, PSA levels, biopsy Gleason score, and TNM staging. The results indicated that there was no statistically significant association between any of these characteristics and PCa. To examine if more aggressive features individually are associated with the variant status, the cases were classified into groups with less aggressive or more aggressive features. Less aggressive characteristics were defined as: age at onset ≥ 65, PSA ≤ 20 ng/ml, Gleason score < 8 (ISUP < 4), and TNM stage < T3, Nx/N0, or Mx/M0. Conversely, more aggressive characteristics were defined as: age at onset < 65, PSA > 20 ng/ml, Gleason score > 6 (ISUP > 1), and TNM stage ≥ T3, N1, or M1. These Gleason score and TNM values were chosen considering the recommendations from Hurwitz and colleagues for defining aggressive PCa (Hurtwitz et al., 2021). T3 stage cancers were also included as aggressive cases to increase the sample size and improve statistical power. PSA > 20 ng/ml was considered as a more aggressive characteristic since it is correlated with worse diagnosis and prognosis (Iwamoto et al., 2019). Comparisons of carrier frequencies of the studied variants between cases with more and less aggressive characteristics, examined individually, did not reveal any significant difference. Finally, to examine whether these variants were carried more commonly in aggressive PCa cases, considering all the characteristics collectively, the carrier frequencies of these variants were compared between aggressive PCa (PSA > 20 ng/mL, or ISUP grade ≥ 4, or T stage 3/4, or N1, or M1) and non-aggressive PCa (PSA ≤ 20 ng/mL, and ISUP grade 1, and T stage < 3, and N0, and M0). Similar classification criteria have been used in previous studies in aggressive PCa (Cheng et al., 2011; Schaid et al., 2020; Sipecky et al., 2020; Chen et al., 2024). However, a recent study suggested that PCa aggressiveness should be classified according to SEER Summary Stage, which categorizes the cancer according to the "distant" (progression) of the disease (Wiese et al., 2023). Nevertheless, the division used in this study made it easier to distinguish clinically significant aggressive PCa from those with less aggressive forms. Consistent with the other comparisons, the carrier frequencies of the studied variants did not differ significantly between individuals with aggressive PCa and those with non-aggressive PCa.

Despite these results, previous studies have found germline variants associated with more aggressive clinicopathological characteristics in PCa. A large-scale study checking PCa risk variants in 17 different genomic regions in 5,895 PCa patients, identified a significant association between PCa aggressiveness and the rs2735839 variant, located downstream of the kallikrein 3 (*KLK3*) gene, which codes for PSA (Kader et al., 2009). Another associated variant was rs10993994 in the microseminoprotein β gene (MSMB). Interestingly, these variants were more common in individuals with less aggressive PCa (Kader et al., 2009). Since these variants are linked to higher PSA levels, there is the possibility that these variants lead to earlier detection in these individuals, including those with less aggressive forms (Ahn et al., 2008; Wiklund et al., 2009). Since most PCa risk variants have been discovered by comparing cases and controls, other approaches, such as comparing less aggressive and more aggressive groups or even metastatic PCa cases, can be more effective in identifying variants associated with disease aggressiveness. For instance, several studies have reported the association of pathogenic variants and PCa aggressiveness through such comparison studies (Xu et al., 2010; Helfand et al., 2015; Darst et al., 2021; Nguyen-Dumon et al., 2020). Thus, these studies suggest that germline variants can indeed be used as early markers for assessing the risk of aggressive PCa.

4.5 Multiple testing correction

A multiple testing correction, such as false discovery rate (FDR) adjustment, was not applied due to the small number of variants analyzed. FDR adjustment is commonly used to control type I errors in null hypothesis testing in large-scale studies, such as GWAS (Sesia et al., 2021). However, applying FDR to a small set of five variants could excessively reduce statistical power and ignore potential associations (Brinster et al., 2018). Future studies analyzing a larger set of variants should consider multiple testing adjustment to enhance statistical power. Strategies such as a prescreening step, which groups correlated SNPs into clusters representing single hypotheses, can improve FDR correction by accounting for linkage disequilibrium between variants (Brzyski et al 2016).

4.6 Limitations

4.6.1 Variant selection

In this study, only five variants could be focused on due to limited resources. However, it would have been interesting to investigate for other variants that appeared in the final list but lacked strong literature support for their association with PCa, such as *ZNF391*, and *TASOR* variants. Moreover, it would have been valuable to explore whether *CDK5RAP3* rs61758369 variant in potential linkage disequilibrium with *HOXB13* rs138213197, has independent effect or just shows significance due to their proximity to *HOXB13* gene. This is important since it has been previously proved that the rs559612720 variant within *SKAP1* gene, located 567 kb from *HOXB13* rs138213197, shows an independent risk effect. Under mutual adjustment, both variants individually carry around a three-fold risk but when inherited together, the risk increases to approximately 11-fold (Dupont et al., 2021). To better assess this, fine-mapping and conditional analysis could be suitable to determine independent risk effect in *CDK5RAP3* rs61758369 variants (Saunders et al., 2014; Dupont et al., 2021).

4.6.2 Formation of cohorts

One of the main challenges encountered in this study was the formation of the cohorts. When deciding which criteria to use for the positive cohort, the criteria established for HPCa families was initially considered: three or more affected first-degree relatives with PCa, prostate cancer diagnosed in three successive generations of paternal or maternal line, or two first-degree relatives both diagnosed with early-onset PCa (age ≤ 55 years) (Carter et al., 1993). However, these criteria were really strict and allowed only a small number of participants to be included. Therefore, criteria closer to those used for familial PCa (FPC) families were chosen. FPC is defined as families with either two first-degree relatives diagnosed with PCa at any age or one first-degree relative and two or more second-degree relatives diagnosed at any age (Ostrander et al., 2004). In the end, individuals with a first degree relative (son, brother, or father) with

PCa, two or more cases of PCa in the family, or two or more cases of HBOC related cancers (breast, ovarian, or prostate cancer) were included, inspired by the germline testing criteria for PCa of NCCN Guidelines Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (Version 1.2022) (Daly et al., 2021).

To be more accurate, pancreatic cancer and melanoma could have included as HBOC-related cancers for the selection of participants (Gumaste et al., 2015; Young et al., 2018; Minoura et al., 2022). Moreover, the inclusion of LS-related cancers (colorectal, endometrial, small bowel, ovarian, urothelial, stomachal, biliary duct, and brain cancers) could have improved the selection of individuals more likely to have hereditary cancer predisposition (Dominguez-Valentin et al., 2020; Curtius et al., 2022). By increasing the number of hereditary cancers, the likelihood of adding participants carrying HPCa-predisposing variants could have been increased. However, broadening the list of cancers could increase the risk of including sporadic cases as familial ones. For instance, only 10 % of all malignant melanomas and colorectal cancer are associated with germline mutations (Valle et al., 2019; Zocchi et al; 2021). This suggests that many cases could be sporadic, resulting from environmental or lifestyle factors rather than hereditary predisposition, potentially making it harder to detect the genetic signal being looked for. Considering the age at the onset of these malignancies could help to improve the selection of cases truly related to hereditary factors, since hereditary cancers are typically diagnosed at an earlier age compared to sporadic cases (Valle et al., 2019; Dominguez-Valentin et al., 2020).

Regarding the negative cohort, the same issue was experienced as with the positive cohort. A negative cohort in which first-degree relatives could not have any type of cancer, and second-degree relatives could not have prostate, breast or ovarian cancer was created. Ideally, the negative cohort should not contain any participant with relatives affected by PCa or cancers associated with HBOC or LS. This approach increases the likelihood of including participants whose relatives might only have sporadic, non-hereditary malignancies. At the same time, it allows us to focus on variants potentially associated specifically with PCa, rather than with other types of cancer.

Difficulties were also encountered when handling RALP and PROMIC datasets. First, the RALP questionnaire had blank spaces to indicate whether the participant’s relative had cancer and, if so, which type. In many cases, these spaces were left empty, raising the question of whether the relative had no cancer or if the participant simply didn’t know about it. Additionally, in many cases, the participant was unsure about the cancer type and wrote a "?" or "joku" instead. For the inclusion of PROMIC participants, the data was obtained already in an Excel table, and only the following cancers were specifically added: prostate, breast, ovarian, large intestine, rectal, bowel, colon, and bladder cancer. This limited the ability to include a broader range of hereditary cancers, but it was sufficient for our criteria. Another challenge with PROMIC data was that it did not specify the number of children, brothers, sisters, uncles, or aunts who had a specific type of cancer. This introduces the possibility that a participant who had two second-degree relatives of the same kind diagnosed with PCa might be counted as only one, potentially excluding them for analysis. On the other hand, including any age at onset threshold in the criteria was difficult because information about the relative's time of diagnosis was missing in many cases in the RALP questionnaires. Additionally, the PROMIC dataset participants did not incorporate the time of diagnosis for any of the relatives.

Questionnaires should include a blank space to allow participants to specify which cancer(s) their relatives have, rather than narrowing the types of cancers asked about. This would also enable the inclusion of information about more than one relative of the same type who may have cancer. If a relative does not have cancer, the participant should clearly state either that the relative does not have cancer or that he does not know, to avoid misinterpretation. Moreover, age at the onset of the disease in relatives should always be asked to enable the use of this information in more strict criteria. Nevertheless, this kind of patient-reported dataset relies on the participant's knowledge of their family's medical history and his memory. Using hospital databases and electronic health records would offer a more accurate approach to ensure the family history of this patients (Chang et al., 2006; Mai et al., 2011; Augustinsson et al., 2018).

4.6.3 Family based study

One problem assessing the families was that the clinical information in the pedigrees was sometimes outdated. To ensure that all participants were at least 50 years old at the time of the last update, we had to exclude several individuals who were under 50 at that time, even though they would now meet the age criteria. This probably reduced the sample size, diminishing the signal of possible associations. Moreover, there is a possibility that patients who were healthy at the time of the last update may have developed PCa since then, which could also impact the results of the analysis.

Hereditary cancer syndromes are strongly associated with HPCa (Dominguez-Valentin et al., 2020; Curtius et al., 2022; Minoura et al., 2022). The inclusion of women in the family-based study could have helped to find association between the variants and HPCa, since same germline variants can predispose to different types of cancer, such as both breast and PCa (Barnes et al., 2022). In future studies, women could be added into the analysis and classify them as affected if they have HBOC- and LS-related cancers diagnosed at an early age at onset, considering the inheritance pattern of cancers in the family. This approach would allow pinpoint variants that are associated with HPCa, HBOC and LS.

4.6.4 Cohort study

When comparing our positive cohort to the general Finnish population (FinnGen) and to PCa cases from a Finnish GWAS (FinnGen), only the allele frequency was available for the selected variants. For the general Finnish population, the number of homozygous individuals for each variant was also provided. Based on this, the carrier frequency in the general Finnish population was calculated using the allele frequency and the number of homozygotes. To estimate the carrier frequency among the PCa cases from the Finnish GWAS, Hardy-Weinberg equilibrium (HWE) was assumed, because genotype counts were not available in FinnGen. However, assuming HWE may overestimate the number of homozygotes, since deleterious alleles are typically under negative selection and are less frequent than expected under HWE. Additionally, rare variants, such as the ones studied here, may show greater deviation from HWE due to factors like population structure (Wang & Shete, 2012; Graffelman et al., 2017). In future studies, access to genotype-level data in FinnGen Sandbox could allow direct assessment of genotype counts, avoiding reliance on HWE assumptions and improving the accuracy of carrier frequency comparisons between groups.

Regarding the negative cohort, only the *PASK* variant was genotyped due to limited resources. If the other four variants were genotyped in the negative cohort, an association between these variants and hereditary forms of PCa could have been assessed by comparing carrier and allele frequencies between PCa patients with family history of PCa and HBOC, and those without such a history. Moreover, this would have allowed us to examine the cumulative effect and synergy between these variants in PCa patients with family history of PCa and HBOC.

Although potential associations between the variants and clinicopathological characteristics of PCa were explored, the number of patients carrying each variant was very small. This limited the statistical power of our analysis, obtaining non-significant results. This issue could be addressed by increasing the sample size through collaborative effort between institutions or by using aggregation methods such as burden tests, which combine rare variants to evaluate their collective association with disease traits, particularly when the variants have similar predicted functional impacts (Lee et al., 2014).

4.7 Future prospects

The identification of *ZBTB46* rs34785134 and *LETM1* rs62623389 as potential variants associated with PCa through family-based and cohort studies, opens the opportunity to farther study the association of these variants with HPCa. To confirm the associations observed, replication in larger family-based studies is needed. As previously mentioned, these should include updated family data and consider factors such as cancer types in female family members, age at onset, and inheritance pattern of cancer in the family to when determining affected status. Moreover, larger cohort studies would also help to verify the results observed in this study by following the selection criteria established for HPCa families. Additionally, the association of these variants should be analyzed in different ethnic populations to confirm their effect in PCa risk, especially in groups with higher PCa prevalence and more aggressive forms, such as men of African ancestry (Tsodikov et al., 2017; Siegel et al., 2022; Soh et al., 2023). However, predisposing germline variants can be more prevalent or exclusive to different populations, partially explaining geographical differences in PCa incidence (Chang et al., 2011; Haiman et al., 2011; Cook et al., 2014; Heidegger et al., 2019). Thus, these variants might be population-specific, and their importance could vary between populations depending on ancestral background.

If similar results are observed in larger family-based studies and cohorts, these variants could be investigated further in functional studies to explore their biological mechanisms and roles in cancer development, progression, and resistance. Recent methods, such as CRISPR-based functional assays, can assess variant pathogenicity, cell mechanisms in disease, and drug responsiveness or resistance in both in vivo and in vitro studies (Shifrut et al., 2018; Niu et al., 2022). These gene-editing approaches can be used not only to study coding variants but also to investigate the effects of non-coding variants. Techniques such as CRISPR-interference (CRISPRi) and CRISPR-activation (CRISPRa) allow the examination of the association between regulatory elements and disease (Qi et al., 2013; Bikar et al., 2013; Cano-Gamez & Trynka, 2020). In addition, when working with GWAS results, these findings can be integrated with functional genomics data to identify the tissues and cell types where the variants have their effect. This is done by analyzing the accumulation of variants in cell-specific regulatory elements (Cano-Gamez & Trynka, 2020). Furthermore, colocalization analysis allows the comparison of GWAS results with expression Quantitative Trait Loci (eQTL) data to examine whether a genetic variant drives both disease association and changes in gene expression (Cano-Gamez & Trynka, 2020). Understanding how these variants contribute to the disease could help identify new treatment targets for PCa.

The confirmation of these variants as novel predisposing markers could contribute to the improvement of germline testing panels. More comprehensive and accurate panels could improve the identification of individuals at high risk, principally those ones with an unclear family history or uncommon clinical presentations (Russo & Giri, 2022). Moreover, if a predisposing germline variant is detected in the patient, cascade testing or further testing in the family should be conducted, potentially benefiting other family members (Giri et al., 2019). Increasing knowledge about predisposing variants also supports early detection and risk assessment. Combining germline variants with biochemical markers has been proved to improve PCa early detection, treatment efficacy and survival rates (Grossman et al., 2018). For instance, targeted PSA levels testing on men carrying *BRCA1*/2 mutations has been demonstrated better identification of aggressive PCa (Bancroft et al., 2014). Incorporating a genetic profile into PCa detection strategies also reduces unnecessary invasive procedures and decreases the number of missed cases that would otherwise go undetected due to low PSA levels (Grönberg et al., 2015). Additionally, implementing germline variant profiles alongside the patient's family history enables the development of risk models for targeted early-detection strategies in high-risk populations (Choi et al., 2020).

If these novel PCa variants are confirmed to be biologically and clinically relevant, their study can also be beneficial for developing new therapeutic strategies and allowing physicians to offer more precise, effective, and individualized care to patients. Certain therapies benefit from the vulnerabilities of tumors caused by germline mutations in the individual. For instance, patients with mutations in DNA repair pathways, such as *BRCA1*, *BRCA2*, or *ATM*, can benefit from targeted therapies like PARP inhibitors (PARPi) and checkpoint inhibitors (Mateo et al., 2019). Moreover, carriers of variants involved in androgen receptor (AR) signaling can benefit from treatment strategies that block AR function or biosynthesis, helping reduce the tumor's androgen dependence and preventing resistance to androgen deprivation therapy (Lunn et al., 1999; Yamada et al., 2001; Hearn et al., 2016; Coutinho et al., 2016; Reiss et al., 2024). Furthermore, certain variants are associated with radiation toxicity and radio-resistance, so integrating genetic profiles into radiotoxicity can help to optimize radiation doses and minimize unwanted side effects (Kerns et al., 2016; Sanchez et al., 2016). Expanding our knowledge of variants that predispose individual to PCa can enhance genetic predisposition assessment, enable earlier detection, improve risk prediction, personalize treatment strategies, and predict disease progression and prognosis.

4.8 Conclusions

The purpose of this study was to identify novel PCa predisposing variants doing a variant selection from Finnish high-risk HPCa families and analyze them through a combination of family-based and cohort studies to help elucidate part of the missing heritability of the disease. The analyzed variants in this study are located in genes previously implicated with PCa, but no variants in these genes have been directly associated with PCa or any other type of cancer.

The family-based study included a GLMM to assess the association between the variant and PCa accounting for within-family correlations, incorporating family as a random effect to correct for family structure, and FBAT to examine whether genetic variants are transmitted to PCa family members more often than expected by chance, testing for both linkage and association by using any pedigree structure, such as extended pedigrees, multiple siblings, or missing parental data. The GLMM results indicated a statistically significant association between *ZBTB46* rs34785134 and *LETM1* rs62623389 variants and PCa. Moreover, the FBAT demonstrated a statistically significant association between *ZBTB46* rs34785134 and PCa in the "absence of linkage", assuming transmissions within nuclear families as independent and suggested a potential association between *LETM1* rs62623389 variant and PCa in the "presence of linkage", adjusting for potential within-family correlations, such as those arising from potential linkage .

In the cohort study, a cohort of PCa patients with family history of PCa and HBOC was compared against a general Finnish population, PCa cases in from a Finnish GWAS, and another cohort PCa patients without family history of PCa and HBOC. Among the analyzed variants, the carrier frequency of the *ZBTB46* rs34785134 and *PASK* rs35129131 was higher in the positive cohort than in both the general Finnish population and the PCa cases in from a Finnish GWAS. However, only the *PASK* rs35129131 variant showed a statistically significant increase in frequency against the general Finnish population. Additionally, the carrier frequency of *PASK* rs35129131 was statistically significantly more than twice as high in PCa patients with a family history of PCa and HBOC compared to those without such a family history, indicating an association with hereditary susceptibility to PCa. On the other hand, no significant associations were found between any of the studied variants and clinicopathological characteristics of the disease such as age at diagnosis, PSA levels, biopsy Gleason score, or TNM staging.

The findings in this study provide the first known evidence supporting a potential association between *ZBTB46* rs34785134 and *PASK* rs35129131 variants, and PCa, particularly in individuals with a strong family history of PCa and HBOC-related cancers. While further functional studies and replication in larger cohorts are necessary, these results highlight the importance of combining family-based and population-based approaches to detect rare variants. Overall, this study shows the value of using data from genetically isolated populations and detailed family histories to find new genetic risk factors for complex diseases like PCa.

5. ACKNOWLEDGEMENTS

I wanted to thank Johanna Schleutker for the opportunity to conduct my master's thesis in the Genetic Cancer Predisposition group and for valuable guidance during this process. I also would like to thank Gudrun Walhström for her dedicated support in this thesis, especially for the time she spent reviewing every detail of this thesis to ensure scientific accuracy. Moreover, I wanted to thank Tero Klemola for all the help and suggestions provided for the statistical analysis in this thesis. I would also like to thank Päivi Onkamo from the Faculty of Biology for her support during this thesis.

In addition, I wanted to thank all the members of Genetic Cancer Predisposition group, who have helped in one way or another during my time with this group. Finally, I wanted to thank my family and friends for the support during this thesis, especially to my wife Marie. Without her encouragement, I would not have chosen to pursue this field of study and certainly would not be writing this thesis today.

ABBREVIATION LIST

ABI3	ABI Family Member 3
ADT	Androgen Deprivation Therapy
ANO7	Anoctamin 7
AR	Androgen Receptors
ASR	Age-Standardized incidence Rate
ATM	Ataxia Telangiectasia Mutated (ATM Serine/Threonine Kinase)
AURKA	Aurora Kinase A
BER	Base Excision Repair
BMI	Body Mass Index
BRCA1	Breast Cancer Gene 1
BRCA2	Breast Cancer Gene 2
BRP1	BRCA1 Interacting Protein 1
CADD	Comboned Annotation Dependent Depletion
CDH1	Cadherin 1
CDK5RAP3	CDK5 Regulatory Subunit Associated Protein 3
CEBPB	CCAAT Enhancer Binding Protein Beta
CHEK2	Checkpoint Kinase 2
CNA	Copy Number Alterations
CNV	Copy Number Variants
CRPC	Castration-Resistant Prostate Cancer
CT	Computed Tomography
DCEI	Dynamic Contrast-Enhanced Image
DDR	DNA Damage Repair
DNAH5	Dynein Axonemal Heavy Chain 5
DWI	Diffusion-Weighted Image

EDTA	Ethylenediaminetetraacetic acid
EPCAM	Epithelial Cellular Adhsesion Molecule
eQTL	Expression Quantitative Trait Loci
ERBT	External Beam Radiation Therapy
ERSPC	European Randomized Study of Screening for Prostate Cancer
FANCA	Fanconi Anemia Complementation Group A
FBAT	Family-Based Association Testing
FDG	18F-Fludeoxyglucose
FDR	False Discovery Rate
FPC	Familial Prostate Cancer
GBD	Global Burden of Disease
GLMM	Generalized Linear Mixed Model
GWAS	Genome-Wide Association Studies
CYP17	Cytochrome P450 Family 17
HBOC	Hereditary Breast and Ovarian Cancer
HBOX13	Homeobox B13
HGPIN	High-Grade Prostatic Intraepithelial Neoplasia
HPCa	Hereditary prostate cancer
HR	Homologous recombination
HSD3B1	Hydroxy-Delta-5-Steroid Dehydrogenase, 3 Beta- And Steroid Delta-Isomerase 1
HWE	Hardy-Weinber Equilibrium
IARC	Internation Agency for Research on Cancer
IDC-P	Intraductal Carcinoma of the Prostate
IQGAP2 IQ	IQ Motif-Containing GTPase Activating Protein 2
ISUP	International Society of Urological Pathology
KDM3B	Histone Lysine Demethylase 3B

LAMC2	Laminin Subunit Gamma 2
LETM1	Leucine Zipper-EF-Hand Containing Transmembrane Protein 1
LS	Lynch Syndrome
LVI	LymphoVascular Invasion
MAF	Minor Allele Frequency
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MHL1	MutL Homolog 1
MSH2	MutS Homolog 2
MSH6	MutS Homolog 6
MMR	DNA Mismatch Repair
mPCa	Metastatic Prostate Cancer
mpMRI	Multiparametric Magnetic Resonance Imaging
NER	Nucleotide excision repair
NHEJ	Non-Homologous End Joining
MRI	Magnetic Resonance Imaging
MSI-H	Microsatellite Instability High
NBN	Nibrin
NCCN	National Comprehensive Cancer Network
NTC	No-Template Control
OR	Odds Ratio
P3H2	Prolyl 3-hydroxylase 2
PALB2	Partner And Localizer Of BRCA2
PARPi	Poly (Adenosine diphosphate-Ribose) Polymerase inhibitors
PASK	PAS Domain Containing Serine/Threonine Kinase
PCR	Polymerase Chain Reaction
PET	Positron Emission Tomography
PMS2	PostMeiotic Segregation increased 2

PIN	Prostatic Intraepithelial Neoplasia
PCa	Prostate Cancer
PRS	Polygenic Risk Score
PREX1	Phosphatidylinositol-3,4,5-trisphosphate Dependent Rac Exchange Factor 1
PSA	Prostate-Specific Antigen
PSMA	68Ga-Prostate-Specific Membrane Antigen
PTEN	Phosphatase and Tensin homolog
RAD51	RAD51 Recombinase
RAD51D	RAD51 Paralog D
RAD54B	RAD54 Homolog B
RAD54L	RAD54 Like
RARP	Robot-Assisted Radical Prostatectomy
REVEL	Rare Exome Variant Ensemble Learner
RP	Radical Prostatectomy
RR	Relative Risk
RT-PCR	Real-Time Polymerase Chain Reaction
SNP	Single Nucleotide Polymorphism
SIRPB1	Signal-Regulatory Protein Beta-1
SNAI1	Snail Family Transcriptional Repressor 1
STK4	Serine/Threonine Kinase 4
T2WI	T2-Weigthed Image
t-NEPC	Treatment-related Neuroendocrine Prostatic Carcinoma
TACC3	Transforming Acidic Coiled-Coil Containing Protein 3
TASOR	Transcription Activation Suppressor
TP53	Tumor Protein 53
TP63	Tumor Protein 63

TPCC	Turku Prostate Cancer Consortium
VOI	Variant Of Interest
VUS	Variant of Uncertain Significance
VEP	Variant Effect Predictor
WES	Whole Genome Sequencing
WGS	Whole Genome Sequencing
WHO	World Health Organization
ZBTB46	Zinc Finger and BTB Domain-Containing Protein 46
ZKSCAN3	Zinc Finger With KRAB And SCAN Domains 3
ZNF391	Zinc Finger Protein 391

REFERENCES

Abida W, Armenia J, Gopalan A, Brennan R, Walsh M, Barron D, Danila D, Rathkopf D, Morris M, Slovin S, McLaughlin B, Curtis K, Hyman DM, Durack JC, Solomon SB, Arcila ME, Zehir A, Syed A, Gao J, Chakravarty D, Vargas HA, Robson ME, Joseph V, Offit K, Donoghue MTA, Abeshouse AA, Kundra R, Heins ZJ, Penson AV, Harris C, Taylor BS, Ladanyi M, Mandelker D, Zhang L, Reuter VE, Kantoff PW, Solit DB, Berger MF, Sawyers CL, Schultz N, Scher HI. (2017) Prospective Genomic Profiling of Prostate Cancer Across Disease States Reveals Germline and Somatic Alterations That May Affect Clinical Decision Making. *JCO Precis Oncol*. Jul;2017:PO.17.00029. doi: 10.1200/PO.17.00029.

Abida W, Cheng ML, Armenia J, Middha S, Autio KA, Vargas HA, Rathkopf D, Morris MJ, Danila DC, Slovin SF, Carbone E, Barnett ES, Hullings M, Hechtman JF, Zehir A, Shia J, Jonsson P, Stadler ZK, Srinivasan P, Laudone VP, Reuter V, Wolchok JD, Socci ND, Taylor BS, Berger MF, Kantoff PW, Sawyers CL, Schultz N, Solit DB, Gopalan A, Scher HI. (2019) Analysis of the Prevalence of Microsatellite Instability in Prostate Cancer and Response to Immune Checkpoint Blockade. *JAMA Oncol*. Apr 1;5 (4):471–478. doi: 10.1001/jamaoncol.2018.5801.

Adank MA, Verhoef S, Oldenburg RA, Schmidt MK, Hooning MJ, Martens JW, Broeks A, Rookus M, Waisfisz Q, Witte BI, Jonker MA, Meijers-Heijboer H. (2013) Excess breast cancer risk in first degree relatives of CHEK2∗1100delC positive familial breast cancer cases. *Eur J Cancer*. May;49 (8):1993–9. doi: 10.1016/j.ejca.2013.01.009.

Agrawal V, Ma X, Hu JC, Barbieri CE, Nagar H. (2020) Trends in Diagnosis and Disparities in Initial Management of High-Risk Prostate Cancer in the US. *JAMA Netw Open*. Aug 3;3 (8):e2014674. doi: 10.1001/jamanetworkopen.2020.14674.

Akbari MR, Wallis CJ, Toi A, Trachtenberg J, Sun P, Narod SA, Nam RK. (2014) The impact of a BRCA2 mutation on mortality from screen-detected prostate cancer. *Br J Cancer*. Sep 9;111 (6):1238–40. doi: 10.1038/bjc.2014.428.

Alizadeh M, Alizadeh S. (2014) Survey of clinical and pathological characteristics and outcomes of patients with prostate cancer. *Glob J Health Sci.* Sep 18;6 (7 Spec No):49–57. doi: 10.5539/gjhs.v6n7p49.

Al Olama AA, Kote-Jarai Z, Berndt SI, Conti DV, Schumacher F, Han Y, Benlloch S, Hazelett DJ, Wang Z, Saunders E, Leongamornlert D, Lindstrom S, Jugurnauth-Little S, Dadaev T, Tymrakiewicz M, Stram DO, Rand K, Wan P, Stram A, Sheng X, Pooler LC, Park K, Xia L, Tyrer J, Kolonel LN, Le Marchand L, Hoover RN, Machiela MJ, Yeager M, Burdette L, Chung CC, Hutchinson A, Yu K, Goh C, Ahmed M, Govindasami K, Guy M, Tammela TL, Auvinen A, Wahlfors T, Schleutker J, Visakorpi T, Leinonen KA, Xu J, Aly M, Donovan J, Travis RC, Key TJ, Siddiq A, Canzian F, Khaw KT, Takahashi A, Kubo M, Pharoah P, Pashayan N, Weischer M, Nordestgaard BG, Nielsen SF, Klarskov P, Røder MA, Iversen P, Thibodeau SN, McDonnell SK, Schaid DJ, Stanford JL, Kolb S, Holt S, Knudsen B, Coll AH, Gapstur SM, Diver WR, Stevens VL, Maier C, Luedeke M, Herkommer K, Rinckleb AE, Strom SS, Pettaway C, Yeboah ED, Tettey Y, Biritwum RB, Adjei AA, Tay E, Truelove A, Niwa S, Chokkalingam AP, Cannon-Albright L, Cybulski C, Wokołorczyk D, Kluźniak W, Park J, Sellers T, Lin HY, Isaacs WB, Partin AW, Brenner H, Dieffenbach AK, Stegmaier C, Chen C, Giovannucci EL, Ma J, Stampfer M, Penney KL, Mucci L, John EM, Ingles SA, Kittles RA, Murphy AB, Pandha H, Michael A, Kierzek AM, Blot W, Signorello LB, Zheng W, Albanes D, Virtamo J, Weinstein S, Nemesure B, Carpten J, Leske C, Wu SY, Hennis A, Kibel AS, Rybicki BA, Neslund-Dudas C, Hsing AW, Chu L, Goodman PJ, Klein EA, Zheng SL, Batra J, Clements J, Spurdle A, Teixeira MR, Paulo P, Maia S, Slavov C, Kaneva R, Mitev V, Witte JS, Casey G, Gillanders EM, Seminara D, Riboli E, Hamdy FC, Coetzee GA, Li Q, Freedman ML, Hunter DJ, Muir K, Gronberg H, Neal DE, Southey M, Giles GG, Severi G; Breast and Prostate Cancer Cohort Consortium (BPC3); PRACTICAL (Prostate Cancer Association Group to Investigate Cancer-Associated Alterations in the Genome) Consortium; COGS (Collaborative Oncological Gene-environment Study) Consortium; GAME-ON/ELLIPSE Consortium; Cook MB, Nakagawa H, Wiklund F, Kraft P, Chanock SJ, Henderson BE, Easton DF, Eeles RA, Haiman CA. (2014) A meta-analysis of 87,040 individuals identifies 23 new susceptibility loci for prostate cancer. *Nat Genet*. Oct;46 (10):1103–9. doi: 10.1038/ng.3094.

Amorino GP, Parsons SJ. (2004) Neuroendocrine cells in prostate cancer. *Crit Rev Eukaryot Gene Expr*.14 (4):287–300. doi: 10.1615/critreveukaryotgeneexpr.v14.i4.40.

Amundadottir LT, Sulem P, Gudmundsson J, Helgason A, Baker A, Agnarsson BA, Sigurdsson A, Benediktsdottir KR, Cazier JB, Sainz J, Jakobsdottir M, Kostic J, Magnusdottir DN, Ghosh S, Agnarsson K, Birgisdottir B, Le Roux L, Olafsdottir A, Blondal T, Andresdottir M, Gretarsdottir OS, Bergthorsson JT, Gudbjartsson D, Gylfason A, Thorleifsson G, Manolescu A, Kristjansson K, Geirsson G, Isaksson H, Douglas J, Johansson JE, Bälter K, Wiklund F, Montie JE, Yu X, Suarez BK, Ober C, Cooney KA, Gronberg H, Catalona WJ, Einarsson GV, Barkardottir RB, Gulcher JR, Kong A, Thorsteinsdottir U, Stefansson K. (2006) A common variant associated with prostate cancer in European and African populations. *Nat Genet.* Jun;38 (6):652–8. doi: 10.1038/ng1808.

Ahn J, Berndt SI, Wacholder S, Kraft P, Kibel AS, Yeager M, Albanes D, Giovannucci E, Stampfer MJ, Virtamo J, Thun MJ, Feigelson HS, Cancel-Tassin G, Cussenot O, Thomas G, Hunter DJ, Fraumeni JF Jr, Hoover RN, Chanock SJ, Hayes RB. (2008) Variation in KLK genes, prostate-specific antigen and risk of prostate cancer. *Nat Genet*. Sep;40(9):1032-4; author reply 1035–6. doi: 10.1038/ng0908-1032

Arbuznikova D, Klotsotyra A, Uhlmann L, Domogalla LC, Steinacker N, Mix M, Niedermann G, Spohn SKB, Freitag MT, Grosu AL, Meyer PT, Gratzke C, Eder M, Zamboglou C, Eder AC. (2024) Exploring the role of combined external beam radiotherapy and targeted radioligand therapy with [177Lu]Lu-PSMA-617 for prostate cancer from bench to bedside. *Theranostics*. Apr 8;14 (6):2560–2572. doi: 10.7150/thno.93249.

Augustinsson A, Ellberg C, Kristoffersson U, Borg Å, Olsson H. (2018) Accuracy of self-reported family history of cancer, mutation status and tumor characteristics in patients with early onset breast cancer. *Acta Oncol.* May;57(5):595–603. doi: 10.1080/0284186X.2017.1404635.

Bagheri A, Nachvak SM, Rezaei M, Moravridzade M, Moradi M, Nelson M. (2018) Dietary patterns and risk of prostate cancer: a factor analysis study in a sample of Iranian men. *Health Promot Perspect*. Apr 18;8 (2):133–138. doi: 10.15171/hpp.2018.17.

Baldessari C, Pipitone S, Molinaro E, Cerma K, Fanelli M, Nasso C, Oltrecolli M, Pirola M, D'Agostino E, Pugliese G, Cerri S, Vitale MG, Madeo B, Dominici M, Sabbatini R. (2023) Bone Metastases and Health in Prostate Cancer: From Pathophysiology to Clinical Implications. *Cancers (Basel).* Feb 28;15 (5):1518. doi: 10.3390/cancers15051518.

Bancroft EK, Page EC, Castro E, Lilja H, Vickers A, Sjoberg D, Assel M, Foster CS, Mitchell G, Drew K, Mæhle L, Axcrona K, Evans DG, Bulman B, Eccles D, McBride D, van Asperen C, Vasen H, Kiemeney LA, Ringelberg J, Cybulski C, Wokolorczyk D, Selkirk C, Hulick PJ, Bojesen A, Skytte AB, Lam J, Taylor L, Oldenburg R, Cremers R, Verhaegh G, van Zelst-Stams WA, Oosterwijk JC, Blanco I, Salinas M, Cook J, Rosario DJ, Buys S, Conner T, Ausems MG, Ong KR, Hoffman J, Domchek S, Powers J, Teixeira MR, Maia S, Foulkes WD, Taherian N, Ruijs M, Helderman-van den Enden AT, Izatt L, Davidson R, Adank MA, Walker L, Schmutzler R, Tucker K, Kirk J, Hodgson S, Harris M, Douglas F, Lindeman GJ, Zgajnar J, Tischkowitz M, Clowes VE, Susman R, Ramón y Cajal T, Patcher N, Gadea N, Spigelman A, van Os T, Liljegren A, Side L, Brewer C, Brady AF, Donaldson A, Stefansdottir V, Friedman E, Chen-Shtoyerman R, Amor DJ, Copakova L, Barwell J, Giri VN, Murthy V, Nicolai N, Teo SH, Greenhalgh L, Strom S, Henderson A, McGrath J, Gallagher D, Aaronson N, Ardern-Jones A, Bangma C, Dearnaley D, Costello P, Eyfjord J, Rothwell J, Falconer A, Gronberg H, Hamdy FC, Johannsson O, Khoo V, Kote-Jarai Z, Lubinski J, Axcrona U, Melia J, McKinley J, Mitra AV, Moynihan C, Rennert G, Suri M, Wilson P, Killick E; IMPACT Collaborators; Moss S, Eeles RA. (2014) Targeted prostate cancer screening in BRCA1 and BRCA2 mutation carriers: results from the initial screening round of the IMPACT study. *Eur Urol.* Sep;66 (3):489–99. doi: 10.1016/j.eururo.2014.01.003. Epub 2014 Jan 15. Erratum in: *Eur Urol.* 2015 Jun;67 (6):e126. doi: 10.1016/j.eururo.2014.12.001.

Banerjee PP, Banerjee S, Brown TR, Zirkin BR. (2018) Androgen action in prostate function and disease. *Am J Clin Exp Urol*. Apr 1;6 (2):62–77. PMID: 29666834; PMCID: PMC5902724.

Barnes DR, Silvestri V, Leslie G, McGuffog L, Dennis J, Yang X, Adlard J, Agnarsson BA, Ahmed M, Aittomäki K, Andrulis IL, Arason A, Arnold N, Auber B, Azzollini J, Balmaña J, Barkardottir RB, Barrowdale D, Barwell J, Belotti M, Benitez J, Berthet P, Boonen SE, Borg Å, Bozsik A, Brady AF, Brennan P, Brewer C, Brunet J, Bucalo A, Buys SS, Caldés T, Caligo MA, Campbell I, Cassingham H, Christensen LL, Cini G, Claes KBM; GEMO Study Collaborators; EMBRACE Collaborators; Cook J, Coppa A, Cortesi L, Damante G, Darder E, Davidson R, de la Hoya M, De Leeneer K, de Putter R, Del Valle J, Diez O, Ding YC, Domchek SM, Donaldson A, Eason J, Eeles R, Engel C, Evans DG, Feliubadaló L, Fostira F, Frone M, Frost D, Gallagher D, Gehrig A, Giraud S, Glendon G, Godwin AK, Goldgar DE, Greene MH, Gregory H, Gross E, Hahnen E, Hamann U, Hansen TVO, Hanson H, Hentschel J, Horvath J; KConFab Investigators; HEBON Investigators; Izatt L, Izquierdo A, James PA, Janavicius R, Jensen UB, Johannsson OT, John EM, Kramer G, Kroeldrup L, Kruse TA, Lautrup C, Lazaro C, Lesueur F, Lopez-Fernández A, Mai PL, Manoukian S, Matrai Z, Matricardi L, Maxwell KN, Mebirouk N, Meindl A, Montagna M, Monteiro AN, Morrison PJ, Muranen TA, Murray A, Nathanson KL, Neuhausen SL, Nevanlinna H, Nguyen-Dumont T, Niederacher D, Olah E, Olopade OI, Palli D, Parsons MT, Pedersen IS, Peissel B, Perez-Segura P, Peterlongo P, Petersen AH, Pinto P, Porteous ME, Pottinger C, Pujana MA, Radice P, Ramser J, Rantala J, Robson M, Rogers MT, Rønlund K, Rump A, Sánchez de Abajo AM, Shah PD, Sharif S, Side LE, Singer CF, Stadler Z, Steele L, Stoppa-Lyonnet D, Sutter C, Tan YY, Teixeira MR, Teulé A, Thull DL, Tischkowitz M, Toland AE, Tommasi S, Toss A, Trainer AH, Tripathi V, Valentini V, van Asperen CJ, Venturelli M, Viel A, Vijai J, Walker L, Wang-Gohrke S, Wappenschmidt B, Whaite A, Zanna I, Offit K, Thomassen M, Couch FJ, Schmutzler RK, Simard J, Easton DF, Chenevix-Trench G, Antoniou AC, Ottini L; Consortium of Investigators of Modifiers of BRCA1 and BRCA2. (2022) Breast and Prostate Cancer Risks for Male BRCA1 and BRCA2 Pathogenic Variant Carriers Using Polygenic Risk Scores. *J Natl Cancer Inst*. Jan 11;114(1):109–122. doi: 10.1093/jnci/djab147.

Barrow PJ, Ingham S, O'Hara C, Green K, McIntyre I, Lalloo F, Hill J, Evans DG. (2013) The spectrum of urological malignancy in Lynch syndrome. *Fam Cancer*. Mar;12 (1):57–63. doi: 10.1007/s10689-012-9573-z.

Bataba E, Babcock K, Isensee KA, Eldhose B, Kohaar I, Chesnut GT, Dobi A. (2024) Germline Mutations and Ancestry in Prostate Cancer. *Curr Oncol Rep*. Feb;26 (2):175–180.

Bates D, Mächler M, Bolker B, Walker S. (2015). Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*, 67(1), 1–48. https://doi.org/10.18637/jss.v067.i01

Bates AS, Kostakopoulos N, Ayers J, Jameson M, Todd J, Lukha R, Cymes W, Chasapi D, Brown N, Bhattacharya Y, Paterson C, Lam TBL. (2020) A Narrative Overview of Active Surveillance for Clinically Localised Prostate Cancer. *Semin Oncol Nurs*. Aug;36 (4):151045. doi: 10.1016/j.soncn.2020.151045.

Beebe-Dimmer JL, Kapron AL, Fraser AM, Smith KR, Cooney KA. (2020) Risk of Prostate Cancer Associated With Familial and Hereditary Cancer Syndromes. *J Clin Oncol*. Jun 1;38 (16):1807–1813. doi: 10.1200/JCO.19.02808.

Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, Iversen P, Bhattacharya S, Carles J, Chowdhury S, Davis ID, de Bono JS, Evans CP, Fizazi K, Joshua AM, Kim CS, Kimura G, Mainwaring P, Mansbach H, Miller K, Noonberg SB, Perabo F, Phung D, Saad F, Scher HI, Taplin ME, Venner PM, Tombal B; PREVAIL Investigators. (2014) Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med.* Jul 31;371 (5):424–33. doi: 10.1056/NEJMoa1405095. Epub 2014 Jun 1.

Beier AK, Puhr M, Stope MB, Thomas C, Erb HHH. (2023) Metabolic changes during prostate cancer development and progression. *J Cancer Res Clin Oncol*. May;149 (5):2259–2270. doi: 10.1007/s00432-022-04371-w.

Bell KJ, Del Mar C, Wright G, Dickinson J, Glasziou P. (2015) Prevalence of incidental prostate cancer: A systematic review of autopsy studies. *Int J Cancer*. Oct 1;137 (7):1749–57.

Berry R, Schroeder JJ, French AJ, McDonnell SK, Peterson BJ, Cunningham JM, Thibodeau SN, Schaid DJ. (2000) Evidence for a prostate cancer-susceptibility locus on chromosome 20. *Am J Hum Genet*. Jul;67(1):82–91. doi: 10.1086/302994.

Bikard D, Jiang W, Samai P, Hochschild A, Zhang F, Marraffini LA. (2013) Programmable repression and activation of bacterial gene expression using an engineered CRISPR-Cas system. *Nucleic Acids Res*. Aug;41(15):7429–37. doi: 10.1093/nar/gkt520.

Bittner N, Merrick G, Taira A, Bennett A, Schattel A, Butler W, Galbreath R, Adamovich E. (2018) Location and Grade of Prostate Cancer Diagnosed by Transperineal Template-guided Mapping Biopsy After Negative Transrectal Ultrasound-guided Biopsy. *Am J Clin Oncol*. Aug;41 (8):723–729. doi: 10.1097/COC.0000000000000352.

Bock CH, Cunningham JM, McDonnell SK, Schaid DJ, Peterson BJ, Pavlic RJ, Schroeder JJ, Klein J, French AJ, Marks A, Thibodeau SN, Lange EM, Cooney KA. (2001) Analysis of the prostate cancer-susceptibility locus HPC20 in 172 families affected by prostate cancer. *Am J Hum Genet*. Mar;68(3):795–801. doi: 10.1086/318797.

Boland CR, Lynch HT. (2013) The history of Lynch syndrome. *Fam Cancer*. Jun;12 (2):145–57. doi: 10.1007/s10689-013-9637-8.

Boonen RACM, Vreeswijk MPG, van Attikum H. (2022) CHEK2 variants: linking functional impact to cancer risk. *Trends Cancer*. Sep;8 (9):759–770. doi: 10.1016/j.trecan.2022.04.009.

Brandt A, Sundquist J, Hemminki K. (2012) Risk for incident and fatal prostate cancer in men with a family history of any incident and fatal cancer. *Ann Oncol.* Jan;23(1):251–256. doi: 10.1093/annonc/mdr056

Bray F, Colombet M, Aitken JF, Bardot A, Eser S, Galceran J, Hagenimana M, Matsuda T, Mery L, Piñeros M, Soerjomataram I, de Vries E, Wiggins C, Won Y-J, Znaor A, Ferlay J, editors (2023). Cancer Incidence in Five Continents, Vol. XII (IARC CancerBase No. 19). Lyon: International Agency for Research on Cancer. https://ci5.iarc.who.int [Read 17.10.2024]

Breyer JP, Avritt TG, McReynolds KM, Dupont WD, Smith JR. (2012) Confirmation of the HOXB13 G84E germline mutation in familial prostate cancer. *Cancer Epidemiol Biomarkers Prev*. Aug;21 (8):1348–53. doi: 10.1158/1055-9965.EPI-12-0495.

Brinster R, Köttgen A, Tayo BO, Schumacher M, Sekula P; CKDGen Consortium. (2018) Control procedures and estimators of the false discovery rate and their application in low-dimensional settings: an empirical investigation. *BMC Bioinformatics*. Mar 2;19(1):78. doi: 10.1186/s12859-018-2081-x.

Brzyski D, Peterson CB, Sobczyk P, Candès EJ, Bogdan M, Sabatti C. (2017) Controlling the Rate of GWAS False Discoveries. *Genetics*. Jan;205(1):61–75. doi: 10.1534/genetics.116.193987.

Bui VM, Mettling C, Jou J, Sun HS. (2020) Genomic amplification of chromosome 20q13.33 is the early biomarker for the development of sporadic colorectal carcinoma. *BMC Med Genomics*. Oct 22;13(Suppl 10):149. doi: 10.1186/s12920-020-00776-z.

Bush WS, Haines J. (2010) Overview of linkage analysis in complex traits. *Curr Protoc Hum Genet*. Jan;Chapter 1:Unit 1.9.1–18. doi: 10.1002/0471142905.hg0109s64

Candi E, Agostini M, Melino G, Bernassola F. (2014) How the TP53 family proteins TP63 and TP73 contribute to tumorigenesis: regulators and effectors. *Hum Mutat*. Jun;35(6):702–14. doi: 10.1002/humu.22523.

Cano-Gamez E, Trynka G. (2020) From GWAS to Function: Using Functional Genomics to Identify the Mechanisms Underlying Complex Diseases. *Front Genet.* May 13;11:424. doi: 10.3389/fgene.2020.00424.

Cardon CM, Beck T, Hall MN, Rutter J. (2012) PAS kinase promotes cell survival and growth through activation of Rho1. *Sci Signal*. Jan 31;5(209):ra9. doi: 10.1126/scisignal.2002435.

Cardon CM, Rutter J. (2012) PAS kinase: integrating nutrient sensing with nutrient partitioning. *Semin Cell Dev Biol.* Aug;23(6):626–30. doi: 10.1016/j.semcdb.2011.12.007.

Carter BS, Beaty TH, Steinberg GD, Childs B, Walsh PC. (1992) Mendelian inheritance of familial prostate cancer. *Proc Natl Acad Sci U S A*. Apr 15;89 (8):3367–71. doi: 10.1073/pnas.89.8.3367.

Carter BS, Bova GS, Beaty TH, Steinberg GD, Childs B, Isaacs WB, Walsh PC. (1993) Hereditary prostate cancer: epidemiologic and clinical features. *J Urol*. Sep;150 (3):797–802. doi: 10.1016/s0022-5347 (17)35617-3.

Castro P, Creighton CJ, Ozen M, Berel D, Mims MP, Ittmann M. (2009) Genomic profiling of prostate cancers from African American men. *Neoplasia*. Mar;11(3):305–12. doi: 10.1593/neo.81530.

Castro E, Goh C, Olmos D, Saunders E, Leongamornlert D, Tymrakiewicz M, Mahmud N, Dadaev T, Govindasami K, Guy M, Sawyer E, Wilkinson R, Ardern-Jones A, Ellis S, Frost D, Peock S, Evans DG, Tischkowitz M, Cole T, Davidson R, Eccles D, Brewer C, Douglas F, Porteous ME, Donaldson A, Dorkins H, Izatt L, Cook J, Hodgson S, Kennedy MJ, Side LE, Eason J, Murray A, Antoniou AC, Easton DF, Kote-Jarai Z, Eeles R. (2013) Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J Clin Oncol*. May 10;31 (14):1748–57. doi: 10.1200/JCO.2012.43.1882. Epub 2013 Apr 8.

Castro E, Goh C, Leongamornlert D, Saunders E, Tymrakiewicz M, Dadaev T, Govindasami K, Guy M, Ellis S, Frost D, Bancroft E, Cole T, Tischkowitz M, Kennedy MJ, Eason

J, Brewer C, Evans DG, Davidson R, Eccles D, Porteous ME, Douglas F, Adlard J, Donaldson A, Antoniou AC, Kote-Jarai Z, Easton DF, Olmos D, Eeles R. (2015a) Effect of BRCA Mutations on Metastatic Relapse and Cause-specific Survival After Radical Treatment for Localised Prostate Cancer. *Eur Urol.* Aug;68 (2):186–93. doi: 10.1016/j.eururo.2014.10.022.

Castro E, Jugurnauth-Little S, Karlsson Q, Al-Shahrour F, Piñeiro-Yañez E, Van de Poll F, Leongamornlert D, Dadaev T, Govindasami K, Guy M, Eeles R, Kote-Jarai Z; UKGPCS, EMBRACE and IMPACT studies. (2015b) High burden of copy number alterations and c-MYC amplification in prostate cancer from BRCA2 germline mutation carriers. *Ann Oncol*. Nov;26 (11):2293–300.

Cave DD, Buonaiuto S, Sainz B Jr, Fantuz M, Mangini M, Carrer A, Di Domenico A, Iavazzo TT, Andolfi G, Cortina C, Sevillano M, Heeschen C, Colonna V, Corona M, Cucciardi A, Di Guida M, Batlle E, De Luca A, Lonardo E. (2022) LAMC2 marks a tumor-initiating cell population with an aggressive signature in pancreatic cancer. *J Exp Clin Cancer Res.* Oct 26;41 (1):315. doi: 10.1186/s13046-022-02516-w.

Chang ET, Smedby KE, Hjalgrim H, Glimelius B, Adami HO. (2006) Reliability of self-reported family history of cancer in a large case-control study of lymphoma. *J Natl Cancer Inst*. Jan 4;98(1):61–8. doi: 10.1093/jnci/djj005.

Chang BL, Spangler E, Gallagher S, Haiman CA, Henderson B, Isaacs W, Benford ML, Kidd LR, Cooney K, Strom S, Ingles SA, Stern MC, Corral R, Joshi AD, Xu J, Giri VN, Rybicki B, Neslund-Dudas C, Kibel AS, Thompson IM, Leach RJ, Ostrander EA, Stanford JL, Witte J, Casey G, Eeles R, Hsing AW, Chanock S, Hu JJ, John EM, Park J, Stefflova K, Zeigler-Johnson C, Rebbeck TR. (2011) Validation of genome-wide prostate cancer associations in men of African descent. *Cancer Epidemiol Biomarkers Prev*. Jan;20 (1):23–32. doi: 10.1158/1055-9965.EPI-10-0698.

Chen YC, Page JH, Chen R, Giovannucci E. (2008) Family history of prostate and breast cancer and the risk of prostate cancer in the PSA era. *Prostate*. Oct 1;68(14):1582–91. doi: 10.1002/pros.20825

Chen Z, Wang L, Wang Q, Li W. (2010) Histone modifications and chromatin organization in prostate cancer. *Epigenomics*. Aug;2 (4):551–60. doi: 10.2217/epi.10.31.

Chen WY, Tsai YC, Siu MK, Yeh HL, Chen CL, Yin JJ, Huang J, Liu YN. (2017) Inhibition of the androgen receptor induces a novel tumor promoter, ZBTB46, for prostate cancer metastasis. *Oncogene*. Nov 9;36 (45):6213–6224. doi: 10.1038/onc.2017.226.

Chen F, Madduri RK, Rodriguez AA, Darst BF, Chou A, Sheng X, Wang A, Shen J, Saunders EJ, Rhie SK, Bensen JT, Ingles SA, Kittles RA, Strom SS, Rybicki BA, Nemesure B, Isaacs WB, Stanford JL, Zheng W, Sanderson M, John EM, Park JY, Xu J, Wang Y, Berndt SI, Huff CD, Yeboah ED, Tettey Y, Lachance J, Tang W, Rentsch CT, Cho K, Mcmahon BH, Biritwum RB, Adjei AA, Tay E, Truelove A, Niwa S, Sellers TA, Yamoah K, Murphy AB, Crawford DC, Patel AV, Bush WS, Aldrich MC, Cussenot O, Petrovics G, Cullen J, Neslund-Dudas CM, Stern MC, Kote-Jarai Z, Govindasami K, Cook MB, Chokkalingam AP, Hsing AW, Goodman PJ, Hoffmann TJ, Drake BF, Hu JJ, Keaton JM, Hellwege JN, Clark PE, Jalloh M, Gueye SM, Niang L, Ogunbiyi O, Idowu MO, Popoola O, Adebiyi AO, Aisuodionoe-Shadrach OI, Ajibola HO, Jamda MA, Oluwole OP, Nwegbu M, Adusei B, Mante S, Darkwa-Abrahams A, Mensah JE, Diop H, Van Den Eeden SK, Blanchet P, Fowke JH, Casey G, Hennis AJ, Lubwama A, Thompson IM Jr, Leach R, Easton DF, Preuss MH, Loos RJ, Gundell SM, Wan P, Mohler JL, Fontham ET, Smith GJ, Taylor JA, Srivastava S, Eeles RA, Carpten JD, Kibel AS, Multigner L, Parent MÉ, Menegaux F, Cancel-Tassin G, Klein EA, Andrews C, Rebbeck TR, Brureau L, Ambs S, Edwards TL, Watya S, Chanock SJ, Witte JS, Blot WJ, Michael Gaziano J, Justice AC, Conti DV, Haiman CA. (2023) Evidence of Novel Susceptibility Variants for Prostate Cancer and a Multiancestry Polygenic Risk Score Associated with Aggressive Disease in Men of African Ancestry. *Eur Urol*. Jul;84(1):13–21. doi: 10.1016/j.eururo.2023.01.022.

Cheng I, Plummer SJ, Neslund-Dudas C, Klein EA, Casey G, Rybicki BA, Witte JS. (2010). Prostate cancer susceptibility variants confer increased risk of disease progression. *Cancer Epidemiol Biomarkers Prev.* Sep;19(9):2124–32. doi: 10.1158/1055-9965.EPI-10-0268.

Choi SW, Mak TS, O'Reilly PF. (2020) Tutorial: a guide to performing polygenic risk score analyses. *Nat Protoc*. Sep;15 (9):2759–2772.

Christensen GB, Baffoe-Bonnie AB, George A, Powell I, Bailey-Wilson JE, Carpten JD, Giles GG, Hopper JL, Severi G, English DR, Foulkes WD, Maehle L, Moller P, Eeles R, Easton D, Badzioch MD, Whittemore AS, Oakley-Girvan I, Hsieh CL, Dimitrov L, Xu

J, Stanford JL, Johanneson B, Deutsch K, McIntosh L, Ostrander EA, Wiley KE, Isaacs SD, Walsh PC, Isaacs WB, Thibodeau SN, McDonnell SK, Hebbring S, Schaid DJ, Lange EM, Cooney KA, Tammela TL, Schleutker J, Paiss T, Maier C, Grönberg H, Wiklund F, Emanuelsson M, Farnham JM, Cannon-Albright LA, Camp NJ; International Consortium for Prostate Cancer Genetics. (2010) Genome-wide linkage analysis of 1,233 prostate cancer pedigrees from the International Consortium for Prostate Cancer Genetics using novel sumLINK and sumLOD analyses. *Prostate*. May 15;70(7):735–44. doi: 10.1002/pros.21106.

Coates PJ, Nenutil R, Holcakova J, Nekulova M, Podhorec J, Svoboda M, Vojtesek B. (2018) p63 isoforms in triple-negative breast cancer: ΔNp63 associates with the basal phenotype whereas TAp63 associates with androgen receptor, lack of BRCA mutation, PTEN and improved survival. *Virchows Arch*. Mar; 472 (3):351–359. doi: 10.1007/s00428-018-2324-2.

Coleman R, Hadji P, Body JJ, Santini D, Chow E, Terpos E, Oudard S, Bruland Ø, Flamen P, Kurth A, Van Poznak C, Aapro M, Jordan K; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. (2020) Bone health in cancer: ESMO Clinical Practice Guidelines. *Ann Oncol*. Dec; 31 (12):1650–1663. doi: 10.1016/j.annonc.2020.07.019.

Cook MB, Wang Z, Yeboah ED, Tettey Y, Biritwum RB, Adjei AA, Tay E, Truelove A, Niwa S, Chung CC, Chokkalingam AP, Chu LW, Yeager M, Hutchinson A, Yu K, Rand KA, Haiman CA; African Ancestry Prostate Cancer GWAS Consortium; Hoover RN, Hsing AW, Chanock SJ. (2014) A genome-wide association study of prostate cancer in West African men. *Hum Genet*. May;133 (5):509–21. doi: 10.1007/s00439-013-1387-z. Epub 2013 Nov 2. Erratum in: *Hum Genet*. 2014 May;133 (5):523.

Cooke EW, Shrieve DC, Tward JD. (2012) Clinical versus pathologic staging for prostate adenocarcinoma: how do they correlate? *Am J Clin Oncol*. 2012 Aug;35 (4):364–8. doi: 10.1097/COC.0b013e31821241fc.

Cooper CS, Eeles R, Wedge DC, Van Loo P, Gundem G, Alexandrov LB, Kremeyer B, Butler A, Lynch AG, Camacho N, Massie CE, Kay J, Luxton HJ, Edwards S, Kote-Jarai Z, Dennis N, Merson S, Leongamornlert D, Zamora J, Corbishley C, Thomas S, Nik-Zainal S, O'Meara S, Matthews L, Clark J, Hurst R, Mithen R, Bristow RG, Boutros PC, Fraser M, Cooke S, Raine K, Jones D, Menzies A, Stebbings L, Hinton J, Teague

J, McLaren S, Mudie L, Hardy C, Anderson E, Joseph O, Goody V, Robinson B, Maddison M, Gamble S, Greenman C, Berney D, Hazell S, Livni N; ICGC Prostate Group; Fisher C, Ogden C, Kumar P, Thompson A, Woodhouse C, Nicol D, Mayer E, Dudderidge T, Shah NC, Gnanapragasam V, Voet T, Campbell P, Futreal A, Easton D, Warren AY, Foster CS, Stratton MR, Whitaker HC, McDermott U, Brewer DS, Neal DE. (2015) Analysis of the genetic phylogeny of multifocal prostate cancer identifies multiple independent clonal expansions in neoplastic and morphologically normal prostate tissue. *Nat Genet*. Apr;47 (4):367–372. doi: 10.1038/ng.3221. Epub 2015 Mar 2. Erratum in: Nat Genet. 2015 Jun;47 (6):689. doi: 10.1038/ng0615-689b.

Cowper-Sal lari R, Zhang X, Wright JB, Bailey SD, Cole MD, Eeckhoute J, Moore JH, Lupien M. (2012) Breast cancer risk-associated SNPs modulate the affinity of chromatin for FOXA1 and alter gene expression. *Nat Genet.* Nov;44 (11):1191–8. doi: 10.1038/ng.2416.

Coutinho I, Day TK, Tilley WD, Selth LA. (2016) Androgen receptor signaling in castration-resistant prostate cancer: a lesson in persistence. *Endocr Relat Cancer*. Dec;23 (12):T179–T197.

Cropp CD, Simpson CL, Wahlfors T, Ha N, George A, Jones MS, Harper U, Ponciano-Jackson D, Green TA, Tammela TL, Bailey-Wilson J, Schleutker J. (2011) Genome-wide linkage scan for prostate cancer susceptibility in Finland: evidence for a novel locus on 2q37.3 and confirmation of signal on 17q21-q22. *Int J Cancer. Nov*. 15;129(10):2400–7. doi: 10.1002/ijc.25906.

Curtius K, Gupta S, Boland CR. (2022) Review article: Lynch Syndrome-a mechanistic and clinical management update. *Aliment Pharmacol Ther*. Apr; 55 (8):960–977. doi: 10.1111/apt.16826.

Cybulski C, Huzarski T, Górski B, Masojć B, Mierzejewski M, Debniak T, Gliniewicz B, Matyjasik J, Złowocka E, Kurzawski G, Sikorski A, Posmyk M, Szwiec M, Czajka R, Narod SA, Lubiński J. (2004) A novel founder CHEK2 mutation is associated with increased prostate cancer risk. *Cancer Res*. Apr 15;64 (8):2677–9. doi: 10.1158/0008-5472.can-04-0341.

Dadaev T, Saunders EJ, Newcombe PJ, Anokian E, Leongamornlert DA, Brook MN, Cieza-Borrella C, Mijuskovic M, Wakerell S, Olama AAA, Schumacher FR, Berndt SI, Benlloch S, Ahmed M, Goh C, Sheng X, Zhang Z, Muir K, Govindasami K, Lophatananon A, Stevens VL, Gapstur SM, Carter BD, Tangen CM, Goodman P, Thompson IM Jr, Batra J, Chambers S, Moya L, Clements J, Horvath L, Tilley W, Risbridger G, Gronberg H, Aly M, Nordström T, Pharoah P, Pashayan N, Schleutker J, Tammela TLJ, Sipeky C, Auvinen A, Albanes D, Weinstein S, Wolk A, Hakansson N, West C, Dunning AM, Burnet N, Mucci L, Giovannucci E, Andriole G, Cussenot O, Cancel-Tassin G, Koutros S, Freeman LEB, Sorensen KD, Orntoft TF, Borre M, Maehle L, Grindedal EM, Neal DE, Donovan JL, Hamdy FC, Martin RM, Travis RC, Key TJ, Hamilton RJ, Fleshner NE, Finelli A, Ingles SA, Stern MC, Rosenstein B, Kerns S, Ostrer H, Lu YJ, Zhang HW, Feng N, Mao X, Guo X, Wang G, Sun Z, Giles GG, Southey MC, MacInnis RJ, FitzGerald LM, Kibel AS, Drake BF, Vega A, Gómez-Caamaño A, Fachal L, Szulkin R, Eklund M, Kogevinas M, Llorca J, Castaño-Vinyals G, Penney KL, Stampfer M, Park JY, Sellers TA, Lin HY, Stanford JL, Cybulski C, Wokolorczyk D, Lubinski J, Ostrander EA, Geybels MS, Nordestgaard BG, Nielsen SF, Weisher M, Bisbjerg R, Røder MA, Iversen P, Brenner H, Cuk K, Holleczek B, Maier C, Luedeke M, Schnoeller T, Kim J, Logothetis CJ, John EM, Teixeira MR, Paulo P, Cardoso M, Neuhausen SL, Steele L, Ding YC, De Ruyck K, De Meerleer G, Ost P, Razack A, Lim J, Teo SH, Lin DW, Newcomb LF, Lessel D, Gamulin M, Kulis T, Kaneva R, Usmani N, Slavov C, Mitev V, Parliament M, Singhal S, Claessens F, Joniau S, Van den Broeck T, Larkin S, Townsend PA, Aukim-Hastie C, Gago-Dominguez M, Castelao JE, Martinez ME, Roobol MJ, Jenster G, van Schaik RHN, Menegaux F, Truong T, Koudou YA, Xu J, Khaw KT, Cannon-Albright L, Pandha H, Michael A, Kierzek A, Thibodeau SN, McDonnell SK, Schaid DJ, Lindstrom S, Turman C, Ma J, Hunter DJ, Riboli E, Siddiq A, Canzian F, Kolonel LN, Le Marchand L, Hoover RN, Machiela MJ, Kraft P; PRACTICAL (Prostate Cancer Association Group to Investigate Cancer-Associated Alterations in the Genome) Consortium; Freedman M, Wiklund F, Chanock S, Henderson BE, Easton DF, Haiman CA, Eeles RA, Conti DV, Kote-Jarai Z. (2018) Fine-mapping of prostate cancer susceptibility loci in a large meta-analysis identifies candidate causal variants. *Nat Commun.* Jun 11;9 (1):2256. doi: 10.1038/s41467-018-04109-8.

Dai Z, Liu P. (2021) High copy number variations, particular transcription factors, and low immunity contribute to the stemness of prostate cancer cells. *J Transl Med.* May 13;19(1):206. doi: 10.1186/s12967-021-02870-x.

Daly MB, Pal T, Berry MP, Buys SS, Dickson P, Domchek SM, Elkhanany A, Friedman S, Goggins M, Hutton ML; CGC; Karlan BY, Khan S, Klein C, Kohlmann W; CGC; Kurian AW, Laronga C, Litton JK, Mak JS; LCGC; Menendez CS, Merajver SD, Norquist BS, Offit K, Pederson HJ, Reiser G; CGC; Senter-Jamieson L; CGC; Shannon KM, Shatsky R, Visvanathan K, Weitzel JN, Wick MJ, Wisinski KB, Yurgelun MB, Darlow SD, Dwyer MA. (2021) Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* Jan 6;19(1):77–102. doi: 10.6004/jnccn.2021.0001.

Daniels VA, Luo J, Paller CJ, Kanayama M. (2024) Therapeutic Approaches to Targeting Androgen Receptor Splice Variants. *Cells*. Jan 4;13(1):104. doi: 10.3390/cells13010104.

Darst BF, Dadaev T, Saunders E, Sheng X, Wan P, Pooler L, Xia LY, Chanock S, Berndt SI, Gapstur SM, Stevens V, Albanes D, Weinstein SJ, Gnanapragasam V, Giles GG, Nguyen-Dumont T, Milne RL, Pomerantz M, Schmidt JA, Mucci L, Catalona WJ, Hetrick KN, Doheny KF, MacInnis RJ, Southey MC, Eeles RA, Wiklund F, Kote-Jarai Z, Conti DV, Haiman CA. (2021) Germline Sequencing DNA Repair Genes in 5545 Men With Aggressive and Nonaggressive Prostate Cancer. *J Natl Cancer Inst*. May 4;113(5):616–625. doi: 10.1093/jnci/djaa132.

Darst BF, Saunders E, Dadaev T, Sheng X, Wan P, Pooler L, Xia LY, Chanock S, Berndt SI, Wang Y, Patel AV, Albanes D, Weinstein SJ, Gnanapragasam V, Huff C, Couch FJ, Wolk A, Giles GG, Nguyen-Dumont T, Milne RL, Pomerantz MM, Schmidt JA, Travis RC, Key TJ, Stopsack KH, Mucci LA, Catalona WJ, Marosy B, Hetrick KN, Doheny KF, MacInnis RJ, Southey MC, Eeles RA, Wiklund F, Conti DV, Kote-Jarai Z, Haiman CA. (2023) Germline Sequencing Analysis to Inform Clinical Gene Panel Testing for Aggressive Prostate Cancer. *JAMA Oncol*. Nov 1;9 (11):1514–1524. doi: 10.1001/jamaoncol.2023.3482.

DeMille D, Grose JH. (2013) PAS kinase: a nutrient sensing regulator of glucose homeostasis. *IUBMB Life*. Nov;65(11):921–9. doi: 10.1002/iub.1219.

Demirel HC, Davis JW. (2018) Multiparametric magnetic resonance imaging: Overview of the technique, clinical applications in prostate biopsy and future directions. *Turk J Urol*. Mar;44 (2):93–102. doi: 10.5152/tud.2018.56056.

Deng Z, Wang L, Hou H, Zhou J, Li X. (2016) Epigenetic regulation of IQGAP2 promotes ovarian cancer progression via activating Wnt/β-catenin signaling. *Int J Oncol*. Jan;48(1):153–60. doi: 10.3892/ijo.2015.3228.

Dieffenbacher S, Nyarangi-Dix J, Giganti F, Bonekamp D, Kesch C, Müller-Wolf MB, Schütz V, Gasch C, Hatiboglu G, Hauffe M, Stenzinger A, Duensing S, Schlemmer HP, Moore CM, Hohenfellner M, Radtke JP. (2021)Standardized Magnetic Resonance Imaging Reporting Using the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation Criteria and Magnetic Resonance Imaging/Transrectal Ultrasound Fusion with Transperineal Saturation Biopsy to Select Men on Active Surveillance. *Eur Urol Focus*. Jan;7 (1):102–110. doi: 10.1016/j.euf.2019.03.001.

Dominguez-Valentin M, Sampson JR, Seppälä TT, Ten Broeke SW, Plazzer JP, Nakken S, Engel C, Aretz S, Jenkins MA, Sunde L, Bernstein I, Capella G, Balaguer F, Thomas H, Evans DG, Burn J, Greenblatt M, Hovig E, de Vos Tot Nederveen Cappel WH, Sijmons RH, Bertario L, Tibiletti MG, Cavestro GM, Lindblom A, Della Valle A, Lopez-Köstner F, Gluck N, Katz LH, Heinimann K, Vaccaro CA, Büttner R, Görgens H, Holinski-Feder E, Morak M, Holzapfel S, Hüneburg R, Knebel Doeberitz MV, Loeffler M, Rahner N, Schackert HK, Steinke-Lange V, Schmiegel W, Vangala D, Pylvänäinen K, Renkonen-Sinisalo L, Hopper JL, Win AK, Haile RW, Lindor NM, Gallinger S, Le Marchand L, Newcomb PA, Figueiredo JC, Thibodeau SN, Wadt K, Therkildsen C, Okkels H, Ketabi Z, Moreira L, Sánchez A, Serra-Burriel M, Pineda M, Navarro M, Blanco I, Green K, Lalloo F, Crosbie EJ, Hill J, Denton OG, Frayling IM, Rødland EA, Vasen H, Mints M, Neffa F, Esperon P, Alvarez K, Kariv R, Rosner G, Pinero TA, Gonzalez ML, Kalfayan P, Tjandra D, Winship IM, Macrae F, Möslein G, Mecklin JP, Nielsen M, Møller P. (2020) Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. *Genet Med*. Jan;22(1):15–25. doi: 10.1038/s41436-019-0596-9. Epub 2019 Jul 24. Erratum in: *Genet Med*. 2020 Sep;22(9):1569. doi: 10.1038/s41436-020-0892-4.

Dong X, Wang L, Taniguchi K, Wang X, Cunningham JM, McDonnell SK, Qian C, Marks AF, Slager SL, Peterson BJ, Smith DI, Cheville JC, Blute ML, Jacobsen SJ, Schaid DJ, Tindall DJ, Thibodeau SN, Liu W. (2003) Mutations in CHEK2 associated with prostate cancer risk. *Am J Hum Genet*. Feb;72 (2):270–80. doi: 10.1086/346094.

Du M, Yuan T, Schilter KF, Dittmar RL, Mackinnon A, Huang X, Tschannen M, Worthey E, Jacob H, Xia S, Gao J, Tillmans L, Lu Y, Liu P, Thibodeau SN, Wang L. (2015) Prostate cancer risk locus at 8q24 as a regulatory hub by physical interactions with multiple genomic loci across the genome. *Hum Mol Genet*. Jan 1;24 (1):154–66. doi: 10.1093/hmg/ddu426.

Duodecim (2023). Eturauhassyöpä. Suomalaisen Lääkäriseuran Duodecimin ja Suomen Urologiyhdistys ry:n asettama työryhmä. Helsinki: Suomalainen Lääkäriseura Duodecim. https://www.kaypahoito.fi/hoi11060#s7_1 [Read 7.4.2024]

Dupont WD, Breyer JP, Johnson SH, Plummer WD, Smith JR. (2021) Prostate cancer risk variants of the HOXB genetic locus. *Sci Rep.* May 31;11(1):11385. doi: 10.1038/s41598-021-89399-7.

Edwards J, Krishna NS, Witton CJ, Bartlett JM. (2003) Gene amplifications associated with the development of hormone-resistant prostate cancer. *Clin Cancer Res*. Nov 1;9 (14):5271–81. PMID: 14614009.

Eeles RA, Olama AA, Benlloch S, Saunders EJ, Leongamornlert DA, Tymrakiewicz M, Ghoussaini M, Luccarini C, Dennis J, Jugurnauth-Little S, Dadaev T, Neal DE, Hamdy FC, Donovan JL, Muir K, Giles GG, Severi G, Wiklund F, Gronberg H, Haiman CA, Schumacher F, Henderson BE, Le Marchand L, Lindstrom S, Kraft P, Hunter DJ, Gapstur S, Chanock SJ, Berndt SI, Albanes D, Andriole G, Schleutker J, Weischer M, Canzian F, Riboli E, Key TJ, Travis RC, Campa D, Ingles SA, John EM, Hayes RB, Pharoah PD, Pashayan N, Khaw KT, Stanford JL, Ostrander EA, Signorello LB, Thibodeau SN, Schaid D, Maier C, Vogel W, Kibel AS, Cybulski C, Lubinski J, Cannon-Albright L, Brenner H, Park JY, Kaneva R, Batra J, Spurdle AB, Clements JA, Teixeira MR, Dicks E, Lee A, Dunning AM, Baynes C, Conroy D, Maranian MJ, Ahmed S, Govindasami K, Guy M, Wilkinson RA, Sawyer EJ, Morgan A, Dearnaley DP, Horwich A, Huddart RA, Khoo VS, Parker CC, Van As NJ, Woodhouse CJ, Thompson A, Dudderidge T, Ogden C, Cooper CS, Lophatananon A, Cox A, Southey MC, Hopper JL, English DR, Aly M, Adolfsson J, Xu J, Zheng SL, Yeager M, Kaaks R, Diver WR, Gaudet MM, Stern MC, Corral R, Joshi AD, Shahabi A, Wahlfors T, Tammela TL, Auvinen A, Virtamo J, Klarskov P, Nordestgaard BG, Røder MA, Nielsen SF, Bojesen SE, Siddiq A, Fitzgerald LM, Kolb S, Kwon EM, Karyadi DM, Blot WJ, Zheng W, Cai Q, McDonnell SK, Rinckleb AE, Drake B, Colditz G, Wokolorczyk D, Stephenson RA, Teerlink C, Muller H, Rothenbacher D, Sellers TA, Lin HY, Slavov C, Mitev V, Lose F, Srinivasan S, Maia S, Paulo P, Lange E, Cooney KA, Antoniou AC, Vincent D, Bacot F, Tessier DC; COGS–Cancer Research UK GWAS–ELLIPSE (part of GAME-ON) Initiative; Australian Prostate Cancer Bioresource; UK Genetic Prostate Cancer Study Collaborators/British Association of Urological Surgeons' Section of Oncology; UK ProtecT (Prostate testing for cancer and Treatment) Study Collaborators; PRACTICAL (Prostate Cancer Association Group to Investigate Cancer-Associated Alterations in the Genome) Consortium; Kote-Jarai Z, Easton DF. (2013) Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. *Nat Genet*. Apr;45 (4):385–91, 391e1-2. doi: 10.1038/ng.2560.

Eeles R, Goh C, Castro E, Bancroft E, Guy M, Al Olama AA, Easton D, Kote-Jarai Z. (2014) The genetic epidemiology of prostate cancer and its clinical implications. *Nat Rev Urol.* Jan;11(1):18–31. doi: 10.1038/nrurol.2013.266.

Egusquiaguirre SP, Liu S, Tošić I, Jiang K, Walker SR, Nicolais M, Saw TY, Xiang M, Bartel K, Nelson EA, Frank DA. (2020) CDK5RAP3 is a co-factor for the oncogenic transcription factor STAT3. *Neoplasia*. Jan;22 (1):47–59. doi: 10.1016/j.neo.2019.10.002.

Elmehrath AO, Afifi AM, Al-Husseini MJ, Saad AM, Wilson N, Shohdy KS, Pilie P, Sonbol MB, Alhalabi O. (2021) Causes of Death Among Patients With Metastatic Prostate Cancer in the US From 2000 to 2016. *JAMA Netw Open*. Aug 2;4 (8):e2119568. doi: 10.1001/jamanetworkopen.2021.19568.

Emadi Baygi M, Soheili ZS, Schmitz I, Sameie S, Schulz WA. (2010) Snail regulates cell survival and inhibits cellular senescence in human metastatic prostate cancer cell lines. *Cell Biol Toxicol*. Dec;26(6):553–67. doi: 10.1007/s10565-010-9163-5.

Epstein JI, Feng Z, Trock BJ, Pierorazio PM. (2012) Upgrading and downgrading of prostate cancer from biopsy to radical prostatectomy: incidence and predictive factors using the modified Gleason grading system and factoring in tertiary grades. *Eur Urol.* May;61 (5):1019-24. doi: 10.1016/j.eururo.2012.01.050.

Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA; Grading Committee. (2016) The 2014 International Society of Urological Pathology (ISUP) Consensus

Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. *Am J Surg Pathol*. Feb;40 (2):244–52. doi: 10.1097/PAS.0000000000000530.

Ewing CM, Ray AM, Lange EM, Zuhlke KA, Robbins CM, Tembe WD, Wiley KE, Isaacs SD, Johng D, Wang Y, Bizon C, Yan G, Gielzak M, Partin AW, Shanmugam V, Izatt T, Sinari S, Craig DW, Zheng SL, Walsh PC, Montie JE, Xu J, Carpten JD, Isaacs WB, Cooney KA. (2012) Germline mutations in HOXB13 and prostate-cancer risk. N Engl J Med. Jan 12;366 (2):141–9. doi: 10.1056/NEJMoa1110000.

Foreman KJ, Marquez N, Dolgert A, Fukutaki K, Fullman N, McGaughey M, Pletcher MA, Smith AE, Tang K, Yuan CW, Brown JC, Friedman J, He J, Heuton KR, Holmberg M, Patel DJ, Reidy P, Carter A, Cercy K, Chapin A, Douwes-Schultz D, Frank T, Goettsch F, Liu PY, Nandakumar V, Reitsma MB, Reuter V, Sadat N, Sorensen RJD, Srinivasan V, Updike RL, York H, Lopez AD, Lozano R, Lim SS, Mokdad AH, Vollset SE, Murray CJL. (2018) Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. *Lancet*. Nov 10;392 (10159):2052–2090. doi: 10.1016/S0140-6736 (18)31694-5.

Fujita K, Hayashi T, Matsushita M, Uemura M, Nonomura N. (2019) Obesity, Inflammation, and Prostate Cancer. *J Clin Med*. Feb 6;8 (2):201. doi: 10.3390/jcm8020201.

Gallagher DJ, Gaudet MM, Pal P, Kirchhoff T, Balistreri L, Vora K, Bhatia J, Stadler Z, Fine SW, Reuter V, Zelefsky M, Morris MJ, Scher HI, Klein RJ, Norton L, Eastham JA, Scardino PT, Robson ME, Offit K. (2010) Germline BRCA mutations denote a clinicopathologic subset of prostate cancer. *Clin Cancer Res*. Apr 1;16 (7):2115–21. doi: 10.1158/1078-0432.CCR-09-2871.

Gandaglia G, Abdollah F, Schiffmann J, Trudeau V, Shariat SF, Kim SP, Perrotte P, Montorsi F, Briganti A, Trinh QD, Karakiewicz PI, Sun M. (2014) Distribution of metastatic sites in patients with prostate cancer: A population-based analysis. *Prostate*. Feb;74 (2):210–6. doi: 10.1002/pros.22742.

GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. (2018) Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. Nov 10;392 (10159):1789–1858. doi: 10.1016/S0140-6736 (18)32279-7. Epub 2018 Nov 8. Erratum in: *Lancet*. 2019 Jun 22;393 (10190):e44. doi: 10.1016/S0140-6736 (19)31047-5.

Ghaleb AM, Bialkowska AB, Snider AJ, Gnatenko DV, Hannun YA, Yang VW, Schmidt VA. (2015) IQ Motif-Containing GTPase-Activating Protein 2 (IQGAP2) Is a Novel Regulator of Colonic Inflammation in Mice. *PLoS One.* Jun 5;10(6):e0129314. doi: 10.1371/journal.pone.0129314.

Gilligan T, Wang PS, Levin R, Kantoff PW, Avorn J. (2004) Racial differences in screening for prostate cancer in the elderly. *Arch Intern Med*. Sep 27;164 (17):1858–64. doi: 10.1001/archinte.164.17.1858.

Giri VN, Beebe-Dimmer JL. (2016) Familial prostate cancer. *Semin Oncol*. 43, 560–565. doi: 10.1053/j.seminoncol.2016.08.001.

Giri VN, Hyatt C, Gomella LG. (2019) Germline Testing for Men With Prostate Cancer: Navigating an Expanding New World of Genetic Evaluation for Precision Therapy and Precision Management. *J Clin Oncol*. Jun 10;37 (17):1455–1459. doi: 10.1200/JCO.18.02181.

Gómez-Acebo I, Dierssen-Sotos T, Fernandez-Navarro P, Palazuelos C, Moreno V, Aragonés N, Castaño-Vinyals G, Jiménez-Monleón JJ, Ruiz-Cerdá JL, Pérez-Gómez B, Ruiz-Dominguez JM, Molero JA, Pollán M, Kogevinas M, Llorca J. (2017) Risk Model for Prostate Cancer Using Environmental and Genetic Factors in the Spanish Multi-Case-Control (MCC) Study. *Sci Rep*. Aug 21;7 (1):8994.

González Del Alba A, Méndez-Vidal MJ, Vazquez S, Castro E, Climent MA, Gallardo E, Gonzalez-Billalabeitia E, Lorente D, Maroto JP, Arranz JA. (2021) SEOM clinical guidelines for the treatment of advanced prostate cancer (2020). *Clin Transl Oncol*. May;23 (5):969–979. doi: 10.1007/s12094-021-02561-5.

Graffelman J, Jain D, Weir B. (2017) A genome-wide study of Hardy-Weinberg equilibrium with next generation sequence data. *Hum Genet*. Jun;136(6):727–741. doi: 10.1007/s00439-017-1786-7.

Grindedal EM, Møller P, Eeles R, Stormorken AT, Bowitz-Lothe IM, Landrø SM, Clark N, Kvåle R, Shanley S, Maehle L. (2009) Germ-line mutations in mismatch repair genes associated with prostate cancer. *Cancer Epidemiol Biomarkers Prev*. Sep;18 (9):2460–7. doi: 10.1158/1055-9965.EPI-09-0058.

Grose JH, Rutter J. (2010) The role of PAS kinase in PASsing the glucose signal. *Sensors (Basel).* 10(6):5668–82. doi: 10.3390/s100605668.

Grossman DC, Curry SJ, Owens DK, Bibbins-Domingo K, Caughey AB, Davidson KW, Doubeni CA, Ebell M, Epling JW Jr, Kemper AR, Krist AH, Kubik M, Landefeld CS, Mangione CM, Silverstein M, Simon MA, Siu AL, Tseng CW. (2018) Screening for Prostate Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. May 8;319 (18):1901–1913. doi: 10.1001/jama.2018.3710. Erratum in: *JAMA*. 2018 Jun 19;319 (23):2443. doi: 10.1001/jama.2018.7453.

Grönberg H, Adolfsson J, Aly M, Nordström T, Wiklund P, Brandberg Y, Thompson J, Wiklund F, Lindberg J, Clements M, Egevad L, Eklund M. (2015) Prostate cancer screening in men aged 50-69 years (STHLM3): a prospective population-based diagnostic study. *Lancet Oncol*. Dec;16 (16):1667–76.

Gudmundsson J, Sulem P, Steinthorsdottir V, Bergthorsson JT, Thorleifsson G, Manolescu A, Rafnar T, Gudbjartsson D, Agnarsson BA, Baker A, Sigurdsson A, Benediktsdottir KR, Jakobsdottir M, Blondal T, Stacey SN, Helgason A, Gunnarsdottir S, Olafsdottir A, Kristinsson KT, Birgisdottir B, Ghosh S, Thorlacius S, Magnusdottir D, Stefansdottir G, Kristjansson K, Bagger Y, Wilensky RL, Reilly MP, Morris AD, Kimber CH, Adeyemo A, Chen Y, Zhou J, So WY, Tong PC, Ng MC, Hansen T, Andersen G, Borch-Johnsen K, Jorgensen T, Tres A, Fuertes F, Ruiz-Echarri M, Asin L, Saez B, van Boven E, Klaver S, Swinkels DW, Aben KK, Graif T, Cashy J, Suarez BK, van Vierssen Trip O, Frigge ML, Ober C, Hofker MH, Wijmenga C, Christiansen C, Rader DJ, Palmer CN, Rotimi C, Chan JC, Pedersen O, Sigurdsson G, Benediktsson R, Jonsson E, Einarsson GV, Mayordomo JI, Catalona WJ, Kiemeney LA, Barkardottir RB, Gulcher JR, Thorsteinsdottir U, Kong A, Stefansson K. (2007) Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. *Nat Genet.* Aug;39 (8):977–83. doi: 10.1038/ng2062.

Gulati R, Gore JL, Etzioni R. (2013) Comparative effectiveness of alternative prostate-specific antigen-based prostate cancer screening strategies: model estimates of potential benefits and harms. *Ann Intern Med*. Feb 5;158 (3):145–53. doi: 10.7326/0003-4819-158-3-201302050-00003.

Gumaste PV, Penn LA, Cymerman RM, Kirchhoff T, Polsky D, McLellan B. (2015) Skin cancer risk in BRCA1/2 mutation carriers. *Br J Dermatol*. Jun;172(6):1498–1506. doi: 10.1111/bjd.13626.

Guo CC, Epstein JI. (2006) Intraductal carcinoma of the prostate on needle biopsy: Histologic features and clinical significance. *Mod Pathol*. Dec;19 (12):1528–35. doi: 10.1038/modpathol.3800702. Epub 2006 Sep 15.

Haiman CA, Chen GK, Blot WJ, Strom SS, Berndt SI, Kittles RA, Rybicki BA, Isaacs WB, Ingles SA, Stanford JL, Diver WR, Witte JS, Hsing AW, Nemesure B, Rebbeck TR, Cooney KA, Xu J, Kibel AS, Hu JJ, John EM, Gueye SM, Watya S, Signorello LB, Hayes RB, Wang Z, Yeboah E, Tettey Y, Cai Q, Kolb S, Ostrander EA, Zeigler-Johnson C, Yamamura Y, Neslund-Dudas C, Haslag-Minoff J, Wu W, Thomas V, Allen GO, Murphy A, Chang BL, Zheng SL, Leske MC, Wu SY, Ray AM, Hennis AJ, Thun MJ, Carpten J, Casey G, Carter EN, Duarte ER, Xia LY, Sheng X, Wan P, Pooler LC, Cheng I, Monroe KR, Schumacher F, Le Marchand L, Kolonel LN, Chanock SJ, Van Den Berg D, Stram DO, Henderson BE. (2011) Genome-wide association study of prostate cancer in men of African ancestry identifies a susceptibility locus at 17q21. *Nat Genet*. Jun;43 (6):570–3. doi: 10.1038/ng.839.

Hall WH, Jani AB, Ryu JK, Narayan S, Vijayakumar S. (2005) The impact of age and comorbidity on survival outcomes and treatment patterns in prostate cancer. *Prostate Cancer Prostatic Dis*. 8 (1):22–30. doi: 10.1038/sj.pcan.4500772.

Han Y, Rand KA, Hazelett DJ, Ingles SA, Kittles RA, Strom SS, Rybicki BA, Nemesure B, Isaacs WB, Stanford JL, Zheng W, Schumacher FR, Berndt SI, Wang Z, Xu J, Rohland N, Reich D, Tandon A, Pasaniuc B, Allen A, Quinque D, Mallick S, Notani D, Rosenfeld MG, Jayani RS, Kolb S, Gapstur SM, Stevens VL, Pettaway CA, Yeboah ED, Tettey Y, Biritwum RB, Adjei AA, Tay E, Truelove A, Niwa S, Chokkalingam AP, John EM, Murphy AB, Signorello LB, Carpten J, Leske MC, Wu SY, Hennis AJM, Neslund-Dudas C, Hsing AW, Chu L, Goodman PJ, Klein EA, Zheng SL, Witte JS, Casey G, Lubwama A, Pooler LC, Sheng X, Coetzee GA, Cook MB, Chanock SJ, Stram DO, Watya S, Blot WJ, Conti DV, Henderson BE, Haiman CA. (2016) Prostate Cancer Susceptibility in Men of African Ancestry at 8q24. *J Natl Cancer Inst*. Jan 27;108 (7):djv431. doi: 10.1093/jnci/djv431.

Harmenberg U, Hamdy FC, Widmark A, Lennernäs B, Nilsson S. (2011) Curative radiation therapy in prostate cancer. *Acta Oncol*. Jun;50 Suppl 1:98–103. doi: 10.3109/0284186X.2010.576115.

Hearn JWD, AbuAli G, Reichard CA, Reddy CA, Magi-Galluzzi C, Chang KH, Carlson R, Rangel L, Reagan K, Davis BJ, Karnes RJ, Kohli M, Tindall D, Klein EA, Sharifi N. (2016) HSD3B1 and resistance to androgen-deprivation therapy in prostate cancer: a retrospective, multicohort study. *Lancet Oncol.* Oct;17 (10):1435–1444. doi: 10.1016/S1470-2045 (16)30227-3.

Heidegger I, Tsaur I, Borgmann H, Surcel C, Kretschmer A, Mathieu R, Visschere P, Valerio M, van den Bergh RCN, Ost P, Tilki D, Gandaglia G, Ploussard G; EAU-YAU Prostate Cancer Working Party. (2019) Hereditary prostate cancer Primetime for genetic testing? *Cancer Treat Rev*. Dec;81:101927. doi: 10.1016/j.ctrv.2019.101927.

Helfand BT, Roehl KA, Cooper PR, McGuire BB, Fitzgerald LM, Cancel-Tassin G, Cornu JN, Bauer S, Van Blarigan EL, Chen X, Duggan D, Ostrander EA, Gwo-Shu M, Zhang ZF, Chang SC, Jeong S, Fontham ET, Smith G, Mohler JL, Berndt SI, McDonnell SK, Kittles R, Rybicki BA, Freedman M, Kantoff PW, Pomerantz M, Breyer JP, Smith JR, Rebbeck TR, Mercola D, Isaacs WB, Wiklund F, Cussenot O, Thibodeau SN, Schaid DJ, Cannon-Albright L, Cooney KA, Chanock SJ, Stanford JL, Chan JM, Witte J, Xu J, Bensen JT, Taylor JA, Catalona WJ. (2015) Associations of prostate cancer risk variants with disease aggressiveness: results of the NCI-SPORE Genetics Working Group analysis of 18,343 cases. *Hum Genet*. Apr;134(4):439–50. doi: 10.1007/s00439-015-1534-9. Epub 2015 Feb 26. PMID: 25715684; PMCID: PMC4586077.

Helgstrand JT, Røder MA, Klemann N, Toft BG, Brasso K, Vainer B, Iversen P. (2017) Diagnostic characteristics of lethal prostate cancer. *Eur J Cancer.* Oct;84:18–26. doi: 10.1016/j.ejca.2017.07.007.

Hemminki K. (2012) Familial risk and familial survival in prostate cancer. *World J Urol*. Apr;30 (2):143–8. doi: 10.1007/s00345-011-0801-1.

Heyn H, Sayols S, Moutinho C, Vidal E, Sanchez-Mut JV, Stefansson OA, Nadal E, Moran S, Eyfjord JE, Gonzalez-Suarez E, Pujana MA, Esteller M. (2014) Linkage of DNA methylation quantitative trait loci to human cancer risk. *Cell Rep*. Apr 24;7 (2):331–338. doi: 10.1016/j.celrep.2014.03.016.

Hinata N, Fujisawa M. (2022) Racial Differences in Prostate Cancer Characteristics and Cancer-Specific Mortality: An Overview. *World J Mens Health*. Apr;40(2):217–227. doi: 10.5534/wjmh.210070.

Hjelmborg JB, Scheike T, Holst K, Skytthe A, Penney KL, Graff RE, Pukkala E, Christensen K, Adami HO, Holm NV, Nuttall E, Hansen S, Hartman M, Czene K, Harris JR, Kaprio J, Mucci LA. (2014) The heritability of prostate cancer in the Nordic Twin Study of Cancer. *Cancer Epidemiol Biomarkers Prev*. Nov;23 (11):2303–10.

Hosgood HD 3rd, Wang WC, Hong YC, Wang JC, Chen K, Chang IS, Chen CJ, Lu D, Yin Z, Wu C, Zheng W, Qian B, Park JY, Kim YH, Chatterjee N, Chen Y, Chang GC, Hsiao CF, Yeager M, Tsai YH, Wei H, Kim YT, Wu W, Zhao Z, Chow WH, Zhu X, Lo YL, Sung SW, Chen KY, Yuenger J, Kim JH, Huang L, Chen YH, Gao YT, Kim JH, Huang MS, Jung TH, Caporaso N, Zhao X, Huan Z, Yu D, Kim CH, Su WC, Shu XO, Kim IS, Bassig B, Chen YM, Cha SI, Tan W, Chen H, Yang TY, Sung JS, Wang CL, Li X, Park KH, Yu CJ, Ryu JS, Xiang Y, Hutchinson A, Kim JS, Cai Q, Landi MT, Lee KM, Hung JY, Park JY, Tucker M, Lin CC, Ren Y, Perng RP, Chen CY, Jin L, Chen KC, Li YJ, Chiu YF, Tsai FY, Yang PC, Fraumeni JF Jr, Seow A, Lin D, Zhou B, Chanock S, Hsiung CA, Rothman N, Lan Q. (2012) Genetic variant in TP63 on locus 3q28 is associated with risk of lung adenocarcinoma among never-smoking females in Asia. *Hum Genet.* Jul;131(7):1197–203. doi: 10.1007/s00439-012-1144-8. Epub 2012 Feb 25. PMID: 22367405; PMCID: PMC3875137.

Houlahan KE, Shiah YJ, Gusev A, Yuan J, Ahmed M, Shetty A, Ramanand SG, Yao CQ, Bell C, O'Connor E, Huang V, Fraser M, Heisler LE, Livingstone J, Yamaguchi TN, Rouette A, Foucal A, Espiritu SMG, Sinha A, Sam M, Timms L, Johns J, Wong A, Murison A, Orain M, Picard V, Hovington H, Bergeron A, Lacombe L, Lupien M, Fradet Y, Têtu B, McPherson JD, Pasaniuc B, Kislinger T, Chua MLK, Pomerantz MM, van der Kwast T, Freedman ML, Mani RS, He HH, Bristow RG, Boutros PC. (2019) Genome-wide germline correlates of the epigenetic landscape of prostate cancer. *Nat Med*. Oct;25 (10):1615–1626. doi: 10.1038/s41591-019-0579-z.

Huang Q, Whitington T, Gao P, Lindberg JF, Yang Y, Sun J, Väisänen MR, Szulkin R, Annala M, Yan J, Egevad LA, Zhang K, Lin R, Jolma A, Nykter M, Manninen A, Wiklund F, Vaarala MH, Visakorpi T, Xu J, Taipale J, Wei GH. (2014) A prostate cancer susceptibility allele at 6q22 increases RFX6 expression by modulating HOXB13 chromatin binding. *Nat Genet*. Feb;46 (2):126–35. doi: 10.1038/ng.2862.

Huang B, Zhang J, Zhang X, Huang C, Hu G, Li S, Xie T, Liu M, Xu Y. (2017) Suppression of LETM1 by siRNA inhibits cell proliferation and invasion of bladder cancer cells. *Oncol Rep*. Nov;38(5):2935–2940. doi: 10.3892/or.2017.5959.

Hurwitz LM, Agalliu I, Albanes D, Barry KH, Berndt SI, Cai Q, Chen C, Cheng I, Genkinger JM, Giles GG, Huang J, Joshu CE, Key TJ, Knutsen S, Koutros S, Langseth H, Li SX, MacInnis RJ, Markt SC, Penney KL, Perez-Cornago A, Rohan TE, Smith-Warner SA, Stampfer MJ, Stopsack KH, Tangen CM, Travis RC, Weinstein SJ, Lang PhD W, Jacobs EJ, Mucci LA, Platz EA, Cook MB; Prostate Cancer Cohort Consortium (PC3) Working Group. (2021) Recommended Definitions of Aggressive Prostate Cancer for Etiologic Epidemiologic Research. *J Natl Cancer Inst.* Jun 1;113(6):727-734. doi: 10.1093/jnci/djaa154. Erratum in: *J Natl Cancer Inst*. 2022 Mar 8;114(3):481. doi: 10.1093/jnci/djab230.

Hövels AM, Heesakkers RA, Adang EM, Jager GJ, Strum S, Hoogeveen YL, Severens JL, Barentsz JO. (2008) The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. Clin Radiol. Apr;63 (4):387–95. doi: 10.1016/j.crad.2007.05.022. Epub 2008 Feb 4.

International Agency for Research on Cancer (2022). GLOBOCAN 2024: Estimated cancer incidence, mortality and prevalence worldwide Lyon, France: IARC; 2022. https://gco.iarc.fr/today/home [Read 14.4.2025]

Ichigotani Y, Yokozaki S, Fukuda Y, Hamaguchi M, Matsuda S. (2002) Forced expression of NESH suppresses motility and metastatic dissemination of malignant cells. *Cancer Res*. Apr 15;62 (8):2215–9. PMID: 11956071.

Ikonen T, Matikainen MP, Syrjäkoski K, Mononen N, Koivisto PA, Rökman A, Seppälä EH, Kallioniemi OP, Tammela TL, Schleutker J. (2003) BRCA1 and BRCA2 mutations have no major role in predisposition to prostate cancer in Finland. *J Med Genet*. Aug;40 (8):e98. doi: 10.1136/jmg.40.8.e98.

Ioannidis NM, Rothstein JH, Pejaver V, Middha S, McDonnell SK, Baheti S, Musolf A, Li Q, Holzinger E, Karyadi D, Cannon-Albright LA, Teerlink CC, Stanford JL, Isaacs WB, Xu J, Cooney KA, Lange EM, Schleutker J, Carpten JD, Powell IJ, Cussenot O, Cancel-Tassin G, Giles GG, MacInnis RJ, Maier C, Hsieh CL, Wiklund F, Catalona WJ, Foulkes WD, Mandal D, Eeles RA, Kote-Jarai Z, Bustamante CD, Schaid DJ, Hastie T, Ostrander EA, Bailey-Wilson JE, Radivojac P, Thibodeau SN, Whittemore AS, Sieh W. (2016) REVEL: An Ensemble Method for Predicting the Pathogenicity of Rare Missense Variants. *Am J Hum Genet*. Oct 6;99 (4):877–885. doi: 10.1016/j.ajhg.2016.08.016.

Isaacs JT. (2018) Resolving the Coffey Paradox: what does the androgen receptor do in normal vs. malignant prostate epithelial cells? *Am J Clin Exp Urol*. Apr 1;6 (2):55–61. PMID: 29666833

Isaacsson Velho P, Silberstein JL, Markowski MC, Luo J, Lotan TL, Isaacs WB, Antonarakis ES. (2018) Intraductal/ductal histology and lymphovascular invasion are associated with germline DNA-repair gene mutations in prostate cancer. *Prostate*. Apr;78(5):401–407. doi: 10.1002/pros.23484.

Iyer RR, Pluciennik A, Burdett V, Modrich PL. (2006) DNA mismatch repair: functions and mechanisms. *Chem Rev.* Feb;106 (2):302–23. doi: 10.1021/cr0404794.

Iwamoto H, Izumi K, Kadono Y, Mizokami A. (2019) Prognosis of patients with prostate cancer and middle range prostate - specific antigen levels of 20 - 100 ng / mL. *Int Braz J Urol*. Jan-Feb;45(1):61–67. doi: 10.1590/S1677-5538.IBJU.2018.0143.

James ND, Tannock I, N'Dow J, Feng F, Gillessen S, Ali SA, Trujillo B, Al-Lazikani B, Attard G, Bray F, Compérat E, Eeles R, Fatiregun O, Grist E, Halabi S, Haran Á, Herchenhorn D, Hofman MS, Jalloh M, Loeb S, MacNair A, Mahal B, Mendes L, Moghul M, Moore C, Morgans A, Morris M, Murphy D, Murthy V, Nguyen PL, Padhani A, Parker C, Rush H, Sculpher M, Soule H, Sydes MR, Tilki D, Tunariu N, Villanti P, Xie LP. (2024) The Lancet Commission on prostate cancer: planning for the surge in cases. *Lancet*. Apr 27;403 (10437):1683–1722. doi: 10.1016/S0140-6736(24)00748-7.

Jiang Y, Zheng Y, Zhang YW, Kong S, Dong J, Wang F, Ziman B, Gery S, Hao JJ, Zhou D, Zhou J, Ho AS, Sinha UK, Chen J, Zhang S, Yin C, Wei DD, Hazawa M, Pan H, Lu Z, Wei WQ, Wang MR, Koeffler HP, Lin DC, Jiang YY. (2024) Reciprocal inhibition between TP63 and STAT1 regulates anti-tumor immune response through interferonγ signaling in squamous cancer. *Nat Commun*. Mar 20;15 (1):2484. doi: 10.1038/s41467-024-46785-9.

Jiang J, Soh PXY, Mutambirwa SBA, Bornman MSR, Haiman CA, Hayes VM, Jaratlerdsiri W. (2024) ANO7 African-ancestral genomic diversity and advanced prostate cancer. *Prostate Cancer Prostatic Dis*. Sep;27 (3):558–565. doi: 10.1038/s41391-023-00722-x.

Jimenez-Sainz J, Jensen RB. Imprecise Medicine: (2021) BRCA2 Variants of Uncertain Significance (VUS), the Challenges and Benefits to Integrate a Functional Assay Workflow with Clinical Decision Rules. *Genes (Basel).* May 20;12 (5):780. doi: 10.3390/genes12050780.

Johnson AM, Zuhlke KA, Plotts C, McDonnell SK, Middha S, Riska SM, Schaid DJ, Thibodeau SN, Douglas JA, Cooney KA. (2014) Mutational landscape of candidate genes in familial prostate cancer. *Prostate*. Oct;74(14):1371–8. doi: 10.1002/pros.22849.

Jung C, Kim RS, Zhang HJ, Lee SJ, Jeng MH. (2004) HOXB13 induces growth suppression of prostate cancer cells as a repressor of hormone-activated androgen receptor signaling. *Cancer Res*. Dec 15;64 (24):9185–92. doi: 10.1158/0008-5472.CAN-04-1330.

Kabir AU, Zeng C, Subramanian M, Wu J, Kim M, Krchma K, Wang X, Halabi CM, Pan H, Wickline SA, Fremont DH, Artyomov MN, Choi K. (2024) ZBTB46 coordinates angiogenesis and immunity to control tumor outcome. *Nat Immunol*. Sep;25 (9):1546–1554. doi: 10.1038/s41590-024-01936-4.

Kader AK, Sun J, Isaacs SD, Wiley KE, Yan G, Kim ST, Fedor H, DeMarzo AM, Epstein JI, Walsh PC, Partin AW, Trock B, Zheng SL, Xu J, Isaacs W. (2009) Individual and cumulative effect of prostate cancer risk-associated variants on clinicopathologic variables in 5,895 prostate cancer patients. *Prostate*. Aug 1;69(11):1195–205. doi: 10.1002/pros.20970.

Kafka M, Surcel C, Heidegger I. (2021) Recent Insights on Genetic Testing in Primary Prostate Cancer. *Mol Diagn Ther*. Jul;25 (4):425–438. doi: 10.1007/s40291-021-00529-3.

Karlsson R, Aly M, Clements M, Zheng L, Adolfsson J, Xu J, Grönberg H, Wiklund F. (2014) A population-based assessment of germline HOXB13 G84E mutation and prostate cancer risk. *Eur Urol*. Jan;65 (1):169–76. doi: 10.1016/j.eururo.2012.07.027.

Kawahara T, Inoue S, Ide H, Kashiwagi E, Ohtake S, Mizushima T, Li P, Li Y, Zheng Y, Uemura H, Netto GJ, Ishiguro H, Miyamoto H. (2016) ZKSCAN3 promotes bladder cancer cell proliferation, migration, and invasion. *Oncotarget*. Aug 16;7 (33):53599–53610. doi: 10.18632/oncotarget.10679.

Kawahara T, Teramoto Y, Li Y, Ishiguro H, Gordetsky J, Yang Z, Miyamoto H. (2020) Impact of Vasectomy on the Development and Progression of Prostate Cancer: Preclinical Evidence. *Cancers (Basel)*. Aug 15;12 (8):2295. doi: 10.3390/cancers12082295.

Kent JW Jr. (2011) Rare variants, common markers: synthetic association and beyond. *Genet Epidemiol*. 35 Suppl 1(Suppl 1):S80–4. doi: 10.1002/gepi.20655.

Kerns SL, Dorling L, Fachal L, Bentzen S, Pharoah PD, Barnes DR, Gómez-Caamaño A, Carballo AM, Dearnaley DP, Peleteiro P, Gulliford SL, Hall E, Michailidou K, Carracedo Á, Sia M, Stock R, Stone NN, Sydes MR, Tyrer JP, Ahmed S, Parliament M, Ostrer H, Rosenstein BS, Vega A, Burnet NG, Dunning AM, Barnett GC, West CM; Radiogenomics Consortium. (2016) Meta-analysis of Genome Wide Association Studies Identifies Genetic Markers of Late Toxicity Following Radiotherapy for Prostate Cancer. *EBioMedicine*. Aug;10:150–63. doi: 10.1016/j.ebiom.2016.07.022.

Khan HM, Cheng HH. (2022) Germline genetics of prostate cancer. *Prostate*. Aug;82 Suppl 1 (Suppl 1):S3–S12. doi: 10.1002/pros.24340.

Kiciński M, Vangronsveld J, Nawrot TS. (2011)An epidemiological reappraisal of the familial aggregation of prostate cancer: a meta-analysis. *PLoS ONE.* 6 (10):e27130.

Kiemeney LA, Sulem P, Besenbacher S, Vermeulen SH, Sigurdsson A, Thorleifsson G, Gudbjartsson DF, Stacey SN, Gudmundsson J, Zanon C, Kostic J, Masson G, Bjarnason H, Palsson ST, Skarphedinsson OB, Gudjonsson SA, Witjes JA, Grotenhuis AJ, Verhaegh GW, Bishop DT, Sak SC, Choudhury A, Elliott F, Barrett JH, Hurst CD, de Verdier PJ, Ryk C, Rudnai P, Gurzau E, Koppova K, Vineis P, Polidoro S, Guarrera S, Sacerdote C, Campagna M, Placidi D, Arici C, Zeegers MP, Kellen E, Gutierrez BS, Sanz-Velez JI, Sanchez-Zalabardo M, Valdivia G, Garcia-Prats MD, Hengstler JG, Blaszkewicz M, Dietrich H, Ophoff RA, van den Berg LH, Alexiusdottir K, Kristjansson K, Geirsson G, Nikulasson S, Petursdottir V, Kong A, Thorgeirsson T, Mungan NA, Lindblom A, van Es MA, Porru S, Buntinx F, Golka K, Mayordomo JI, Kumar R, Matullo G, Steineck G, Kiltie AE, Aben KK, Jonsson E, Thorsteinsdottir U, Knowles MA, Rafnar T, Stefansson K. (2010) A sequence variant at 4p16.3 confers susceptibility to urinary bladder cancer. *Nat Genet*. May;42(5):415–9. doi: 10.1038/ng.558.

Kiessling A, Weigle B, Fuessel S, Ebner R, Meye A, Rieger MA, Schmitz M, Temme A, Bachmann M, Wirth MP, Rieber EP. (2005) D-TMPP: a novel androgen-regulated gene preferentially expressed in prostate and prostate cancer that is the first characterized member of an eukaryotic gene family. *Prostate*. Sep 1;64(4):387–400. doi: 10.1002/pros.20250.

Kim CW, Roh SA, Tak KH, Koh BM, Ha YJ, Cho DH, Kim SY, Kim YS, Kim JC. ZKSCAN3 (2016) Facilitates Liver Metastasis of Colorectal Cancer Associated with CEA-expressing Tumor. *Anticancer Res*. May;36 (5):2397–406.

Kruithof-de Julio M, Shibata M, Desai N, Reynon M, Halili MV, Hu YP, Price SM, Abate-Shen C, Shen MM. (2013) Canonical Wnt signaling regulates Nkx3.1 expression and luminal epithelial differentiation during prostate organogenesis. *Dev Dyn*. Oct;242 (10):1160–71. doi: 10.1002/dvdy.24008.

Kohaar, I.; Petrovics, G.; Srivastava, S. (2019) A Rich Array of Prostate Cancer Molecular Biomarkers: Opportunities and Challenges. *Int. J. Mol. Sci.* 20, 1813. doi: 10.3390/ijms20081813.

Kohaar I, Zhang X, Tan SH, Nousome D, Babcock K, Ravindranath L, Sukumar G, Mcgrath-Martinez E, Rosenberger J, Alba C, Ali A, Young D, Chen Y, Cullen J, Rosner IL, Sesterhenn IA, Dobi A, Chesnut G, Turner C, Dalgard C, Wilkerson MD, Pollard HB, Srivastava S, Petrovics G. (2022) Germline mutation landscape of DNA damage repair genes in African Americans with prostate cancer highlights potentially targetable RAD genes. *Nat Commun*. Mar 15;13 (1):1361. doi: 10.1038/s41467-022-28945-x.

Kote-Jarai Z, Jugurnauth S, Mulholland S, Leongamornlert DA, Guy M, Edwards S, Tymrakiewitcz M, O'Brien L, Hall A, Wilkinson R, Al Olama AA, Morrison J, Muir K, Neal D, Donovan J, Hamdy F, Easton DF, Eeles R; UKGPCS Collaborators; British Association of Urological Surgeons' Section of Oncology. (2009) A recurrent truncating germline mutation in the BRIP1/FANCJ gene and susceptibility to prostate cancer. *Br J Cancer*. Jan 27;100 (2):426–30. doi: 10.1038/sj.bjc.6604847.

Kote-Jarai Z, Leongamornlert D, Saunders E, Tymrakiewicz M, Castro E, Mahmud N, Guy M, Edwards S, O'Brien L, Sawyer E, Hall A, Wilkinson R, Dadaev T, Goh C, Easton D; UKGPCS Collaborators; Goldgar D, Eeles R. (2011) BRCA2 is a moderate penetrance gene contributing to young-onset prostate cancer: implications for genetic testing in prostate cancer patients. *Br J Cancer*. Oct 11;105 (8):1230–4. doi: 10.1038/bjc.2011.383.

Ku SY, Gleave ME, Beltran H. (2019) Towards precision oncology in advanced prostate cancer. *Nat. Rev. Urol*. 16, 645–654. doi: 10.1038/s41585-019-0237-8.

Kudo-Saito C, Shirako H, Takeuchi T, Kawakami Y. (2009) Cancer metastasis is accelerated through immunosuppression during Snail-induced EMT of cancer cells. *Cancer Cell*. Mar 3;15(3):195–206. doi: 10.1016/j.ccr.2009.01.023.

Kurian AW, Abrahamse P, Ward KC, Hamilton AS, Deapen D, Berek JS, Hoang L, Yussuf A, Dolinsky J, Brown K, Slavin T, Hofer TP, Katz SJ. (2021) Association of Family Cancer History With Pathogenic Variants in Specific Breast Cancer Susceptibility Genes. *JCO Precis Oncol*. Dec 22;5:PO.21.00261. doi: 10.1200/PO.21.00261.

Labbé DP, Nowak DG, Deblois G, Lessard L, Giguère V, Trotman LC, Tremblay ML. (2014) Prostate cancer genetic-susceptibility locus on chromosome 20q13 is amplified and coupled to androgen receptor-regulation in metastatic tumors. *Mol Cancer Res*. Feb;12(2):18–-9. doi: 10.1158/1541-7786.MCR-13-0477.

Laitinen VH, Wahlfors T, Saaristo L, Rantapero T, Pelttari LM, Kilpivaara O, Laasanen SL, Kallioniemi A, Nevanlinna H, Aaltonen L, Vessella RL, Auvinen A, Visakorpi T, Tammela TL, Schleutker J. (2013) HOXB13 G84E mutation in Finland: population-based analysis of prostate, breast, and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev.* Mar;22 (3):452–60. doi: 10.1158/1055-9965.EPI-12-1000-T.

Laitinen VH, Akinrinade O, Rantapero T, Tammela TL, Wahlfors T, Schleutker J. (2016) Germline copy number variation analysis in Finnish families with hereditary prostate cancer. *Prostate*. Feb 15;76(3):316–24. doi: 10.1002/pros.23123.

Laird NM, Horvath S, Xu X. (2000) Implementing a unified approach to family-based tests of association. *Genet Epidemiol*. 19 Suppl 1:S36–42. doi: 10.1002/1098-2272(2000)19:1+<::AID-GEPI6>3.0.CO;2-M.

Lake SL, Blacker D, Laird NM. (2000) Family-based tests of association in the presence of linkage. *Am J Hum Genet*. Dec;67(6):1515–25. doi: 10.1086/316895.

Lasky-Su J, Murphy A, Won S, Lange C. (2011) Family-based association methods. In: Zeggini E, Morris A, editors. Analysis of Complex Disease Association Studies. p. 231–250. Academic Press; Cambridge.

Latini FR, Hemerly JP, Freitas BC, Oler G, Riggins GJ, Cerutti JM. (2011) ABI3 ectopic expression reduces in vitro and in vivo cell growth properties while inducing senescence. *BMC Cancer*. 11:11. doi: 10.1186/1471-2407-11-11.

Lazzeroni LC, Lange K. (1998) A conditional inference framework for extending the transmission/disequilibrium test. *Hum Hered.* Mar-Apr;48(2):67–81. doi: 10.1159/000022784.

Lee J, Demissie K, Lu SE, Rhoads GG. (2007) Cancer incidence among Korean-American immigrants in the United States and native Koreans in South Korea. *Cancer Control*. Jan;14 (1):78–85. doi: 10.1177/107327480701400111.

Lee S, Abecasis GR, Boehnke M, Lin X. (2014) Rare-variant association analysis: study designs and statistical tests. *Am J Hum Genet*. Jul 3;95(1):5–23. doi: 10.1016/j.ajhg.2014.06.009.

Lee J, Lee WK, Seol MY, Lee SG, Kim D, Kim H, Park J, Jung SG, Chung WY, Lee EJ, Jo YS. (2016) Coupling of LETM1 up-regulation with oxidative phosphorylation and platelet-derived growth factor receptor signaling via YAP1 transactivation. *Oncotarget*. Oct 11;7(41):66728–66739. doi: 10.18632/oncotarget.11456.

Lee S, Cho YE, Kim JY, Park JH. (2018) ZKSCAN3 Upregulation and Its Poor Clinical Outcome in Uterine Cervical Cancer. *Int J Mol Sci.* Sep 20;19 (10):2859. doi: 10.3390/ijms19102859.

Lehmann ML, Selinski S, Blaszkewicz M, Orlich M, Ovsiannikov D, Moormann O, Guballa C, Kress A, Truss MC, Gerullis H, Otto T, Barski D, Niegisch G, Albers P, Frees S, Brenner W, Thüroff JW, Angeli-Greaves M, Seidel T, Roth G, Dietrich H, Ebbinghaus

R, Prager HM, Bolt HM, Falkenstein M, Zimmermann A, Klein T, Reckwitz T, Roemer HC, Löhlein D, Weistenhöfer W, Schöps W, Beg AE, Aslam M, Bánfi G, Romics I, Ickstadt K, Schwender H, Winterpacht A, Hengstler JG, Golka K. (2010) Rs710521[A] on chromosome 3q28 close to TP63 is associated with increased urinary bladder cancer risk. *Arch Toxicol*. Dec;84(12):967–78. doi: 10.1007/s00204-010-0617-6.

Lenis AT, Ravichandran V, Brown S, Alam SM, Katims A, Truong H, Reisz PA, Vasselman S, Nweji B, Autio KA, Morris MJ, Slovin SF, Rathkopf D, Danila D, Woo S, Vargas HA, Laudone VP, Ehdaie B, Reuter V, Arcila M, Berger MF, Viale A, Scher HI, Schultz N, Gopalan A, Donoghue MTA, Ostrovnaya I, Stopsack KH, Solit DB, Abida W. (2024) Microsatellite Instability, Tumor Mutational Burden, and Response to Immune Checkpoint Blockade in Patients with Prostate Cancer. *Clin Cancer Res*. Sep 3;30(17):3894–3903. doi: 10.1158/1078-0432.CCR-23-3403

Lenth RV. (2023). emmeans: Estimated Marginal Means, aka Least-Squares Means (R package version 1.8.8). https://CRAN.R-project.org/package=emmeans

Leongamornlert D, Mahmud N, Tymrakiewicz M, Saunders E, Dadaev T, Castro E, Goh C, Govindasami K, Guy M, O'Brien L, Sawyer E, Hall A, Wilkinson R, Easton D; UKGPCS Collaborators; Goldgar D, Eeles R, Kote-Jarai Z. (2012) Germline BRCA1 mutations increase prostate cancer risk. *Br J Cancer*. May 8;106 (10):1697–701. doi: 10.1038/bjc.2012.146.

Li N, Zheng Y, Xuan C, Lin Z, Piao L, Liu S. (2015) LETM1 overexpression is correlated with the clinical features and survival outcome of breast cancer. *Int J Clin Exp Pathol*. Oct 1;8 (10):12893–900. PMID: 26722481; PMCID: PMC4680426.

Li M, Tan T, Geng Y, Tao Y, Pan J, Zhang J, Xu Q, Shen H, Zuo L, Chen Y. (2023) HOXB13 facilitates hepatocellular carcinoma progression by activating AKT/mTOR signaling pathway. *Ann Hepatol*. Jan–Feb;28 (1):100759. doi: 10.1016/j.aohep.2022.100759.

Li X, Heyer WD. (2008) Homologous recombination in DNA repair and DNA damage tolerance. *Cell Res*. Jan;18 (1):99–113. doi: 10.1038/cr.2008.1.

Liang H, Liu Y, Guo J, Dou M, Zhang X, Hu L, Chen J. (2023) Progression in immunotherapy for advanced prostate cancer. *Front Oncol.* Feb 28;13:1126752. doi: 10.3389/fonc.2023.1126752.

Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K. (2000) Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med*. Jul 13;343 (2):78–85.

Lifshitz K, Ber Y, Margel D. (2021) Role of Metabolic Syndrome in Prostate Cancer Development. *Eur Urol Focus*. May;7 (3):508–512. doi: 10.1016/j.euf.2021.04.022.

Lilja H, Ulmert D, Vickers AJ. (2008) Prostate-specific antigen and prostate cancer: prediction, detection and monitoring. *Nat Rev Cancer*. Apr;8 (4):268–78. doi: 10.1038/nrc2351. Erratum in: *Nat Rev Cancer*. May;8 (5):403.

Lim ET, Würtz P, Havulinna AS, Palta P, Tukiainen T, Rehnström K, Esko T, Mägi R, Inouye M, Lappalainen T, Chan Y, Salem RM, Lek M, Flannick J, Sim X, Manning A, Ladenvall C, Bumpstead S, Hämäläinen E, Aalto K, Maksimow M, Salmi M, Blankenberg S, Ardissino D, Shah S, Horne B, McPherson R, Hovingh GK, Reilly MP, Watkins H, Goel A, Farrall M, Girelli D, Reiner AP, Stitziel NO, Kathiresan S, Gabriel S, Barrett JC, Lehtimäki T, Laakso M, Groop L, Kaprio J, Perola M, McCarthy MI, Boehnke M, Altshuler DM, Lindgren CM, Hirschhorn JN, Metspalu A, Freimer NB, Zeller T, Jalkanen S, Koskinen S, Raitakari O, Durbin R, MacArthur DG, Salomaa V, Ripatti S, Daly MJ, Palotie A; Sequencing Initiative Suomi (SISu) Project. (2014) Distribution and medical impact of loss-of-function variants in the Finnish founder population. *PLoS Genet*. Jul 31;10 (7):e1004494. doi: 10.1371/journal.pgen.1004494.

Lim JT, Tan YQ, Valeri L, Lee J, Geok PP, Chia SE, Ong CN, Seow WJ. (2019) Association between serum heavy metals and prostate cancer risk A multiple metal analysis. *Environ Int*. Nov;132:105109. doi: 10.1016/j.envint.2019.105109.

Litwin MS, Tan HJ. (2017) The Diagnosis and Treatment of Prostate Cancer: A Review. *JAMA*. Jun 27;317 (24):2532–2542. doi: 10.1001/jama.2017.7248.

Liu YN, Niu S, Chen WY, Zhang Q, Tao Y, Chen WH, Jiang KC, Chen X, Shi H, Liu A, Li J, Li Y, Lee YC, Zhang X, Huang J. (2019) Leukemia Inhibitory Factor Promotes Castration-resistant Prostate Cancer and Neuroendocrine Differentiation by Activated ZBTB46. *Clin Cancer Res*. Jul 1;25 (13):4128–4140. doi: 10.1158/1078-0432.CCR-18-3239.

Liu YY, Xiao FF, Yang BJ, Li X, Xu SN, Chen ZW, Li P, Huang YX, Fu XM, Huang XQ, Zheng GL, Chen JP, Hou Y. (2020) Zinc finger and BTB domain-containing protein 46 is essential for survival and proliferation of acute myeloid leukemia cell line but dispensable for normal hematopoiesis. *Chin Med J (Engl)*. Jul 20;133 (14):1688–1695. doi: 10.1097/CM9.0000000000000878.

Liu M, Cai R, Wang T, Yang X, Wang M, Kuang Z, Xie Y, Zhang J, Zheng Y. (2021) LAMC2 promotes the proliferation of cancer cells and induce infiltration of macrophages in non-small cell lung cancer. *Ann Transl Med*. Sep;9 (17):1392. doi: 10.21037/atm-21-4507.

Liu YN, Chen WY, Yeh HL, Chen WH, Jiang KC, Li HR, Dung PVT, Chen ZQ, Lee WJ, Hsiao M, Huang J, Wen YC. (2024) MCTP1 increases the malignancy of androgen-deprived prostate cancer cells by inducing neuroendocrine differentiation and EMT. *Sci Signal.* Jun 11;17 (840):eadc9142. doi: 10.1126/scisignal.adc9142.

Loeb S, Eastham JA. (2021) Diagnosis and staging of prostate cancer. In: Partin AW, Dmochowski RR, Kavoussi LR, Peters CA, eds. Campbell-Walsh-Wein Urology. 12th ed. Chap 152. Elsevier, Philadelphia.

Lonergan PE, Tindall DJ. (2011) Androgen receptor signaling in prostate cancer development and progression. *J Carcinog*. 10:20. doi: 10.4103/1477-3163.83937.

Lord CJ, Ashworth A. (2012) The DNA damage response and cancer therapy. *Nature*. Jan 18;481 (7381):287–94. doi: 10.1038/nature10760.

Lowe JS, Anderson PG (2015) Human histology. 4th Edition. Chapter 16: p. 330–331. Mosby Ltd, Alabama.

Lunetta KL, Faraone SV, Biederman J, Laird NM. (2000) Family-based tests of association and linkage that use unaffected sibs, covariates, and interactions. *Am J Hum Genet*. Feb;66(2):605–14. doi: 10.1086/302782.

Lunn RM, Bell DA, Mohler JL, Taylor JA. (1999) Prostate cancer risk and polymorphism in 17 hydroxylase (CYP17) and steroid reductase (SRD5A2). *Carcinogenesis*. 1999 Sep;20 (9):1727–31. doi: 10.1093/carcin/20.9.1727.

McCarroll SA. (2008) Extending genome-wide association studies to copy-number variation. *Hum Mol Genet*. Oct 15;17 (R2):R135–42. doi: 10.1093/hmg/ddn282.

Mai PL, Garceau AO, Graubard BI, Dunn M, McNeel TS, Gonsalves L, Gail MH, Greene MH, Willis GB, Wideroff L. (2011) Confirmation of family cancer history reported in a population-based survey. *J Natl Cancer Inst.* May 18;103(10):788–97. doi: 10.1093/jnci/djr114.

Mak GW, Chan MM, Leong VY, Lee JM, Yau TO, Ng IO, Ching YP. (2011) Overexpression of a novel activator of PAK4, the CDK5 kinase-associated protein CDK5RAP3, promotes hepatocellular carcinoma metastasis. *Cancer Res*. Apr 15;71 (8):2949–58. doi: 10.1158/0008-5472.CAN-10-4046.

Mancuso N, Rohland N, Rand KA, Tandon A, Allen A, Quinque D, Mallick S, Li H, Stram A, Sheng X, Kote-Jarai Z, Easton DF, Eeles RA; PRACTICAL consortium; Le Marchand L, Lubwama A, Stram D, Watya S, Conti DV, Henderson B, Haiman CA, Pasaniuc B, Reich D. (2016) The contribution of rare variation to prostate cancer heritability. *Nat Genet.* Jan;48 (1):30–5. doi: 10.1038/ng.3446.

Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, McCarthy MI, Ramos EM, Cardon LR, Chakravarti A, Cho JH, Guttmacher AE, Kong A, Kruglyak L, Mardis E, Rotimi CN, Slatkin M, Valle D, Whittemore AS, Boehnke M, Clark AG, Eichler EE, Gibson G, Haines JL, Mackay TF, McCarroll SA, Visscher PM. (2009) Finding the missing heritability of complex diseases. *Nature*. Oct 8;461(7265):747–53. doi: 10.1038/nature08494.

Martin RM, Donovan JL, Turner EL, Metcalfe C, Young GJ, Walsh EI, Lane JA, Noble S, Oliver SE, Evans S, Sterne JAC, Holding P, Ben-Shlomo Y, Brindle P, Williams NJ, Hill EM, Ng SY, Toole J, Tazewell MK, Hughes LJ, Davies CF, Thorn JC, Down E, Davey Smith G, Neal DE, Hamdy FC; CAP Trial Group. (2018) Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality: The CAP Randomized Clinical Trial. *JAMA*. 2018 Mar 6;319 (9):883–895. doi: 10.1001/jama.2018.0154

Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, Nava Rodrigues D, Robinson D, Omlin A, Tunariu N, Boysen G, Porta N, Flohr P, Gillman A, Figueiredo I, Paulding C, Seed G, Jain S, Ralph C, Protheroe A, Hussain S, Jones R, Elliott T, McGovern U, Bianchini D, Goodall J, Zafeiriou Z, Williamson CT, Ferraldeschi R, Riisnaes R, Ebbs B, Fowler G, Roda D, Yuan W, Wu YM, Cao X, Brough R, Pemberton H, A'Hern R, Swain A, Kunju LP, Eeles R, Attard G, Lord CJ, Ashworth

A, Rubin MA, Knudsen KE, Feng FY, Chinnaiyan AM, Hall E, de Bono JS. (2015) DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. *N Engl J Med*. Oct 29;373 (18):1697–708. doi: 10.1056/NEJMoa1506859.

Mateo J, Lord CJ, Serra V, Tutt A, Balmaña J, Castroviejo-Bermejo M, Cruz C, Oaknin A, Kaye SB, de Bono JS. (2019) A decade of clinical development of PARP inhibitors in perspective. *Ann Oncol.* Sep 1;30 (9):1437-1447. doi: 10.1093/annonc/mdz192.

May M, Kaufmann O, Hammermann F, Loy V, Siegsmund M. (2007) Prognostic impact of lymphovascular invasion in radical prostatectomy specimens. *BJU Int*. Mar;99 (3):539–44. doi: 10.1111/j.1464-410X.2006.06650.x.

McDonald AC, Vira MA, Vidal AC, Gan W, Freedland SJ, Taioli E. (2014) Association between systemic inflammatory markers and serum prostate-specific antigen in men without prostatic disease the 2001-2008 National Health and Nutrition Examination Survey. *Prostate*. 2014 May;74 (5):561–7. doi: 10.1002/pros.22782.

McLaren W, Gil L, Hunt SE, Riat HS, Ritchie GR, Thormann A, Flicek P, Cunningham F. (2016) The Ensembl Variant Effect Predictor. *Genome Biol*. Jun 6;17 (1):122. doi: 10.1186/s13059-016-0974-4.

Meredith MM, Liu K, Darrasse-Jeze G, Kamphorst AO, Schreiber HA, Guermonprez P, Idoyaga J, Cheong C, Yao KH, Niec RE, Nussenzweig MC. (2012) Expression of the zinc finger transcription factor zDC (Zbtb46, Btbd4) defines the classical dendritic cell lineage. *J Exp Med*. Jun 4;209(6):1153–65. doi: 10.1084/jem.20112675.

Merseburger AS, Alcaraz A, von Klot CA. (2016) Androgen deprivation therapy as backbone therapy in the management of prostate cancer. *Onco Targets Ther*. Nov 29;9:7263–7274. doi: 10.2147/OTT.S117176.

Minoura Y, Takahashi M, Maeda H, Kuwahara S, Tachikawa H, Yamamoto M, Tomioka N, Watanabe K, Sakurai A. (2022) Significance of prostate/pancreatic/skin cancer family history for detecting BRCA2 pathogenic variant careers among patients with breast cancer. *Breast Cancer*. Sep;29(5):808–813. doi: 10.1007/s12282-022-01360-2.

Mohanty SK, Lobo A, Cheng L. (2023) The 2022 revision of the World Health Organization classification of tumors of the urinary system and male genital organs: advances and challenges. *Hum Pathol*. Jun;136:123–143. doi: 10.1016/j.humpath.2022.08.006.

Mohler JL, Antonarakis ES, Armstrong AJ, D'Amico AV, Davis BJ, Dorff T, Eastham JA, Enke CA, Farrington TA, Higano CS, Horwitz EM, Hurwitz M, Ippolito JE, Kane CJ, Kuettel MR, Lang JM, McKenney J, Netto G, Penson DF, Plimack ER, Pow-Sang JM, Pugh TJ, Richey S, Roach M, Rosenfeld S, Schaeffer E, Shabsigh A, Small EJ, Spratt DE, Srinivas S, Tward J, Shead DA, & Freedman-Cass D. A. (2019) Prostate Cancer, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network. *J Natl Compr Canc Netw*, 17 (5), 479–505. doi: 10.6004/jnccn.2019.0023.

Mollica V, Di Nunno V, Santoni M, Cimadamore A, Scarpelli M, Lopez-Beltran A, Cheng L, Mariani C, Battelli N, Montironi R, Massari F. (2020) An evaluation of current prostate cancer diagnostic approaches with emphasis on liquid biopsies and prostate cancer. *Expert Rev Mol Diagn*. Feb;20 (2):207–217. doi: 10.1080/14737159.2019.1684265.

Moore CM, Giganti F, Albertsen P, Allen C, Bangma C, Briganti A, Carroll P, Haider M, Kasivisvanathan V, Kirkham A, Klotz L, Ouzzane A, Padhani AR, Panebianco V, Pinto P, Puech P, Rannikko A, Renard-Penna R, Touijer K, Turkbey B, van Poppel H, Valdagni R, Walz J, Schoots I. (2017) Reporting Magnetic Resonance Imaging in Men on Active Surveillance for Prostate Cancer: The PRECISE Recommendations-A Report of a European School of Oncology Task Force. *Eur Urol*. Apr;71 (4):648–655. doi: 10.1016/j.eururo.2016.06.011.

Moraes L, Zanchin NIT, Cerutti JM. (2017) ABI3, a component of the WAVE2 complex, is potentially regulated by PI3K/AKT pathway. *Oncotarget*. Jun 29;8 (40):67769–67781. doi: 10.18632/oncotarget.18840.

Moreira DM, Howard LE, Sourbeer KN, Amarasekara HS, Chow LC, Cockrell DC, Pratson CL, Hanyok BT, Aronson WJ, Kane CJ, Terris MK, Amling CL, Cooperberg MR, Freedland SJ. (2017) Predicting Time From Metastasis to Overall Survival in Castration-Resistant Prostate Cancer: Results From SEARCH. *Clin Genitourin Cancer*. Feb;15 (1):60–66.e2. doi: 10.1016/j.clgc.2016.08.018.

Moses KA, Sprenkle PC, Bahler C, Box G, Carlsson SV, Catalona WJ, Dahl DM, Dall'Era M, Davis JW, Drake BF, Epstein JI, Etzioni RB, Farrington TA, Garraway IP, Jarrard D, Kauffman E, Kaye D, Kibel AS, LaGrange CA, Maroni P, Ponsky L, Reys B, Salami SS, Sanchez A, Seibert TM, Shaneyfelt TM, Smaldone MC, Sonn G, Tyson MD, Vapiwala N, Wake R, Washington S, Yu A, Yuh B, Berardi RA, Freedman-Cass DA.

(2023) NCCN Guidelines® Insights: Prostate Cancer Early Detection, Version 1.2023. *J Natl Compr Canc Netw.* Mar;21 (3):236–246. doi: 10.6004/jnccn.2023.0014.

Mucci LA, Hjelmborg JB, Harris JR, Czene K, Havelick DJ, Scheike T, Graff RE, Holst K, Möller S, Unger RH, McIntosh C, Nuttall E, Brandt I, Penney KL, Hartman M, Kraft P, Parmigiani G, Christensen K, Koskenvuo M, Holm NV, Heikkilä K, Pukkala E, Skytthe A, Adami HO, Kaprio J; Nordic Twin Study of Cancer (NorTwinCan) Collaboration. (2016) Familial Risk and Heritability of Cancer Among Twins in Nordic Countries. *JAMA*. Jan 5;315 (1):68–76. doi: 10.1001/jama.2015.17703. Erratum in: JAMA. 2016 Feb 23;315 (8):822. doi: 10.1001/jama.2016.0197.

Muranen TA, Mavaddat N, Khan S, Fagerholm R, Pelttari L, Lee A, Aittomäki K, Blomqvist C, Easton DF, Nevanlinna H. (2016) Polygenic risk score is associated with increased disease risk in 52 Finnish breast cancer families. *Breast Cancer Res Treat*. Aug;158(3):463–9. doi: 10.1007/s10549-016-3897-6.

Möller K, Kluth M, Ahmed M, Burkhardt L, Möller-Koop C, Büscheck F, Weidemann S, Tsourlakis MC, Minner S, Heinzer H, Huland H, Graefen M, Sauter G, Schlomm T, Dum D, Simon R. (2021) Chromosome 5 harbors two independent deletion hotspots at 5q13 and 5q21 that characterize biologically different subsets of aggressive prostate cancer. Int J Cancer. Feb 1;148(3):748–758. doi: 10.1002/ijc.33344.

Na R, Zheng SL, Han M, Yu H, Jiang D, Shah S, Ewing CM, Zhang L, Novakovic K, Petkewicz J, Gulukota K, Helseth DL Jr, Quinn M, Humphries E, Wiley KE, Isaacs SD, Wu Y, Liu X, Zhang N, Wang CH, Khandekar J, Hulick PJ, Shevrin DH, Cooney KA, Shen Z, Partin AW, Carter HB, Carducci MA, Eisenberger MA, Denmeade SR, McGuire M, Walsh PC, Helfand BT, Brendler CB, Ding Q, Xu J, Isaacs WB. (2017) Germline Mutations in ATM and BRCA1/2 Distinguish Risk for Lethal and Indolent Prostate Cancer and are Associated with Early Age at Death. *Eur Urol.* May;71 (5):740–747. doi: 10.1016/j.eururo.2016.11.033.

Nakagawa H, Fujita M. (2018) Whole genome sequencing analysis for cancer genomics and precision medicine. *Cancer Sci*. Mar;109(3):513–522. doi: 10.1111/cas.13505.

National Cancer Institute (2025). Prostate cancer statistics. SEER Cancer Statistics. https://seer.cancer.gov/statfacts/html/prost.html Data source(s): SEER Incidence Data, November 2024 Submission (1975-2022), SEER 21 registries. [Read 2.4.2025]

Netto GJ, Amin MB, Kench JG. (2022) Tumours of the prostate: Introduction. In: WHO Classification of Tumours Editorial Board. Urinary and male genital tumours. 5th ed., vol. 8. IARC Press, Lyon.

Nguyen-Dumont T, MacInnis RJ, Steen JA, Theys D, Tsimiklis H, Hammet F, Mahmoodi M, Pope BJ, Park DJ, Mahmood K, Severi G, Bolton D, Milne RL, Giles GG, Southey MC. (2020) Rare germline genetic variants and risk of aggressive prostate cancer. *Int J Cancer*. Oct 15;147(8):2142–2149. doi: 10.1002/ijc.33024.

Niclis C, Román MD, Osella AR, Eynard AR, Díaz Mdel P. (2015) Traditional Dietary Pattern Increases Risk of Prostate Cancer in Argentina: Results of a Multilevel Modeling and Bias Analysis from a Case-Control Study. *J Cancer Epidemiol*. 2015:179562. doi: 10.1155/2015/179562.

Nicolosi P, Ledet E, Yang S, Michalski S, Freschi B, O'Leary E, Esplin ED, Nussbaum RL, Sartor O. (2019) Prevalence of Germline Variants in Prostate Cancer and Implications for Current Genetic Testing Guidelines. *JAMA Oncol*. Apr 1;5 (4):523–528.

Niu Y, Ferreira Azevedo CA, Li X, Kamali E, Haagen Nielsen O, Storgaard Sørensen C, Frödin M. (2022) Multiparametric and accurate functional analysis of genetic sequence variants using CRISPR-Select. *Nat Genet*. Dec;54(12):1983–1993. doi: 10.1038/s41588-022-01224-7.

Näslund-Koch C, Nordestgaard BG, Bojesen SE. (2016) Increased Risk for Other Cancers in Addition to Breast Cancer for CHEK2*1100delC Heterozygotes Estimated From the Copenhagen General Population Study. *J Clin Oncol*. Apr 10;34 (11):1208–16. doi: 10.1200/JCO.2015.63.3594.

Okuda H, Toyota M, Ishida W, Furihata M, Tsuchiya M, Kamada M, Tokino T, Shuin T. (2006) Epigenetic inactivation of the candidate tumor suppressor gene HOXB13 in human renal cell carcinoma. *Oncogene*. Mar 16;25 (12):1733–42. doi: 10.1038/sj.onc.1209200.

Ooms J. (2024). writexl: Export Data Frames to Excel 'xlsx' Format (R package version 1.5.0). https://CRAN.R-project.org/package=writexl

Orozco G, Barrett JC, Zeggini E. (2010) Synthetic associations in the context of genome-wide association scan signals. *Hum Mol Genet*. Oct 15;19(R2):R137-44. doi: 10.1093/hmg/ddq368.

Osterburg C, Dötsch V. (2022) Structural diversity of p63 and p73 isoforms. *Cell Death Differ*. May;29(5):921–937. doi: 10.1038/s41418-022-00975-4.

Ostrander EA, Markianos K, Stanford JL. (2004) Finding prostate cancer susceptibility genes. *Annu Rev Genomics Hum Genet.* 5:151–75. doi: 10.1146/annurev. genom.5.061903. 180044.

Ott J, Wang J, Leal SM. (2015) Genetic linkage analysis in the age of whole-genome sequencing. *Nat Rev Genet*. May;16 (5):275–84. doi: 10.1038/nrg3908. Epub 2015 Mar 31.

Pacheco-Barcia V, Muñoz A, Castro E, Ballesteros AI, Marquina G, González-Díaz I, Colomer R, Romero-Laorden N. (2022) The Homologous Recombination Deficiency Scar in Advanced Cancer: Agnostic Targeting of Damaged DNA Repair. *Cancers (Basel)*. Jun 15;14 (12):2950. doi: 10.3390/cancers14122950.

Pardo LA, Beane Freeman LE, Lerro CC, Andreotti G, Hofmann JN, Parks CG, Sandler DP, Lubin JH, Blair A, Koutros S. (2020) Pesticide exposure and risk of aggressive prostate cancer among private pesticide applicators. *Environ Health*. Mar 5;19 (1):30. doi: 10.1186/s12940-020-00583-0.

Patel AR, Klein EA. (2009) Risk factors for prostate cancer. *Nat Clin Pract Urol*. Feb;6(2):87–95. doi: 10.1038/ncpuro1290

Patel D, Chaudhary J. (2012) Increased expression of bHLH transcription factor E2A (TCF3) in prostate cancer promotes proliferation and confers resistance to doxorubicin induced apoptosis. *Biochem Biophys Res Commun*. May 25;422 (1):146–51. doi: 10.1016/j.bbrc.2012.04.126.

Piao L, Feng Y, Yang Z, Qi W, Li H, Han H, Xuan Y. (2019) LETM1 is a potential cancer stem-like cell marker and predicts poor prognosis in colorectal adenocarcinoma. *Pathol Res Pract*. Jul;215 (7):152437. doi: 10.1016/j.prp.2019.152437.

Piao L, Li H, Feng Y, Li X, Cui Y, Xuan Y. (2020) Leucine Zipper-EF-Hand Containing Transmembrane Protein 1 Is a Potential Prognostic Biomarker and Promotes Cell Progression in Prostate Cancer. *Cancer Manag Res*. Mar 6;12:1649–1660. doi: 10.2147/CMAR.S236482.

Pierce BL, Friedrichsen-Karyadi DM, McIntosh L, Deutsch K, Hood L, Ostrander EA, Austin MA, Stanford JL. (2007) Genomic scan of 12 hereditary prostate cancer families having an occurrence of pancreas cancer. *Prostate*. Mar 1;67(4):410–5. doi: 10.1002/pros.20527.

Pilarski R. (2019) The Role of BRCA Testing in Hereditary Pancreatic and Prostate Cancer Families. *Am Soc Clin Oncol Educ Book*. Jan;39:79–86. doi: 10.1200/ EDBK_238977.

Pitkäniemi J, Malila N, Heikkinen S, Seppä K. (2022) Cancer in Finland 2022. Cancer Society of Finland, Helsinki 2024.https://syoparekisteri.fi/assets/files/2024/06/Cancer_2022_EN.pdf [Read 19.4.2025]

Previtali V, Bagnolini G, Ciamarone A, Ferrandi G, Rinaldi F, Myers SH, et al. (2024) New horizons of synthetic lethality in cancer: current development and future perspectives. J *Med Chem*. 67:11488–521. doi: 10.1021/acs.jmedchem.4c00113.

Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, Garofalo A, Gulati R, Carreira S, Eeles R, Elemento O, Rubin MA, Robinson D, Lonigro R, Hussain M, Chinnaiyan A, Vinson J, Filipenko J, Garraway L, Taplin ME, AlDubayan S, Han GC, Beightol M, Morrissey C, Nghiem B, Cheng HH, Montgomery B, Walsh T, Casadei S, Berger M, Zhang L, Zehir A, Vijai J, Scher HI, Sawyers C, Schultz N, Kantoff PW, Solit D, Robson M, Van Allen EM, Offit K, de Bono J, Nelson PS. (2016) Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. *N Engl J Med*. Aug 4;375 (5):443–53.

Qi LS, Larson MH, Gilbert LA, Doudna JA, Weissman JS, Arkin AP, Lim WA. (2013) Repurposing CRISPR as an RNA-guided platform for sequence-specific control of gene expression. *Cell*. Feb 28;152(5):1173–83. doi: 10.1016/j.cell.2013.02.022. Erratum in: *Cell*. 2021 Feb 4;184(3):844. doi: 10.1016/j.cell.2021.01.019.

R Core Team. (2024). R: A language and environment for statistical computing. R Foundation for Statistical Computing. https://www.R-project.org/

Rabinowitz D, Laird NM. (2000) A unified approach to adjusting association tests for population admixture with arbitrary pedigree structure and arbitrary missing marker information. *Hum Hered*. Jul-Aug;50(4):211–23. doi: 10.1159/000022918. PMID: 10782012.

Raghallaigh H, Eeles R. (2022) Genetic predisposition to prostate cancer: an update. *Fam Cancer.* Jan;21 (1):101–114. doi: 10.1007/s10689-021-00227-3.

Raith F, O'Donovan DH, Lemos C, Politz O, Haendler B. (2023) Addressing the Reciprocal Crosstalk between the AR and the PI3K/AKT/mTOR Signaling Pathways for Prostate Cancer Treatment. *Int J Mol Sci*. Jan 24;24 (3):2289. doi: 10.3390/ijms24032289.

Ramanand SG, Chen Y, Yuan J, Daescu K, Lambros MB, Houlahan KE, Carreira S, Yuan W, Baek G, Sharp A, Paschalis A, Kanchwala M, Gao Y, Aslam A, Safdar N, Zhan X, Raj GV, Xing C, Boutros PC, de Bono J, Zhang MQ, Mani RS. (2020) The landscape of RNA polymerase II-associated chromatin interactions in prostate cancer. *J Clin Invest*. Aug 3;130 (8):3987–4005. doi: 10.1172/JCI134260.

Rantapero T, Wahlfors T, Kähler A, Hultman C, Lindberg J, Tammela TL, Nykter M, Schleutker J, Wiklund F. (2020) Inherited DNA Repair Gene Mutations in Men with Lethal Prostate Cancer. *Genes (Basel).* Mar 14;11 (3):314. doi: 10.3390/genes11030314.

Rebello RJ, Oing C, Knudsen KE, Loeb S, Johnson DC, Reiter RE, Gillessen S, Van der Kwast T, Bristow RG. (2021) Prostate cancer. *Nat Rev Dis Primers*. Feb 4;7(1):9. doi: 10.1038/s41572-020-00243-0.

Rebbeck TR. (2017) Prostate Cancer Genetics: Variation by Race, Ethnicity, and Geography. *Semin. Radiat. Oncol*. 27, 3–10. doi: 10.1016/j.semradonc.2016.08.002.

Reese AC. (2016) Clinical and pathologic staging of prostate cancer. In: Mydlo JH, Godec CJ, editors. Prostate Cancer. 2nd ed., p. 353–360. Academic Press, Cambridge. Available from: https://doi.org/10.1016/B978-0-12-800077-9.00039-6

Reiss AB, Vasalani S, Albert J, Drewes W, Li K, Srivastava A, De Leon J, Katz AE. (2024) The Effect of Androgen Deprivation Therapy on the Cardiovascular System in Advanced Prostate Cancer. *Medicina* (Kaunas). Oct 22;60 (11):1727. doi: 10.3390/medicina60111727.

Ren ZJ, Cao DH, Zhang Q, Ren PW, Liu LR, Wei Q, Wei WR, Dong Q. (2019) First-degree family history of breast cancer is associated with prostate cancer risk: a systematic review and meta-analysis. *BMC Cancer*. Sep 2;19(1):871. doi: 10.1186/s12885-019-6055-9.

Rentzsch P, Witten D, Cooper GM, Shendure J, Kircher M. (2019) CADD: predicting the deleteriousness of variants throughout the human genome. *Nucleic Acids Res*. Jan 8;47 (D1):D886–D894. doi: 10.1093/nar/gky1016.

Riaz F, Sultana S, Asad L, Mirjat D, Shazi MI, Zia MK, Aziz N, Abdel-Maksoud MA, Saleh IA, Al-Hawadi JS, Zomot N, Almutairi SM, Ali A. (2024) Analyzing the mutational landscape of prostate cancer susceptibility genes through next-generation sequencing (NGS). *Am J Transl Res*. Sep 15;16 (9):4450–4465. doi: 10.62347/QRIF7244.

Rice MA, Malhotra SV, Stoyanova T. (2019) Second-Generation Antiandrogens: From Discovery to Standard of Care in Castration Resistant Prostate Cancer. *Front Oncol*. Aug 28;9:801. doi: 10.3389/fonc.2019.00801.

Richman EL, Kenfield SA, Stampfer MJ, Giovannucci EL, Zeisel SH, Willett WC, Chan JM. (2012) Choline intake and risk of lethal prostate cancer: incidence and survival. *Am J Clin Nutr*. Oct;96 (4):855–63. doi: 10.3945/ajcn.112.039784.

Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM, Montgomery B, Taplin ME, Pritchard CC, Attard G, Beltran H, Abida W, Bradley RK, Vinson J, Cao X, Vats P, Kunju LP, Hussain M, Feng FY, Tomlins SA, Cooney KA, Smith DC, Brennan C, Siddiqui J, Mehra R, Chen Y, Rathkopf DE, Morris MJ, Solomon SB, Durack JC, Reuter VE, Gopalan A, Gao J, Loda M, Lis RT, Bowden M, Balk SP, Gaviola G, Sougnez C, Gupta M, Yu EY, Mostaghel EA, Cheng HH, Mulcahy H, True LD, Plymate SR, Dvinge H, Ferraldeschi R, Flohr P, Miranda S, Zafeiriou Z, Tunariu N, Mateo J, Perez-Lopez R, Demichelis F, Robinson BD, Sboner A, Schiffman M, Nanus DM, Tagawa ST, Sigaras A, Eng KW, Elemento O, Sboner A, Heath EI, Scher HI, Pienta KJ, Kantoff P, de Bono JS, Rubin MA, Nelson PS, Garraway LA, Sawyers CL, Chinnaiyan AM. (2015) Integrative Clinical Genomics of Advanced Prostate Cancer. *Cell*. Jul 16;162 (2):454. doi: 10.1016/j.cell.2015.06.053.

Roeder K, Bacanu SA, Wasserman L, Devlin B. (2006) Using linkage genome scans to improve power of association in genome scans. *Am J Hum Genet*. Feb;78 (2):243–52.

Rowe SP, Gorin MA, Allaf ME, Pienta KJ, Tran PT, Pomper MG, Ross AE, Cho SY. (2016) PET imaging of prostate-specific membrane antigen in prostate cancer: current state of the art and future challenges. *Prostate Cancer Prostatic Dis*. Sep;19 (3):223–30. doi: 10.1038/pcan.2016.13. Epub 2016 May 3.

Rumpf F, Plym A, Vaselkiv JB, Penney KL, Preston MA, Kibel AS, Mucci LA, Salari K. (2024) Impact of Family History and Germline Genetic Risk Single Nucleotide Polymorphisms on Long-Term Outcomes of Favorable-Risk Prostate Cancer. *J Urol.* Jun;211(6):754–764. doi: 10.1097/JU.0000000000003927.

Rusak B, Kluźniak W, Wokołorczykv D, Stempa K, Kashyap A, Gronwald J, Huzarski T, Dębniak T, Jakubowska A, Masojć B, Akbari MR, Narodv SA, Lubiński J, Cybulski C. (2019) Inherited NBN Mutations and Prostate Cancer Risk and Survival. *Cancer Res Treat*. Jul;51 (3):1180–1187. doi: 10.4143/crt.2018.532.

Russo J, Giri VN. (2022) Germline testing and genetic counselling in prostate cancer. *Nat Rev Urol.* Jun;19 (6):331–343. doi: 10.1038/s41585-022-00580-7.

Russo A, Incorvaia L, Capoluongo E, Tagliaferri P, Gori S, Cortesi L, Genuardi M, Turchetti D, De Giorgi U, Di Maio M, Barberis M, Dessena M, Del Re M, Lapini A, Luchini C, Jereczek-Fossa BA, Sapino A, Cinieri S; Italian Scientific Societies. (2022) Implementation of preventive and predictive BRCA testing in patients with breast, ovarian, pancreatic, and prostate cancer: a position paper of Italian Scientific Societies. *ESMO Open*. Jun;7 (3):100459. doi: 10.1016/j.esmoop.2022.100459.

Ryan S, Jenkins MA, Win AK. (2014) Risk of prostate cancer in Lynch syndrome: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev*. Mar;23 (3):437–49. doi: 10.1158/1055-9965.EPI-13-1165.

Sanchez A, Schoenfeld JD, Nguyen PL, Fiorentino M, Chowdhury D, Stampfer MJ, Sesso HD, Giovannucci E, Mucci LA, Shui IM. (2016) Common variation in BRCA1 may have a role in progression to lethal prostate cancer after radiation treatment. *Prostate Cancer Prostatic Dis*. Jun;19 (2):197–201. doi: 10.1038/pcan.2016.4.

Sartor O, Yang S, Ledet E, Moses M, Nicolosi P. (2020) Inherited DNA-repair gene mutations in African American men with prostate cancer. *Oncotarget*. Jan 28;11 (4):440–442. doi: 10.18632/oncotarget.27456.

Satpathy AT, KC W, Albring JC, Edelson BT, Kretzer NM, Bhattacharya D, Murphy TL, Murphy KM. (2012) Zbtb46 expression distinguishes classical dendritic cells and their committed progenitors from other immune lineages. *J Exp Med*. Jun 4;209(6):1135–52. doi: 10.1084/jem.20120030.

Saunders EJ, Dadaev T, Leongamornlert DA, Jugurnauth-Little S, Tymrakiewicz M, Wiklund F, Al Olama AA, Benlloch S, Neal DE, Hamdy FC, Donovan JL, Giles GG, Severi G, Gronberg H, Aly M, Haiman CA, Schumacher F, Henderson BE, Lindstrom S, Kraft P, Hunter DJ, Gapstur S, Chanock S, Berndt SI, Albanes D, Andriole G, Schleutker J, Weischer M, Nordestgaard BG, Canzian F, Campa D, Riboli E, Key TJ, Travis RC, Ingles SA, John EM, Hayes RB, Pharoah P, Khaw KT, Stanford JL, Ostrander EA, Signorello LB, Thibodeau SN, Schaid D, Maier C, Kibel AS, Cybulski C, Cannon-Albright L, Brenner H, Park JY, Kaneva R, Batra J, Clements JA, Teixeira MR, Xu J, Mikropoulos C, Goh C, Govindasami K, Guy M, Wilkinson RA, Sawyer EJ, Morgan A; COGS-CRUK GWAS-ELLIPSE (Part of GAME-ON) Initiative; UK Genetic Prostate Cancer Study Collaborators; UK ProtecT Study Collaborators; PRACTICAL Consortium; Easton DF, Muir K, Eeles RA, Kote-Jarai Z. (2014) Fine-mapping the HOXB region detects common variants tagging a rare coding allele: evidence for synthetic association in prostate cancer. *PLoS Genet*. Feb 13;10 (2):e1004129. doi: 10.1371/journal.pgen.1004129.

Saunders EJ, Kote-Jarai Z, Eeles RA. (2021) Identification of Germline Genetic Variants that Increase Prostate Cancer Risk and Influence Development of Aggressive Disease. *Cancers (Basel)*. Feb 12;13(4):760. doi: 10.3390/cancers13040760.

Sathyanarayana UG, Padar A, Suzuki M, Maruyama R, Shigematsu H, Hsieh JT, Frenkel EP, Gazdar AF. (2003) Aberrant promoter methylation of laminin-5-encoding genes in prostate cancers and its relationship to clinicopathological features. *Clin Cancer Res*. Dec 15;9 (17):6395–400. PMID: 14695140.

Sayan M, Tuac Y, Akgul M, Pratt GK, Rowan MD, Akbulut D, Kucukcolak S, Tjio E, Moningi S, Leeman JE, Orio PF, Nguyen PL, D'Amico AV, Aktan C. (2024) Prognostic Significance of the Cribriform Pattern in Prostate Cancer: Clinical Outcomes and Genomic Alterations. *Cancers (Basel)*. Mar 22;16 (7):1248. doi: 10.3390/cancers16071248.

Schaeffer EM, Srinivas S, Adra N, An Y, Barocas D, Bitting R, Bryce A, Chapin B, Cheng HH, D'Amico AV, Desai N, Dorff T, Eastham JA, Farrington TA, Gao X, Gupta S, Guzzo T, Ippolito JE, Kuettel MR, Lang JM, Lotan T, McKay RR, Morgan T, Netto G, Pow-Sang JM, Reiter R, Roach M, Robin T, Rosenfeld S, Shabsigh A, Spratt D, Teply BA, Tward J, Valicenti R, Wong JK, Shead DA, Snedeker J, Freedman-Cass DA. (2023)

Prostate Cancer, Version 4.2023, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. Oct;21 (10):1067–1096. doi: 10.6004/jnccn.2023.0050.

Schaid DJ, McDonnell SK, FitzGerald LM, DeRycke L, Fogarty Z, Giles GG, MacInnis RJ, Southey MC, Nguyen-Dumont T, Cancel-Tassin G, Cussenot O, Whittemore AS, Sieh W, Ioannidis NM, Hsieh CL, Stanford JL, Schleutker J, Cropp CD, Carpten J, Hoegel J, Eeles R, Kote-Jarai Z, Ackerman MJ, Klein CJ, Mandal D, Cooney KA, Bailey-Wilson JE, Helfand B, Catalona WJ, Wiklund F, Riska S, Bahetti S, Larson MC, Cannon Albright L, Teerlink C, Xu J, Isaacs W, Ostrander EA, Thibodeau SN. (2021) Two-stage Study of Familial Prostate Cancer by Whole-exome Sequencing and Custom Capture Identifies 10 Novel Genes Associated with the Risk of Prostate Cancer. *Eur Urol*. Mar;79(3):353–361. doi: 10.1016/j.eururo.2020.07.038.

Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Zappa M, Nelen V, Kwiatkowski M, Lujan M, Määttänen L, Lilja H, Denis LJ, Recker F, Paez A, Bangma CH, Carlsson S, Puliti D, Villers A, Rebillard X, Hakama M, Stenman UH, Kujala P, Taari K, Aus G, Huber A, van der Kwast TH, van Schaik RH, de Koning HJ, Moss SM, Auvinen A; ERSPC Investigators. (2014) Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet*. Dec 6;384 (9959):2027–35. doi: 10.1016/S0140-6736 (14)60525-0.

Schumacher FR, Schmit SL, Jiao S, Edlund CK, Wang H, Zhang B, Hsu L, Huang SC, Fischer CP, Harju JF, Idos GE, Lejbkowicz F, Manion FJ, McDonnell K, McNeil CE, Melas M, Rennert HS, Shi W, Thomas DC, Van Den Berg DJ, Hutter CM, Aragaki AK, Butterbach K, Caan BJ, Carlson CS, Chanock SJ, Curtis KR, Fuchs CS, Gala M, Giovannucci EL, Gogarten SM, Hayes RB, Henderson B, Hunter DJ, Jackson RD, Kolonel LN, Kooperberg C, Küry S, LaCroix A, Laurie CC, Laurie CA, Lemire M, Levine D, Ma J, Makar KW, Qu C, Taverna D, Ulrich CM, Wu K, Kono S, West DW, Berndt SI, Bezieau S, Brenner H, Campbell PT, Chan AT, Chang-Claude J, Coetzee GA, Conti DV, Duggan D, Figueiredo JC, Fortini BK, Gallinger SJ, Gauderman WJ, Giles G, Green R, Haile R, Harrison TA, Hoffmeister M, Hopper JL, Hudson TJ, Jacobs E, Iwasaki M, Jee SH, Jenkins M, Jia WH, Joshi A, Li L, Lindor NM, Matsuo K, Moreno V, Mukherjee B, Newcomb PA, Potter JD, Raskin L, Rennert G, Rosse S, Severi G, Schoen RE, Seminara D, Shu XO, Slattery ML, Tsugane S, White E, Xiang

YB, Zanke BW, Zheng W, Le Marchand L, Casey G, Gruber SB, Peters U. (2015) Genome-wide association study of colorectal cancer identifies six new susceptibility loci. *Nat Commun*. Jul 7;6:7138. doi: 10.1038/ncomms8138. Erratum in: Nat Commun. 2015 Oct 26;6:8739. doi: 10.1038/ncomms9739.. Kury, Sebastian; Giocannucci, Edward L. and Lemire, Mathiew [Corrected to Küry, Sébastien; Giovannucci, Edward L. and Lemire, Mathieu]. PMID: 26151821; PMCID: PMC4967357.

Schumacher FR, Al Olama AA, Berndt SI, Benlloch S, Ahmed M, Saunders EJ, Dadaev T, Leongamornlert D, Anokian E, Cieza-Borrella C, Goh C, Brook MN, Sheng X, Fachal L, Dennis J, Tyrer J, Muir K, Lophatananon A, Stevens VL, Gapstur SM, Carter BD, Tangen CM, Goodman PJ, Thompson IM Jr, Batra J, Chambers S, Moya L, Clements J, Horvath L, Tilley W, Risbridger GP, Gronberg H, Aly M, Nordström T, Pharoah P, Pashayan N, Schleutker J, Tammela TLJ, Sipeky C, Auvinen A, Albanes D, Weinstein S, Wolk A, Håkansson N, West CML, Dunning AM, Burnet N, Mucci LA, Giovannucci E, Andriole GL, Cussenot O, Cancel-Tassin G, Koutros S, Beane Freeman LE, Sorensen KD, Orntoft TF, Borre M, Maehle L, Grindedal EM, Neal DE, Donovan JL, Hamdy FC, Martin RM, Travis RC, Key TJ, Hamilton RJ, Fleshner NE, Finelli A, Ingles SA, Stern MC, Rosenstein BS, Kerns SL, Ostrer H, Lu YJ, Zhang HW, Feng N, Mao X, Guo X, Wang G, Sun Z, Giles GG, Southey MC, MacInnis RJ, FitzGerald LM, Kibel AS, Drake BF, Vega A, Gómez-Caamaño A, Szulkin R, Eklund M, Kogevinas M, Llorca J, Castaño-Vinyals G, Penney KL, Stampfer M, Park JY, Sellers TA, Lin HY, Stanford JL, Cybulski C, Wokolorczyk D, Lubinski J, Ostrander EA, Geybels MS, Nordestgaard BG, Nielsen SF, Weischer M, Bisbjerg R, Røder MA, Iversen P, Brenner H, Cuk K, Holleczek B, Maier C, Luedeke M, Schnoeller T, Kim J, Logothetis CJ, John EM, Teixeira MR, Paulo P, Cardoso M, Neuhausen SL, Steele L, Ding YC, De Ruyck K, De Meerleer G, Ost P, Razack A, Lim J, Teo SH, Lin DW, Newcomb LF, Lessel D, Gamulin M, Kulis T, Kaneva R, Usmani N, Singhal S, Slavov C, Mitev V, Parliament M, Claessens F, Joniau S, Van den Broeck T, Larkin S, Townsend PA, Aukim-Hastie C, Gago-Dominguez M, Castelao JE, Martinez ME, Roobol MJ, Jenster G, van Schaik RHN, Menegaux F, Truong T, Koudou YA, Xu J, Khaw KT, Cannon-Albright L, Pandha H, Michael A, Thibodeau SN, McDonnell SK, Schaid DJ, Lindstrom S, Turman C, Ma J, Hunter DJ, Riboli E, Siddiq A, Canzian F, Kolonel LN, Le Marchand L, Hoover RN, Machiela MJ, Cui Z, Kraft P, Amos CI, Conti DV, Easton DF, Wiklund F, Chanock SJ, Henderson BE, Kote-Jarai Z, Haiman CA, Eeles RA; Profile Study; Australian Prostate Cancer BioResource (APCB); IMPACT Study; Canary PASS Investigators; Breast and Prostate Cancer Cohort Consortium (BPC3); PRACTICAL (Prostate Cancer Association Group to Investigate Cancer-Associated Alterations in the Genome) Consortium; Cancer of the Prostate in Sweden (CAPS); Prostate Cancer Genome-wide Association Study of Uncommon Susceptibility Loci (PEGASUS); Genetic Associations and Mechanisms in Oncology (GAME-ON)/Elucidating Loci Involved in Prostate Cancer Susceptibility (ELLIPSE) Consortium. (2018) Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci. *Nat Genet*. Jul;50 (7):928–936. doi: 10.1038/s41588-018-0330-6.

Seppälä EH, Ikonen T, Mononen N, Autio V, Rökman A, Matikainen MP, Tammela TL, Schleutker J. (2003) CHEK2 variants associate with hereditary prostate cancer. *Br J Cancer*. Nov 17;89 (10):1966–70. doi: 10.1038/sj.bjc.6601425.

Sesia M, Bates S, Candès E, Marchini J, Sabatti C. (2021) False discovery rate control in genome-wide association studies with population structure. *Proc Natl Acad Sci U S A*. Oct 5;118(40):e2105841118. doi: 10.1073/pnas.2105841118.

Shen MM, Abate-Shen C. (2010) Molecular genetics of prostate cancer: new prospects for old challenges. *Genes Dev*. Sep 15;24 (18):1967–2000. doi: 10.1101/gad.1965810.

Shen Q, Wang H, Zhang L. (2023) TP63 Functions as a Tumor Suppressor Regulated by GAS5/miR-221-3p Signaling Axis in Human Non-Small Cell Lung Cancer Cells. *Cancer Manag Res*. Feb 24;15:217–231. doi: 10.2147/CMAR.S387781.

Shi H, Bevier M, Johansson R, Grzybowska E, Chen B, Eyfjörd JE, Hamann U, Manjer J, Enquist K, Henriksson R, Carlson J, Brandt A, Lascorz J, Butkiewicz D, Pamula-Pilat J, Tecza K, Herms S, Hoffmann P, Hemminki K, Lenner P, Försti A. (2011) Single nucleotide polymorphisms in the 20q13 amplicon genes in relation to breast cancer risk and clinical outcome. *Breast Cancer Res Treat*. Dec;130(3):905–16. doi: 10.1007/s10549-011-1600-5.

Shifrut E, Carnevale J, Tobin V, Roth TL, Woo JM, Bui CT, Li PJ, Diolaiti ME, Ashworth A, Marson A. (2018) Genome-wide CRISPR Screens in Primary Human T Cells Reveal

Key Regulators of Immune Function. *Cell*. Dec 13;175(7):1958–1971.e15. doi: 10.1016/j.cell.2018.10.024.

Shivapurkar N, Sood S, Wistuba II, Virmani AK, Maitra A, Milchgrub S, Minna JD, Gazdar AF. (1999) Multiple regions of chromosome 4 demonstrating allelic losses in breast carcinomas. *Cancer Res.* Aug 1;59(15):3576–80. PMID: 10446964.

Shivapurkar N, Maitra A, Milchgrub S, Gazdar AF. (2001) Deletions of chromosome 4 occur early during the pathogenesis of colorectal carcinoma. *Hum Pathol*. Feb;32(2):169–77. doi: 10.1053/hupa.2001.21560.

Sibley K, Bell S, Knowles MA. (2000) Redefining a critical region of LOH on 4p16.3 in bladder cancer. *Genes Chromosomes Cancer.* Dec;29(4):378–9. doi: 10.1002/1098-2264(2000)9999:9999<::aid-gcc1045>3.0.co;2-k.

Siegel RL, Miller KD, Fuchs HE, Jemal A. (2022) Cancer statistics, 2022. *CA Cancer J Clin.* Jan;72(1):7-33. doi: 10.3322/caac.21708.

Silva FC, Valentin MD, Ferreira Fde O, Carraro DM, Rossi BM. (2009) Mismatch repair genes in Lynch syndrome: a review. *Sao Paulo Med J.* Jan;127 (1):46–51. doi: 10.1590/s1516-31802009000100010.

Sipeky C, Gao P, Zhang Q, Wang L, Ettala O, Talala KM, Tammela TLJ, Auvinen A, Wiklund F, Wei GH, Schleutker J. (2018) Synergistic Interaction of HOXB13 and CIP2A Predisposes to Aggressive Prostate Cancer. *Clin Cancer Res*. Dec 15;24 (24):6265–6276. doi: 10.1158/1078-0432.CCR-18-0444.

Sipeky C, Talala KM, Tammela TLJ, Taari K, Auvinen A, Schleutker J. (2020) Prostate cancer risk prediction using a polygenic risk score. *Sci Rep.* Oct 13;10(1):17075. doi: 10.1038/s41598-020-74172-z.

Smith SC, Palanisamy N, Zuhlke KA, Johnson AM, Siddiqui J, Chinnaiyan AM, Kunju LP, Cooney KA, Tomlins SA. (2014) HOXB13 G84E-related familial prostate cancers: a clinical, histologic, and molecular survey. *Am J Surg Pathol*. May;38 (5):615–26. doi: 10.1097/PAS.0000000000000090.

Smith JM, Hedman AC, Sacks DB. (2015) IQGAPs choreograph cellular signaling from the membrane to the nucleus. *Trends Cell Biol*. Mar;25 (3):171–84. doi: 10.1016/j.tcb.2014.12.005.

Soh PXY, Mmekwa N, Petersen DC, Gheybi K, van Zyl S, Jiang J, Patrick SM, Campbell R, Jaratlerdseri W, Mutambirwa SBA, Bornman MSR, Hayes VM. (2023) Prostate cancer genetic risk and associated aggressive disease in men of African ancestry. *Nat Commun.* Dec 5;14(1):8037. doi: 10.1038/s41467-023-43726-w.

Solberg N, Machon O, Machonova O, Krauss S. (2012) Mouse Tcf3 represses canonical Wnt signaling by either competing for β-catenin binding or through occupation of DNA-binding sites. *Mol Cell Biochem*. Jun;365 (1–2):53–63. doi: 10.1007/s11010-012-1243-9.

Srigley JR, Delahunt B, Egevad L, Samaratunga H, Yaxley J, Evans AJ. (2016) One is the new six: The International Society of Urological Pathology (ISUP) patient-focused approach to Gleason grading. *Can Urol Assoc J*. Sep-Oct;10 (9–10):339–341. doi: 10.5489/cuaj.4146.

Stern MC, Van Den Berg D, Yuan JM, Conti DV, Gago-Dominguez M, Pike MC, Xiang YB, Gao YT, Cortessis VK. (2009) Sequence variant on 3q28 and urinary bladder cancer risk: findings from the Los Angeles-Shanghai bladder case-control study. Cancer *Epidemiol Biomarkers Prev.* Nov;18(11):3057–61. doi: 10.1158/1055-9965.EPI-09-0492.

Suarez BK, Lin J, Burmester JK, Broman KW, Weber JL, Banerjee TK, Goddard KA, Witte JS, Elston RC, Catalona WJ. (2000) A genome screen of multiplex sibships with prostate cancer. *Am J Hum Genet*. Mar;66(3):933–44. doi: 10.1086/302818.

Subudhi SK, Siddiqui BA, Aparicio AM, Yadav SS, Basu S, Chen H, Jindal S, Tidwell RSS, Varma A, Logothetis CJ, Allison JP, Corn PG, Sharma P. (2021) Combined CTLA-4 and PD-L1 blockade in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer is associated with increased myeloid and neutrophil immune subsets in the bone microenvironment. *J Immunother Cancer*. Oct;9 (10):e002919. doi: 10.1136/jitc-2021-002919.

Sultanov R, Mulyukina A, Zubkova O, Fedoseeva A, Bogomazova A, Klimina K, Larin A, Zatsepin T, Prikazchikova T, Lukina M, Bogomiakova M, Sharova E, Generozov E, Lagarkova M, Arapidi G. (2024) TP63-TRIM29 axis regulates enhancer methylation and chromosomal instability in prostate cancer. *Epigenetics Chromatin*. Mar 14;17 (1):6. doi: 10.1186/s13072-024-00529-7.

Sutherland DEK, Azad AA, Murphy DG, Eapen RS, Kostos L, Hofman MS. (2024) Role of FDG PET/CT in Management of Patients with Prostate Cancer. *Semin Nucl Med*. Jan;54 (1):4–13. doi: 10.1053/j.semnuclmed.2023.06.005.

Sundquist K, Sundquist J, Ji J. (2015) Contribution of shared environmental factors to familial aggregation of common cancers: an adoption study in Sweden. *Eur J Cancer Prev*. Mar;24 (2):162–4. doi: 10.1097/CEJ.0000000000000101.

Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. (2021) Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* Feb 4. doi: 10.3322/caac.21660.

Tang T, Wang J, Zhang L, Cheng Y, Saleh L, Gu Y, Zhang H. (2021) IQGAP2 acts as an independent prognostic factor and is related to immunosuppression in DLBCL. *BMC Cancer*. May 25;21 (1):603. doi: 10.1186/s12885-021-08086-y.

Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Théodore C, James ND, Turesson I, Rosenthal MA, Eisenberger MA; TAX 327 Investigators. (2004) Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med.* Oct 7;351 (15):1502–12. doi: 10.1056/NEJMoa040720.

Taylor RA, Fraser M, Livingstone J, Espiritu SM, Thorne H, Huang V, Lo W, Shiah YJ, Yamaguchi TN, Sliwinski A, Horsburgh S, Meng A, Heisler LE, Yu N, Yousif F, Papargiris M, Lawrence MG, Timms L, Murphy DG, Frydenberg M, Hopkins JF, Bolton D, Clouston D, McPherson JD, van der Kwast T, Boutros PC, Risbridger GP, Bristow RG. (2017) Germline BRCA2 mutations drive prostate cancers with distinct evolutionary trajectories. *Nat Commun*. Jan 9;8:13671. doi: 10.1038/ncomms13671.

Tesone AJ, Rutkowski MR, Brencicova E, Svoronos N, Perales-Puchalt A, Stephen TL, Allegrezza MJ, Payne KK, Nguyen JM, Wickramasinghe J, Tchou J, Borowsky ME, Rabinovich GA, Kossenkov AV, Conejo-Garcia JR. (2016) Satb1 Overexpression Drives Tumor-Promoting Activities in Cancer-Associated Dendritic Cells. *Cell Rep.* Feb 23;14 (7):1774–1786. doi: 10.1016/j.celrep.2016.01.056.

Thalgott, M, Kron M, Brath JM, Ankerst DP, Thompson IM, Gschwend JE, Herkommer K. (2018) Men with family history of prostate cancer have a higher risk of disease recurrence after radical prostatectomy. *World J. Urol*. 36, 177–185. doi: 10.1007/s00345-017-2122-5.

Tortora GJ, Derrickson BH (2017) Tortora's principles of anatomy and physiology, Global edition. 15 ed., p. 1056–1070. Wiley, New Jersey.

Trendowski MR, Sample C, Baird T, Sadeghpour A, Moon D, Ruterbusch JJ, Beebe-Dimmer JL, Cooney KA. (2022) Germline Variants in DNA Damage Repair Genes and HOXB13 Among Black Patients With Early-Onset Prostate Cancer. *JCO Precis Oncol*. Nov;6:e2200460. doi: 10.1200/PO.22.00460.

Tsodikov A, Gulati R, de Carvalho TM, Heijnsdijk EAM, Hunter-Merrill RA, Mariotto AB, de Koning HJ, Etzioni R. (2017) Is prostate cancer different in black men? Answers from 3 natural history models. *Cancer*. Jun 15;123(12):2312–2319. doi: 10.1002/cncr.30687.

Tu R, Zhong D, Li P, Li Y, Chen Z, Hu F, Yuan G, Chen Z, Yu S, Song J. (2023) PTPN13 rs989902 and CHEK2 rs738722 are associated with esophageal cancer. *Ann Med*. 55 (2):2281659. doi: 10.1080/07853890.2023.2281659.

Tuffaha H, Edmunds K, Fairbairn D, Roberts MJ, Chambers S, Smith DP, Horvath L, Arora S, Scuffham P. (2024) Guidelines for genetic testing in prostate cancer: a scoping review. *Prostate Cancer Prostatic Dis*. Dec;27 (4):594–603. doi: 10.1038/s41391-023-00676-0.

Turun yliopistollinen keskussairaala (TYKS) (2025) Syöpätaudit Genomiikka ammattilaiselle.https://www.tyks.fi/ammattilaiselle/ammattilaisten-palvelut-jaohjeet/genomiikka-ammattilaiselle/syopataudit [Read 8.4.2024]

Valle L, Vilar E, Tavtigian SV, Stoffel EM. (2019) Genetic predisposition to colorectal cancer: syndromes, genes, classification of genetic variants and implications for precision medicine. *J Pathol*. Apr;247(5):574–588. doi: 10.1002/path.5229.

Vietri MT, D'Elia G, Caliendo G, Resse M, Casamassimi A, Passariello L, Albanese L, Cioffi M, Molinari AM. (2021) Hereditary Prostate Cancer: Genes Related, Target Therapy and Prevention. *Int J Mol Sci*. Apr 4;22(7):3753. doi: 10.3390/ijms22073753.

Virlogeux V, Graff RE, Hoffmann TJ, Witte JS. (2015) Replication and heritability of prostate cancer risk variants: impact of population-specific factors. *Cancer Epidemiol Biomarkers Prev.* Jun;24(6):938–43. doi: 10.1158/1055-9965.EPI-14-1372.

Viswanathan SR, Ha G, Hoff AM, Wala JA, Carrot-Zhang J, Whelan CW, Haradhvala NJ, Freeman SS, Reed SC, Rhoades J, Polak P, Cipicchio M, Wankowicz SA, Wong A, Kamath T, Zhang Z, Gydush GJ, Rotem D; PCF/SU2C International Prostate Cancer Dream Team; Love JC, Getz G, Gabriel S, Zhang CZ, Dehm SM, Nelson PS, Van Allen EM, Choudhury AD, Adalsteinsson VA, Beroukhim R, Taplin ME, Meyerson M. (2018) Structural Alterations Driving Castration-Resistant Prostate Cancer Revealed by Linked-Read Genome Sequencing. *Cell*. Jul 12;174 (2):433447.e19. doi: 10.1016/j.cell.2018.05.036.

Waldeck-Weiermair M, Jean-Quartier C, Rost R, Khan MJ, Vishnu N, Bondarenko AI, Imamura H, Malli R, Graier WF. (2011) Leucine zipper EF hand-containing transmembrane protein 1 (Letm1) and uncoupling proteins 2 and 3 (UCP2/3) contribute to two distinct mitochondrial Ca2+ uptake pathways. *J Biol Chem.* Aug 12;286(32):28444–55. doi: 10.1074/jbc.M111.244517.

Walker MG, Volkmuth W, Sprinzak E, Hodgson D, Klingler T. (1999) Prediction of gene function by genome-scale expression analysis: prostate cancer-associated genes. *Genome Res.* Dec;9(12):1198–203. doi: 10.1101/gr.9.12.1198.

Walsh PC. (2017) The Search for the Missing Heritability of Prostate Cancer. *Eur Urol*. Nov;72 (5):657–659. doi: 10.1016/j.eururo.2017.04.003.

Walter SD, Hu J, Talala K, Tammela T, Taari K, Auvinen A. (2021) Estimating the rate of overdiagnosis with prostate cancer screening: evidence from the Finnish component of the European Randomized Study of Screening for Prostate Cancer. *Cancer Causes Control.* Nov;32 (11):1299–1313. doi: 10.1007/s10552-021-01480-8.

Wang J, Shete S. (2012) Testing departure from Hardy-Weinberg proportions. *Methods Mol Biol.* 850:77–102. doi: 10.1007/978-1-61779-555-8_6.

Wang Y, Dai B, Ye D. (2015) CHEK2 mutation and risk of prostate cancer: a systematic review and meta-analysis. *Int J Clin Exp Med*. Sep 15;8 (9):15708–15. PMID: 26629066; PMCID: PMC4658955.

Wang L, Paller CJ, Hong H, De Felice A, Alexander GC, Brawley O. (2021) Comparison of Systemic Treatments for Metastatic Castration-Sensitive Prostate Cancer: A Systematic Review and Network Meta-analysis. *JAMA Oncol*. Mar 1;7 (3):412–420. doi: 10.1001/jamaoncol.2020.6973.

Wang A, Shen J, Rodriguez AA, Saunders EJ, Chen F, Janivara R, Darst BF, Sheng X, Xu Y, Chou AJ, Benlloch S, Dadaev T, Brook MN, Plym A, Sahimi A, Hoffman TJ, Takahashi A, Matsuda K, Momozawa Y, Fujita M, Laisk T, Figuerêdo J, Muir K, Ito S, Liu X; Biobank Japan Project; Uchio Y, Kubo M, Kamatani Y, Lophatananon A, Wan P, Andrews C, Lori A, Choudhury PP, Schleutker J, Tammela TLJ, Sipeky C, Auvinen A, Giles GG, Southey MC, MacInnis RJ, Cybulski C, Wokolorczyk D, Lubinski J, Rentsch CT, Cho K, Mcmahon BH, Neal DE, Donovan JL, Hamdy FC, Martin RM, Nordestgaard BG, Nielsen SF, Weischer M, Bojesen SE, Røder A, Stroomberg HV, Batra J, Chambers S, Horvath L, Clements JA, Tilly W, Risbridger GP, Gronberg H, Aly M, Szulkin R, Eklund M, Nordstrom T, Pashayan N, Dunning AM, Ghoussaini M, Travis RC, Key TJ, Riboli E, Park JY, Sellers TA, Lin HY, Albanes D, Weinstein S, Cook MB, Mucci LA, Giovannucci E, Lindstrom S, Kraft P, Hunter DJ, Penney KL, Turman C, Tangen CM, Goodman PJ, Thompson IM Jr, Hamilton RJ, Fleshner NE, Finelli A, Parent MÉ, Stanford JL, Ostrander EA, Koutros S, Beane Freeman LE, Stampfer M, Wolk A, Håkansson N, Andriole GL, Hoover RN, Machiela MJ, Sørensen KD, Borre M, Blot WJ, Zheng W, Yeboah ED, Mensah JE, Lu YJ, Zhang HW, Feng N, Mao X, Wu Y, Zhao SC, Sun Z, Thibodeau SN, McDonnell SK, Schaid DJ, West CML, Barnett G, Maier C, Schnoeller T, Luedeke M, Kibel AS, Drake BF, Cussenot O, Cancel-Tassin G, Menegaux F, Truong T, Koudou YA, John EM, Grindedal EM, Maehle L, Khaw KT, Ingles SA, Stern MC, Vega A, Gómez-Caamaño A, Fachal L, Rosenstein BS, Kerns SL, Ostrer H, Teixeira MR, Paulo P, Brandão A, Watya S, Lubwama A, Bensen JT, Butler EN, Mohler JL, Taylor JA, Kogevinas M, Dierssen-Sotos T, Castaño-Vinyals G, Cannon-Albright L, Teerlink CC, Huff CD, Pilie P, Yu Y, Bohlender RJ, Gu J, Strom SS, Multigner L, Blanchet P, Brureau L, Kaneva R, Slavov C, Mitev V, Leach RJ, Brenner H, Chen X, Holleczek B, Schöttker B, Klein EA, Hsing AW, Kittles RA, Murphy AB, Logothetis CJ, Kim J, Neuhausen SL, Steele L, Ding YC, Isaacs WB, Nemesure B, Hennis AJM, Carpten J, Pandha H, Michael A, De Ruyck K, De Meerleer G, Ost P, Xu J, Razack A, Lim J, Teo SH, Newcomb LF, Lin DW, Fowke JH, Neslund-Dudas CM, Rybicki BA, Gamulin M, Lessel D, Kulis T, Usmani N, Abraham A, Singhal S, Parliament M, Claessens F, Joniau S, Van den Broeck T, Gago-Dominguez M, Castelao JE, Martinez ME, Larkin S, Townsend PA, Aukim-Hastie C, Bush WS, Aldrich MC, Crawford DC, Srivastava S, Cullen J, Petrovics G, Casey G, Wang Y, Tettey Y, Lachance J, Tang W, Biritwum RB, Adjei AA, Tay E, Truelove A, Niwa S, Yamoah K, Govindasami K, Chokkalingam AP, Keaton JM, Hellwege JN, Clark PE, Jalloh M, Gueye SM, Niang L, Ogunbiyi O, Shittu O, Amodu O, Adebiyi AO, Aisuodionoe-Shadrach OI, Ajibola HO, Jamda MA, Oluwole OP, Nwegbu M, Adusei B, Mante S, Darkwa-Abrahams A, Diop H, Gundell SM, Roobol MJ, Jenster G, van Schaik RHN, Hu JJ, Sanderson M, Kachuri L, Varma R, McKean-Cowdin R, Torres M, Preuss MH, Loos RJF, Zawistowski M, Zöllner S, Lu Z, Van Den Eeden SK, Easton DF, Ambs S, Edwards TL, Mägi R, Rebbeck TR, Fritsche L, Chanock SJ, Berndt SI, Wiklund F, Nakagawa H, Witte JS, Gaziano JM, Justice AC, Mancuso N, Terao C, Eeles RA, Kote-Jarai Z, Madduri RK, Conti DV, Haiman CA. (2023) Characterizing prostate cancer risk through multi-ancestry genome-wide discovery of 187 novel risk variants. *Nat Genet*. Dec;55 (12):2065–2074. doi: 10.1038/s41588-023-01534-4.

Wasim S, Lee SY, Kim J. (2022) Complexities of Prostate Cancer. *Int J Mol Sci*. 2022 Nov 17;23 (22):14257. doi: 10.3390/ijms232214257.

Watson PA, Arora VK, Sawyers CL. (2015) Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. *Nat Rev Cancer*. Dec;15 (12):701–11. doi: 10.1038/nrc4016.

Wei G, Zhang X, Liu S, Hou W, Dai Z. (2024) Comprehensive data mining reveals RTK/RAS signaling pathway as a promoter of prostate cancer lineage plasticity through transcription factors and CNV. *Sci Rep*. May 22;14 (1):11688. doi: 10.1038/s41598-024-62256-z.

Weigl K, Chang-Claude J, Knebel P, Hsu L, Hoffmeister M, Brenner H. (2018) Strongly enhanced colorectal cancer risk stratification by combining family history and genetic risk score. *Clin Epidemiol*. Jan 19;10:143–152. doi: 10.2147/CLEP.S145636.

Wein AJ, Roehrborn CG, Strand DW. (2021) Benign Prostatic Hyperplasia: Etiology, Pathophysiology, Epidemiology, and Natural History. In Campbell-Walsh-Wein Urology, 12th ed. Elsevier Philadelphia.

Wen Y, Zhu C, Li N, Li Z, Cheng Y, Dong J, Zhu M, Wang Y, Dai J, Ma H, Jin G, Dai M, Hu Z, Shen H. (2019) Fine Mapping in Chromosome 3q28 Identified Two Variants Associated with Lung Cancer Risk in Asian Population. *J Cancer*. Apr 21;10(8):1862–1869. doi: 10.7150/jca.28379.

Wen YC, Liu CL, Yeh HL, Chen WH, Jiang KC, Tram VTN, Hsiao M, Huang J, Chen WY, Liu YN. PCK1 regulates neuroendocrine differentiation in a positive feedback loop of LIF/ZBTB46 signalling in castration-resistant prostate cancer. *Br J Cancer*. 2022 Mar;126 (5):778–790. doi: 10.1038/s41416-021-01631-3.

Wenzel M, Preisser F, Hoeh B, Schroeder M, Würnschimmel C, Steuber T, Heinzer H, Banek S, Ahrens M, Becker A, Karakiewicz PI, Chun FKH, Kluth LA, Mandel P. (2021) Impact of Time to Castration Resistance on Survival in Metastatic Hormone Sensitive Prostate Cancer Patients in the Era of Combination Therapies. *Front Oncol*. Apr 23;11:659135. doi: 10.3389/fonc.2021.659135.

White CD, Khurana H, Gnatenko DV, Li Z, Odze RD, Sacks DB, Schmidt VA. (2010) IQGAP1 and IQGAP2 are reciprocally altered in hepatocellular carcinoma. *BMC Gastroenterol.* Oct 26;10:125. doi: 10.1186/1471-230X-10-125.

Whitington T, Gao P, Song W, Ross-Adams H, Lamb AD, Yang Y, Svezia I, Klevebring D, Mills IG, Karlsson R, Halim S, Dunning MJ, Egevad L, Warren AY, Neal DE, Grönberg H, Lindberg J, Wei GH, Wiklund F. (2016) Gene regulatory mechanisms underpinning prostate cancer susceptibility. *Nat Genet.* Apr;48 (4):387–97. doi: 10.1038/ng.3523.

Wickham H, Bryan J. (2023). readxl: Read Excel Files (R package version 1.4.3). https://CRAN.R-project.org/package=readxl

Wickham H, Girlich M. (2023). readr: Read Rectangular Text Data (R package version 2.1.4). https://CRAN.R-project.org/package=readr

Wickham H, François R, Henry L, Müller K. (2023). dplyr: A Grammar of Data Manipulation (R package version 1.1.4). https://CRAN.R-project.org/package=dplyr

Wiese D, DuBois TD, Sorice KA, Fang CY, Ragin C, Daly MB, Reese AC, Henry KA, Lynch SM. (2023) Defining aggressive prostate cancer: a geospatial perspective. *BMC Cancer*. Aug 14;23(1):754. doi: 10.1186/s12885-023-11281-8.

Wiklund F, Zheng SL, Sun J, Adami HO, Lilja H, Hsu FC, Stattin P, Adolfsson J, Cramer SD, Duggan D, Carpten JD, Chang BL, Isaacs WB, Grönberg H, Xu J. (2009) Association of reported prostate cancer risk alleles with PSA levels among men without a diagnosis of prostate cancer. *Prostate*. Mar 1;69(4):419–27. doi: 10.1002/pros.20908.

Wilkes DC, Sailer V, Xue H, Cheng H, Collins CC, Gleave M, Wang Y, Demichelis F, Beltran H, Rubin MA, Rickman DS. (2017) A germline FANCA alteration that is associated with increased sensitivity to DNA damaging agents. *Cold Spring Harb Mol Case Stud*. Sep;3 (5):a001487. doi: 10.1101/mcs.a001487.

Williams H, Powell IJ. (2009) Epidemiology, pathology, and genetics of prostate cancer among African Americans compared with other ethnicities. In: Verma M, ed. Cancer epidemiology. p. 439–53. Humana Press, Totowa (NJ).

Wilson TK, Zishiri OT. (2024) Prostate Cancer: A Review of Genetics, Current Biomarkers and Personalised Treatments. *Cancer Rep (Hoboken)*. Oct;7 (10):e70016. doi: 10.1002/cnr2.70016.

Witte JS, Mefford J, Plummer SJ, Liu J, Cheng I, Klein EA, Rybicki BA, Casey G. (2013) HOXB13 mutation and prostate cancer: studies of siblings and aggressive disease. *Cancer Epidemiol Biomarkers Prev*. Apr;22 (4):675–80. doi: 10.1158/1055-9965.EPI-12-1154.

Wu Y, Chen H, Jiang G, Mo Z, Ye D, Wang M, Qi J, Lin X, Zheng SL, Zhang N, Na R, Ding Q, Xu J, Sun Y. (2018) Genome-wide Association Study (GWAS) of Germline Copy Number Variations (CNVs) Reveal Genetic Risks of Prostate Cancer in Chinese population. *J Cancer*. Feb 27;9 (5):923–928. doi: 10.7150/jca.22802.

Wu J, Huang H, Huang Q, Qiu R, Huang M, Meng D. (2020) A functional variant rs1464938 in the promoter of fibroblast growth factor 12 is associated with an increased risk of bladder transitional cell carcinoma. *Cytokine*. Dec; 136: 155294. doi: 10.1016/j.cyto.2020.155294.

Wu G, Dong Z, Dong Y, Chen Y, Zhu H, Ding D, Cui Y, Wang Y, Xu Y, Chen H. (2024) LncRNA CTBP1-AS inhibits TP63-mediated activation of S100A14 during prostate cancer progression. *Cancer Sci*. May;115 (5):1492–1504. doi: 10.1111/cas.16138. Epub 2024 Mar 13.

Xie Y, Yan J, Cutz JC, Rybak AP, He L, Wei F, Kapoor A, Schmidt VA, Tao L, Tang D. (2012) IQGAP2, A candidate tumour suppressor of prostate tumorigenesis. *Biochim Biophys Acta*. Jun;1822 (6):875–84. doi: 10.1016/j.bbadis.2012.02.019.

Xie Y, Zheng L, Tao L. (2019) Downregulation of IQGAP2 Correlates with Prostate Cancer Recurrence and Metastasis. *Transl Oncol*. Feb;12 (2):236–244. doi: 10.1016/j.tranon.2018.10.009.

Xu J, Dimitrov L, Chang BL, Adams TS, Turner AR, Meyers DA, Eeles RA, Easton DF, Foulkes WD, Simard J, Giles GG, Hopper JL, Mahle L, Moller P, Bishop T, Evans C, Edwards S, Meitz J, Bullock S, Hope Q, Hsieh CL, Halpern J, Balise RN, Oakley-Girvan I, Whittemore AS, Ewing CM, Gielzak M, Isaacs SD, Walsh PC, Wiley KE, Isaacs WB, Thibodeau SN, McDonnell SK, Cunningham JM, Zarfas KE, Hebbring S, Schaid DJ, Friedrichsen DM, Deutsch K, Kolb S, Badzioch M, Jarvik GP, Janer M, Hood L, Ostrander EA, Stanford JL, Lange EM, Beebe-Dimmer JL, Mohai CE, Cooney KA, Ikonen T, Baffoe-Bonnie A, Fredriksson H, Matikainen MP, Tammela TLj, Bailey-Wilson J, Schleutker J, Maier C, Herkommer K, Hoegel JJ, Vogel W, Paiss T, Wiklund F, Emanuelsson M, Stenman E, Jonsson BA, Gronberg H, Camp NJ, Farnham J, Cannon-Albright LA, Seminara D; ACTANE Consortium. (2005) A combined genomewide linkage scan of 1,233 families for prostate cancer-susceptibility genes conducted by the international consortium for prostate cancer genetics. *Am J Hum Genet.* Aug;77(2):219–29. doi: 10.1086/432377.

Xu J, Zheng SL, Isaacs SD, Wiley KE, Wiklund F, Sun J, Kader AK, Li G, Purcell LD, Kim ST, Hsu FC, Stattin P, Hugosson J, Adolfsson J, Walsh PC, Trent JM, Duggan D, Carpten J, Grönberg H, Isaacs WB. (2010) Inherited genetic variant predisposes to aggressive but not indolent prostate cancer. *Proc Natl Acad Sci U S A*. Feb 2;107(5):2136–40. doi: 10.1073/pnas.0914061107.

Xu J, Lange EM, Lu L, Zheng SL, Wang Z, Thibodeau SN, Cannon-Albright LA, Teerlink CC, Camp NJ, Johnson AM, Zuhlke KA, Stanford JL, Ostrander EA, Wiley KE, Isaacs SD, Walsh PC, Maier C, Luedeke M, Vogel W, Schleutker J, Wahlfors T, Tammela T, Schaid D, McDonnell SK, DeRycke MS, Cancel-Tassin G, Cussenot O, Wiklund F, Grönberg H, Eeles R, Easton D, Kote-Jarai Z, Whittemore AS, Hsieh CL, Giles GG, Hopper JL, Severi G, Catalona WJ, Mandal D, Ledet E, Foulkes WD, Hamel N, Mahle L, Moller P, Powell I, Bailey-Wilson JE, Carpten JD, Seminara D, Cooney KA, Isaacs WB; International Consortium for Prostate Cancer Genetics. (2013) HOXB13 is a susceptibility gene for prostate cancer: results from the International Consortium for

Prostate Cancer Genetics (ICPCG). *Hum Genet*. Jan;132 (1):5–14. doi: 10.1007/s00439-012-1229-4.

Xu L, Shao Y, Ren L, Liu X, Li Y, Xu J, Ye Y. (2020) IQGAP2 Inhibits Migration and Invasion of Gastric Cancer Cells via Elevating SHIP2 Phosphatase Activity. *Int J Mol Sci*. Mar 13;21(6):1968. doi: 10.3390/ijms21061968.

Xue Y, Mezzavilla M, Haber M, McCarthy S, Chen Y, Narasimhan V, Gilly A, Ayub Q, Colonna V, Southam L, Finan C, Massaia A, Chheda H, Palta P, Ritchie G, Asimit J, Dedoussis G, Gasparini P, Palotie A, Ripatti S, Soranzo N, Toniolo D, Wilson JF, Durbin R, Tyler-Smith C, Zeggini E. (2017) Enrichment of low-frequency functional variants revealed by whole-genome sequencing of multiple isolated European populations. *Nat Commun*. Jun 23;8:15927. doi: 10.1038/ncomms15927.

Yamada Y, Watanabe M, Murata M, Yamanaka M, Kubota Y, Ito H, Katoh T, Kawamura J, Yatani R, Shiraishi T. (2001) Impact of genetic polymorphisms of 17-hydroxylase cytochrome P-450 (CYP17) and steroid 5alpha-reductase type II (SRD5A2) genes on prostate-cancer risk among the Japanese population. *Int J Cancer*. Jun 1;92 (5):683–6. doi: 10.1002/1097-0215 (20010601)92:5<683::aid-ijc1255>3.0.co;2-4.

Yamaguchi TN, Houlahan KE, Zhu H, Kurganovs N, Livingstone J, Fox NS, Yuan J, Sietsma Penington J, Jung CH, Schwarz T, Jaratlerdsiri W, van Riet J, Georgeson P, Mangiola S, Taraszka K, Lesurf R, Jiang J, Chow K, Heisler LE, Shiah YJ, Ramanand SG, Clarkson MJ, Nguyen A, Espiritu SMG, Stuchbery R, Jovelin R, Huang V, Bell C, O'Connor E, McCoy PJ, Lalansingh CM, Cmero M, Salcedo A, Chan EKF, Liu LY, Stricker PD, Bhandari V, Bornman RMS, Sendorek DHS, Lonie A, Prokopec SD, Fraser M, Peters JS, Foucal A, Mutambirwa SBA, Mcintosh L, Orain M, Wakefield M, Picard V, Park DJ, Hovington H, Kerger M, Bergeron A, Sabelnykova V, Seo JH, Pomerantz MM, Zaitlen N, Waszak SM, Gusev A, Lacombe L, Fradet Y, Ryan A, Kishan AU, Lolkema MP, Weischenfeldt J, Têtu B, Costello AJ, Hayes VM, Hung RJ, He HH, McPherson JD, Pasaniuc B, van der Kwast T, Papenfuss AT, Freedman ML, Pope BJ, Bristow RG, Mani RS, Corcoran NM, Reimand J, Hovens CM, Boutros PC. (2025) The Germline and Somatic Origins of Prostate Cancer Heterogeneity. *Cancer Discov*. May 2;15(5):988–1017. doi: 10.1158/2159-8290.CD-23-0882.

Yang L, Hamilton SR, Sood A, Kuwai T, Ellis L, Sanguino A, Lopez-Berestein G, Boyd DD. (2008) The previously undescribed ZKSCAN3 (ZNF306) is a novel "driver" of colorectal cancer progression. *Cancer Res.* Jun 1;68 (11):4321–30. doi: 10.1158/0008-5472.CAN-08-0407.

Yang L, Wang H, Kornblau SM, Graber DA, Zhang N, Matthews JA, Wang M, Weber DM, Thomas SK, Shah JJ, Zhang L, Lu G, Zhao M, Muddasani R, Yoo SY, Baggerly KA, Orlowski RZ. (2011) Evidence of a role for the novel zinc-finger transcription factor ZKSCAN3 in modulating Cyclin D2 expression in multiple myeloma. *Oncogene*. Mar 17;30 (11):1329–40. doi: 10.1038/onc.2010.515.

Yang Z, Ni W, Cui C, Qi W, Piao L, Xuan Y. (2018) Identification of LETM1 as a marker of cancer stem-like cells and predictor of poor prognosis in esophageal squamous cell carcinoma. *Hum Pathol*. Nov;81:148–156. doi: 10.1016/j.humpath.2018.07.001.

Ye Z, Zheng M, Zeng Y, Wei S, Wang Y, Lin Z, Shu C, Xie Y, Zheng Q, Chen L. (2020) Bioinformatics Analysis Reveals an Association Between Cancer Cell Stemness, Gene Mutations, and the Immune Microenvironment in Stomach Adenocarcinoma. *Front Genet*. Dec 11;11:595477. doi: 10.3389/fgene.2020.595477. Erratum in: Front Genet. 2022 Feb 14;13:828664. doi: 10.3389/fgene.2022.828664.

Yeo C, Lee HJ, Lee EO. (2019) Serum promotes vasculogenic mimicry through the EphA2/VE-cadherin/AKT pathway in PC-3 human prostate cancer cells. *Life Sci.* Mar 15;221:267–273. doi: 10.1016/j.lfs.2019.02.043.

Yoshida R. (2021) Hereditary breast and ovarian cancer (HBOC): review of its molecular characteristics, screening, treatment, and prognosis. *Breast Cancer*. Nov;28 (6):1167–1180. doi: 10.1007/s12282-020-01148-2.

Young EL, Thompson BA, Neklason DW, Firpo MA, Werner T, Bell R, Berger J, Fraser A, Gammon A, Koptiuch C, Kohlmann WK, Neumayer L, Goldgar DE, Mulvihill SJ, Cannon-Albright LA, Tavtigian SV. (2018) Pancreatic cancer as a sentinel for hereditary cancer predisposition. *BMC Cancer*. Jun 27;18(1):697. doi: 10.1186/s12885-018-4573-5.

Yu J, Yu C, Jiang K, Yang G, Yang S, Tan S, Li T, Liang H, He Q, Wei F, Li Y, Cheng J, Wang F. (2024) Unveiling potential: urinary exosomal mRNAs as non-invasive biomarkers for early prostate cancer diagnosis. *BMC Urol*. Aug 1;24 (1):163. doi: 10.1186/s12894-024-01540-6.

Zhang X, Jing Y, Qin Y, Hunsucker S, Meng H, Sui J, Jiang Y, Gao L, An G, Yang N, Orlowski RZ, Yang L. (2012) The zinc finger transcription factor ZKSCAN3 promotes prostate cancer cell migration. *Int J Biochem Cell Biol*. Jul;44 (7):1166–73. doi: 10.1016/j.biocel.2012.04.005.

Zhang W, van Gent DC, Incrocci L, van Weerden WM, Nonnekens J. (2020) Role of the DNA damage response in prostate cancer formation, progression and treatment. *Prostate Cancer Prostatic Dis.* Mar;23(1):24–37. doi: 10.1038/s41391-019-0153-2. Epub 2019 Jun 13. Erratum in: Prostate Cancer Prostatic Dis. 2020 Mar;23(1):194. doi: 10.1038/s41391-019-0162-1

Zhao DD, Zhao X, Li WT. (2020) Identification of differentially expressed metastatic genes and their signatures to predict the overall survival of uveal melanoma patients by bioinformatics analysis. *Int J Ophthalmol*. Jul 18;13 (7):1046–1053. doi: 10.18240/ijo.2020.07.05.

Zhen JT, Syed J, Nguyen KA, Leapman MS, Agarwal N, Brierley K, Llor X, Hofstatter E, Shuch B. (2018) Genetic testing for hereditary prostate cancer: Current status and limitations. *Cancer*. Aug 1;124 (15):3105–3117. doi: 10.1002/cncr.31316. Epub 2018 Apr 18. Erratum in: *Cancer*. 2019 Jul 1;125 (13):2325. doi: 10.1002/cncr.32070.

Zheng SL, Xu J, Isaacs SD, Wiley K, Chang B, Bleecker ER, Walsh PC, Trent JM, Meyers DA, Isaacs WB. (2001) Evidence for a prostate cancer linkage to chromosome 20 in 159 hereditary prostate cancer families. *Hum Genet*. May;108(5):430–5. doi: 10.1007/s004390100513.

Zhu S, Yoon K, Sterneck E, Johnson PF, Smart RC. (2002) CCAAT/enhancer binding protein-beta is a mediator of keratinocyte survival and skin tumorigenesis involving oncogenic Ras signaling. *Proc Natl Acad Sci U S A*. Jan 8;99(1): 207–12. doi: 10.1073/pnas.012437299.

Zhu M, Wen X, Liu X, Wang Y, Liang C, Tu J. (2017) Association between 8q24 rs6983267 polymorphism and cancer susceptibility: a meta-analysis involving 170,737 subjects. *Oncotarget*. Jul 4;8 (34):57421–57439. doi: 10.18632/oncotarget.18960.

Zhu Y, Liang L, Li J, Zeng J, Yao H, Wu L. (2023) Establishing Molecular Subgroups of CD8+ T Cell-Associated Genes in the Ovarian Cancer Tumour Microenvironment and

Predicting the Immunotherapy Response. *Biomedicines*. Aug 28;11 (9):2399. doi: 10.3390/biomedicines11092399.

Zocchi L, Lontano A, Merli M, Dika E, Nagore E, Quaglino P, Puig S, Ribero S. (2021) Familial Melanoma and Susceptibility Genes: A Review of the Most Common Clinical and Dermoscopic Phenotypic Aspect, Associated Malignancies and Practical Tips for Management. *J Clin Med*. Aug 23;10(16):3760. doi: 10.3390/jcm10163760.

Zuk O, Schaffner SF, Samocha K, Do R, Hechter E, Kathiresan S, Daly MJ, Neale BM, Sunyaev SR, Lander ES. (2014) Searching for missing heritability: designing rare variant association studies. *Proc Natl Acad Sci U S A*. Jan 28;111 (4):E455–64. doi: 10.1073/pnas.1322563111.

APPENDICES

Appendix 1 – Families pedigrees

Pedigrees are presented in numerical order, with the year of the last update shown next to each family number. They include family members genotyped and included in the analysis (in bold), those who were genotyped but excluded from the analysis due to being under 50 years of age (in red), and family members not genotyped but included in the FBAT (in italics). The pedigrees also show any type of cancer (ca) affecting any numbered family member.

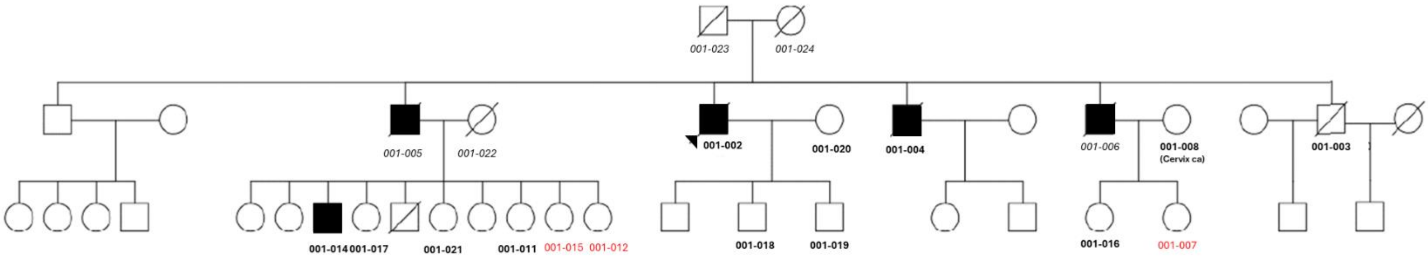
☐	Male	⧄	Deceased male
■	Male affected with PCa	■	Deceased male affected with PCa
○	Female	⌀	Deceased female
◥	Index relative		

000-000 Participant only numbered for FBAT

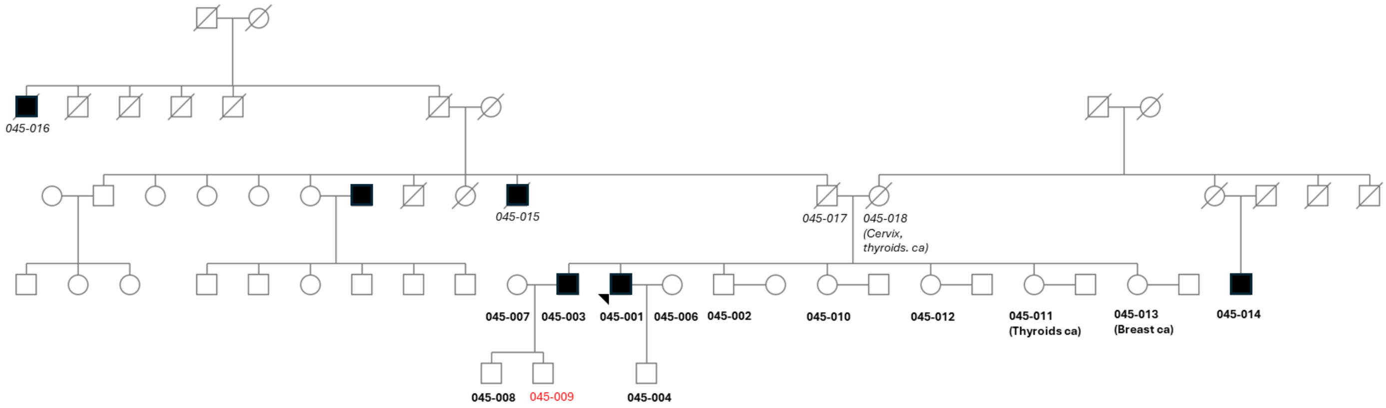
000-000 Participant genotyped and used for analysis

000-000 Participant genotyped but not used for analyzed

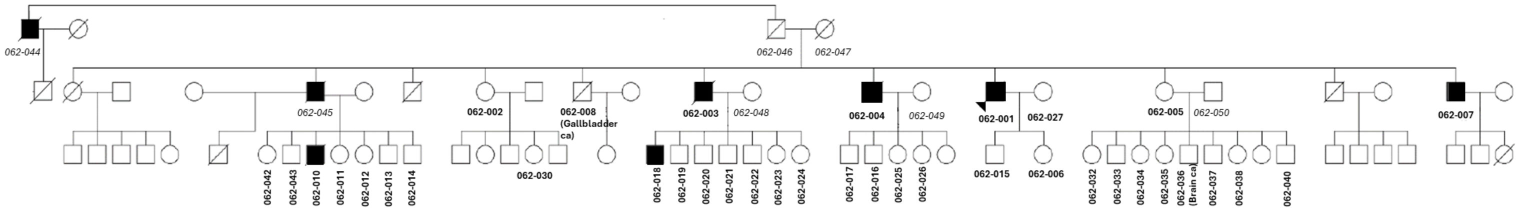
001 (2010)



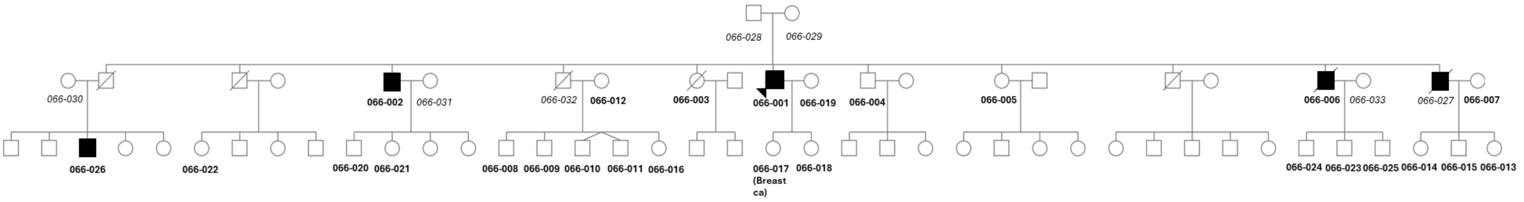
045 (2007)



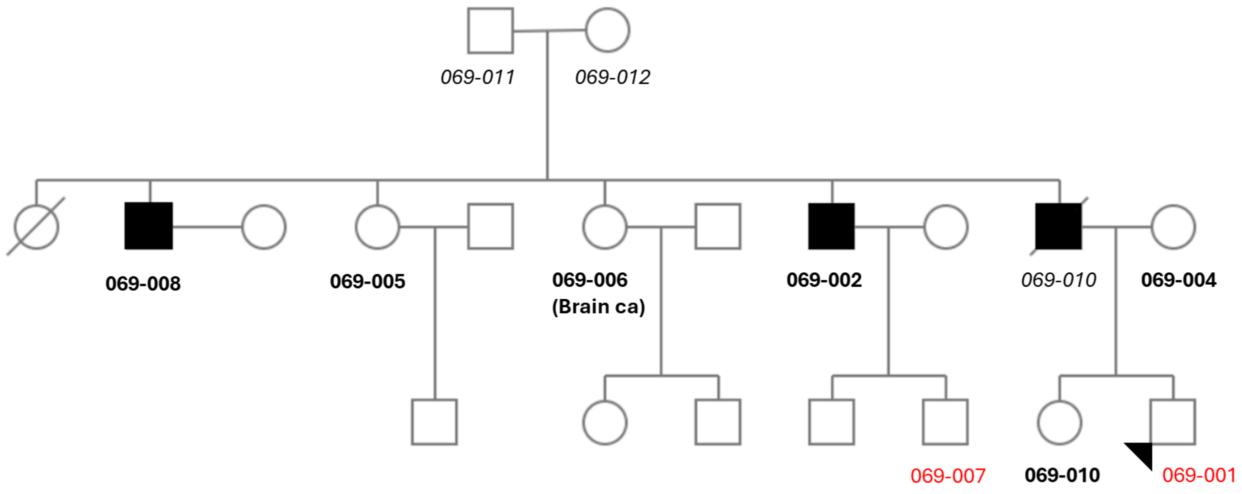
062 (2012)



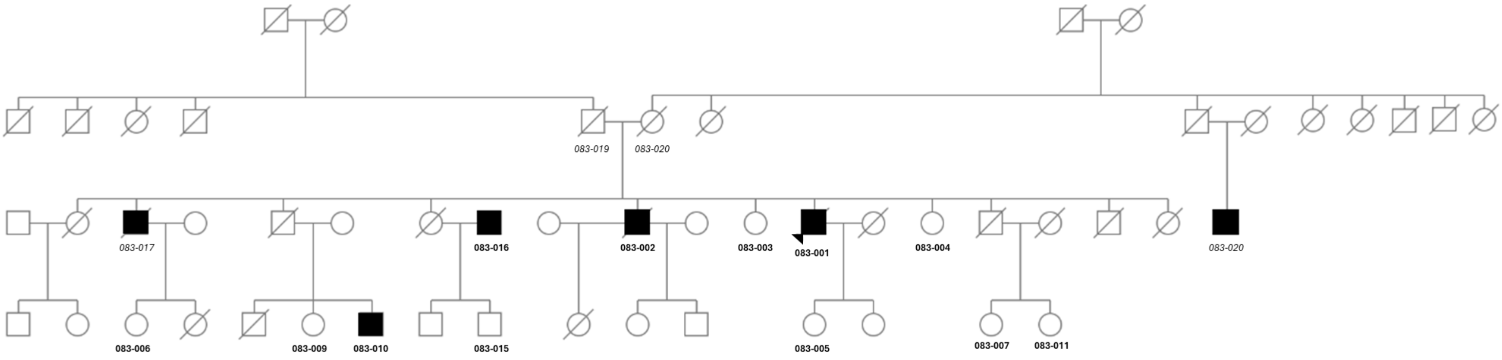
066 (2013)



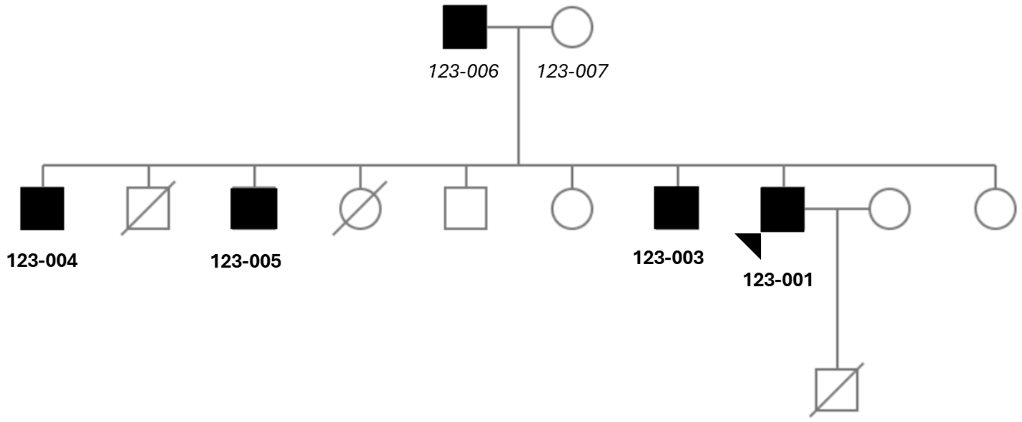
069 (2007)



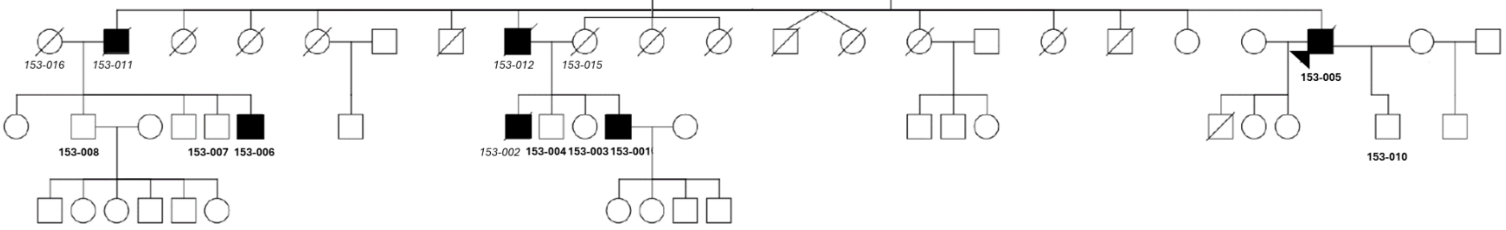
083 (2015)



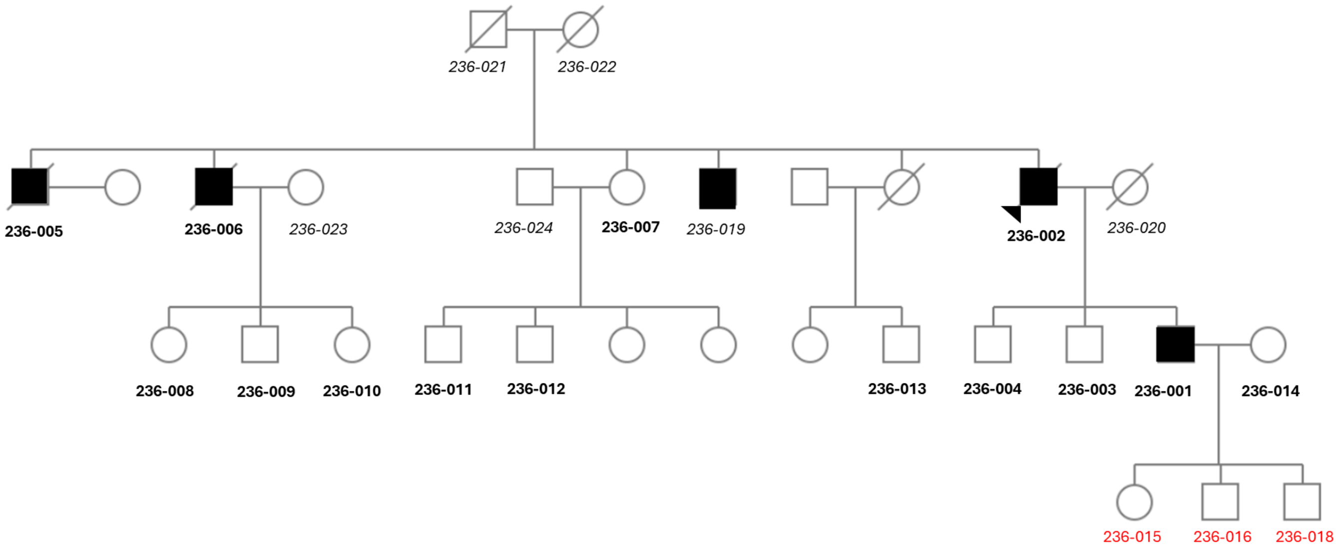
123 (2007)



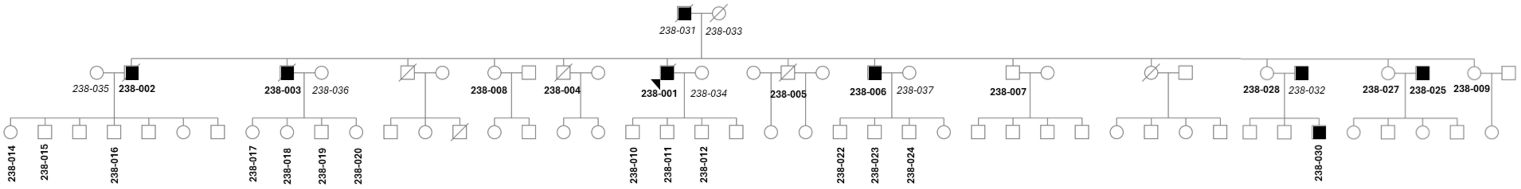
153 (2013



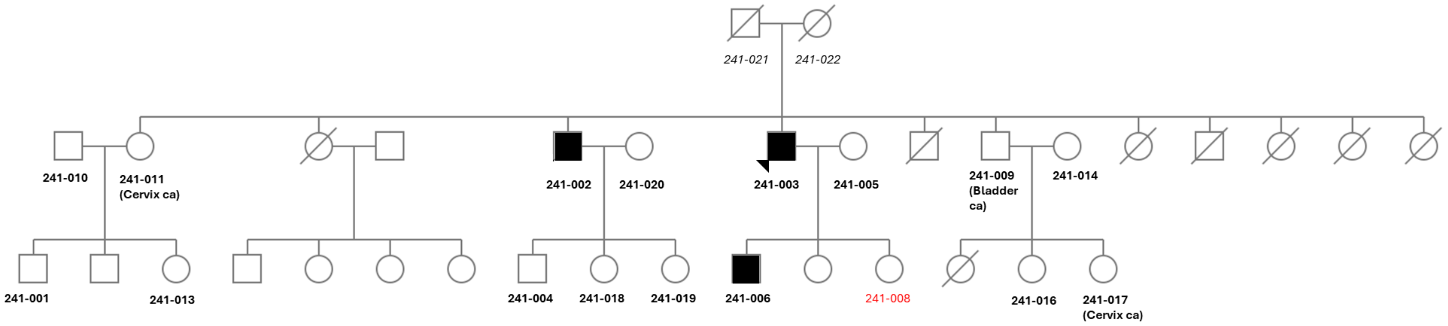
236 (2007)



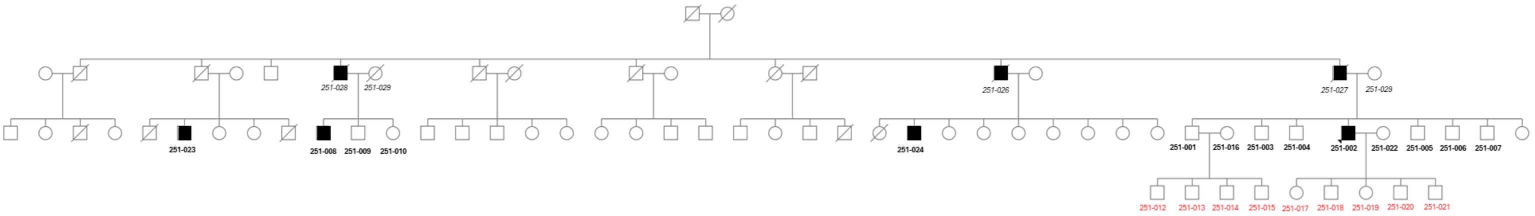
238 (2007)



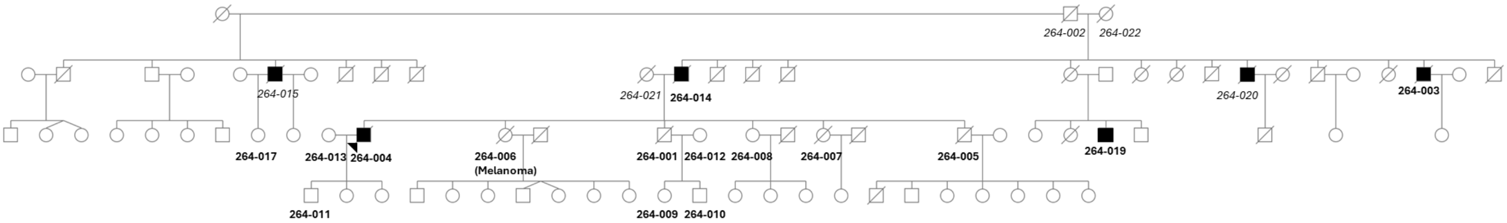
241 (2007)



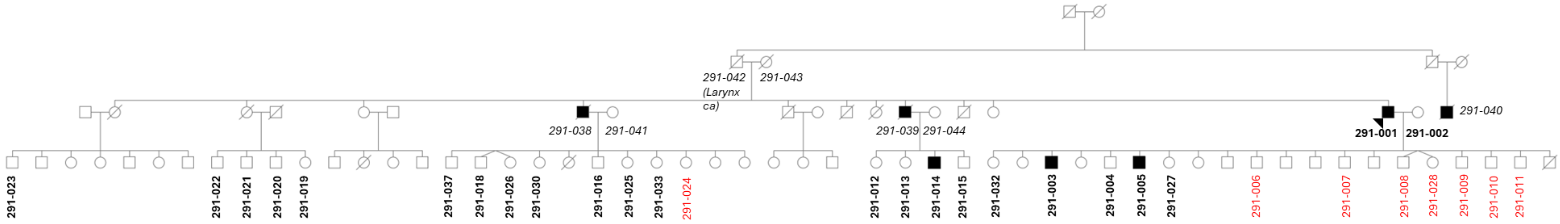
251 (2015)



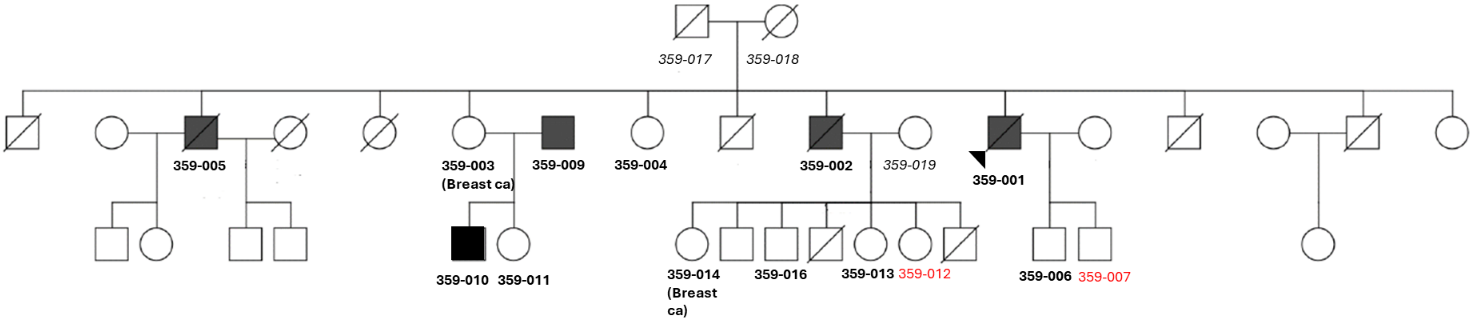
264 (2007)



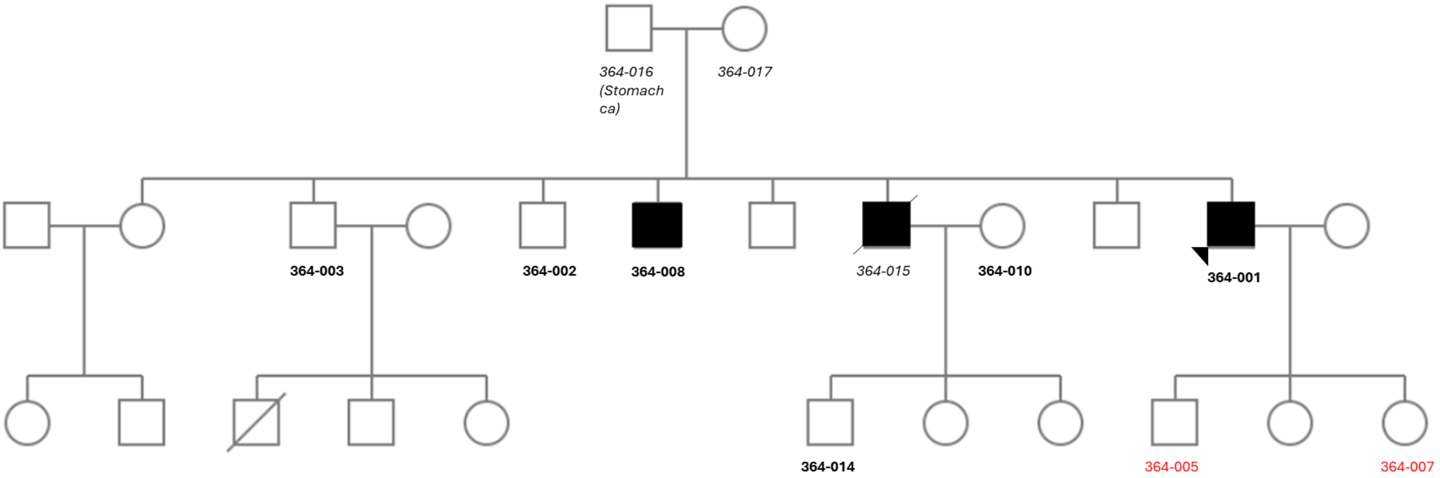
291 (2008)



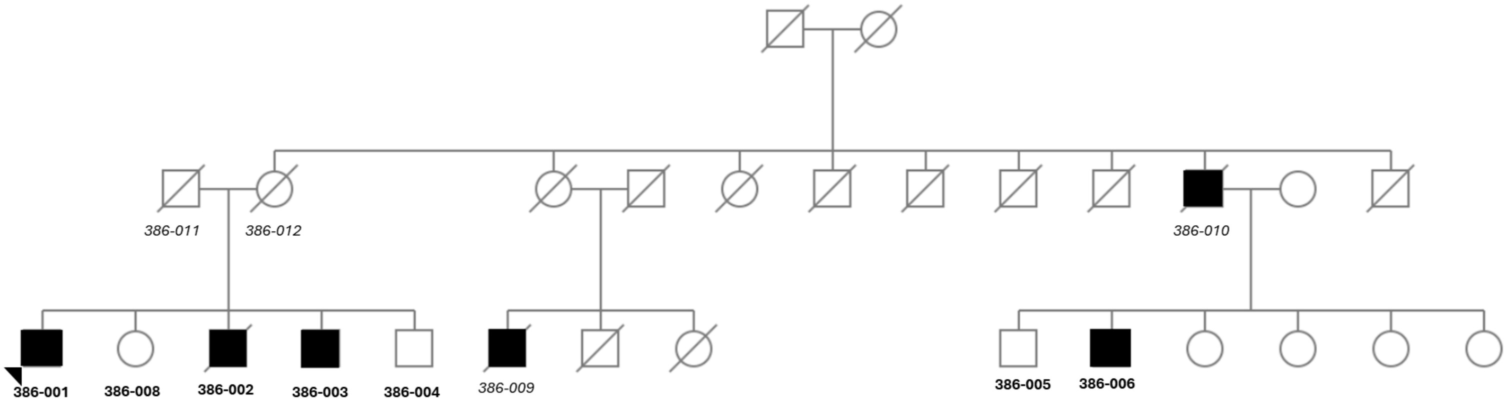
359 (2007)



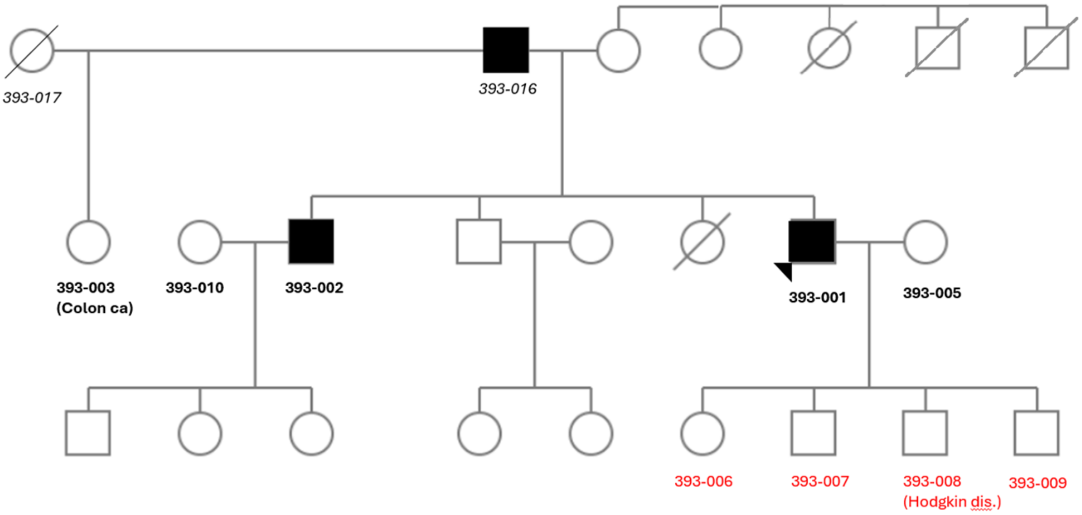
364 (2007)



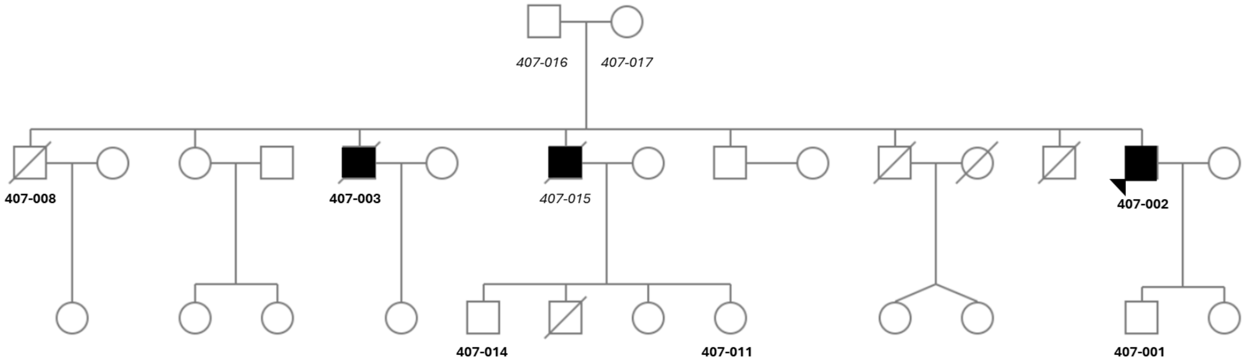
386 (2012)



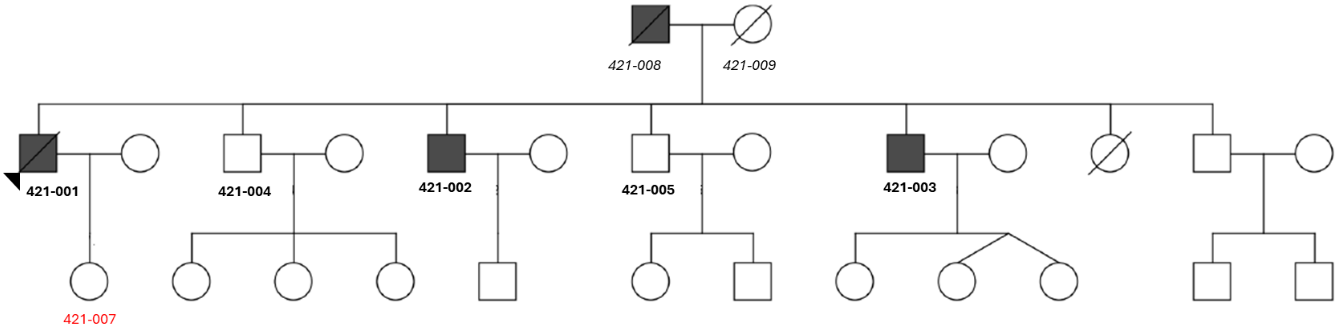
393 (2007)



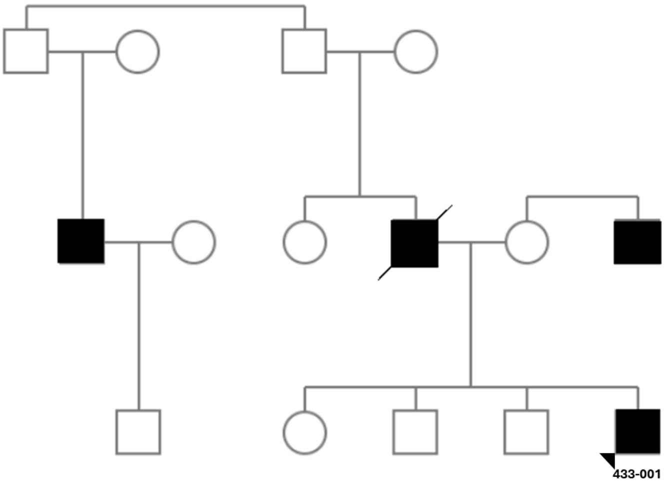
407 (2007)



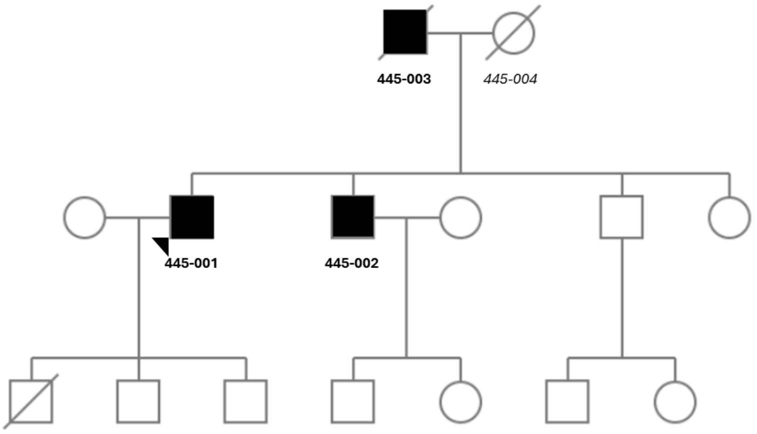
421 (2007)



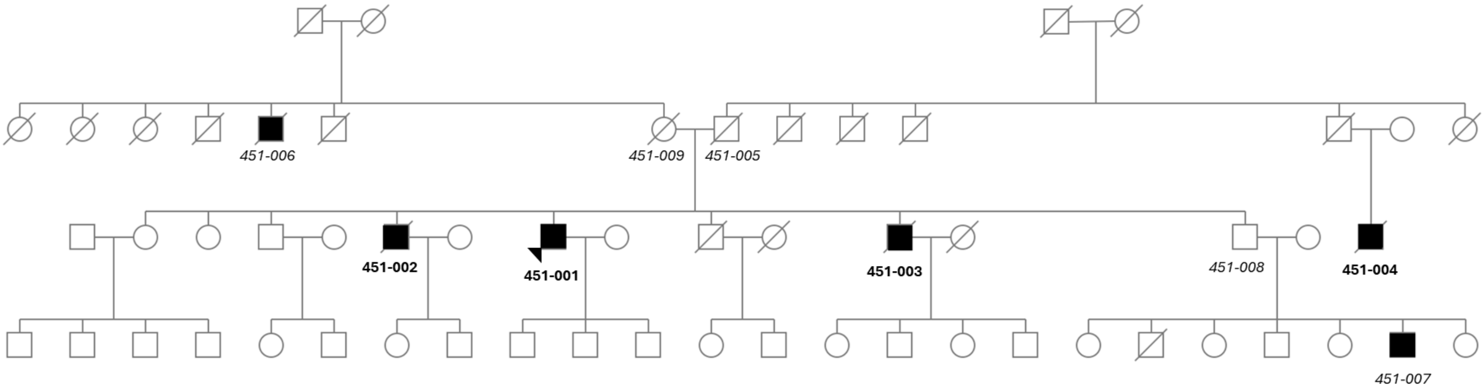
433 (2015)



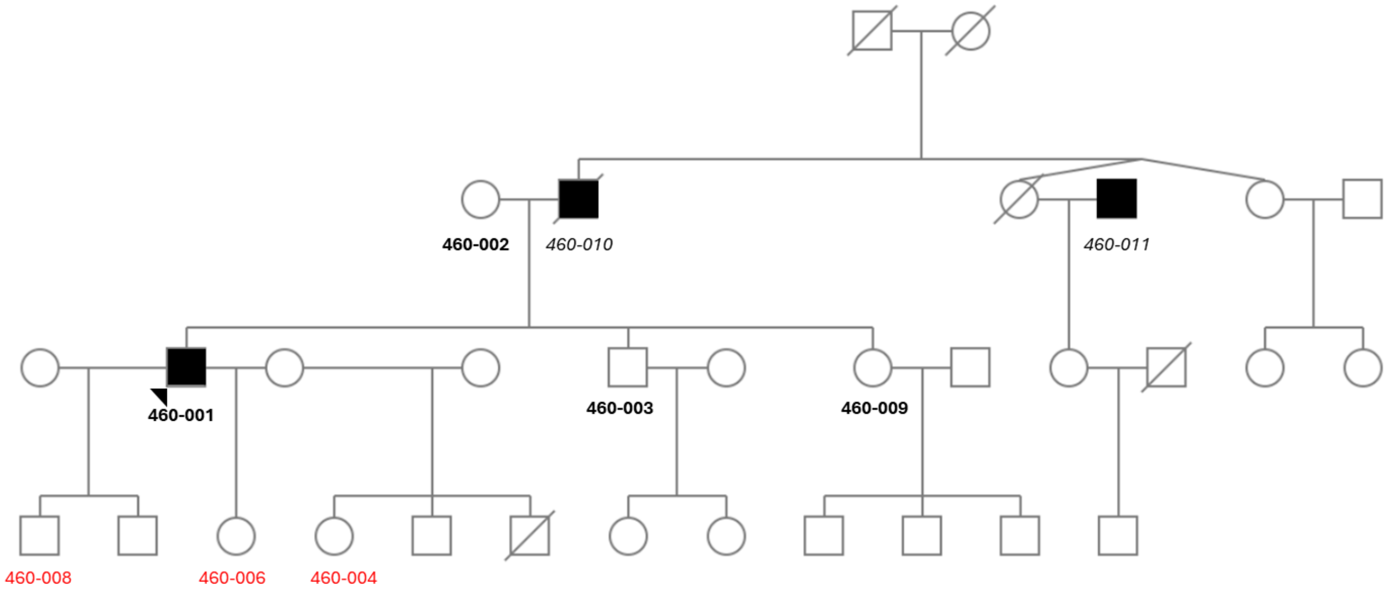
445 (2015)



451 (2015)



460 (2014)


460-002
460-010
460-011
460-001
460-003
460-009
460-008
460-006
460-004

Appendix 2 – Literature review for final variant selection

Gene function and gene association with prostate, as well as other types of cancer of the 13 selected genes for the final variant selection.

Gene	Gene function *	Gene association with cancer [†]	Gene association with PCa [†]
HOXB13	Homeobox Protein Hox-B13. "Sequence-specific transcription factor, that belongs to the homeobox gene family and is part of a developmental regulatory system that provides cells with specific positional identities on the anterior-posterior axis".	"*HOXB13* is a novel candidate tumor suppressor gene in renal cell carcinoma and its inactivation may play an important role in both RCC tumorigenesis and progression" (Okuda et al., 2005). "*HOXB13* facilitates hepatocellular carcinoma progression by activating AKT/mTOR signaling pathway" (Li et al., 2023).	"Risk of prostate cancer is greatly elevated by the inheritance of a known germline mutation of *HOXB13* in men of European ancestry" (Ewing et al., 2012; Witte et al., 2013; Breyer et al., 2014; Karlsson et al., 2014; Sipeky et al., 2018).
ABI3	ABI Family Member 3. "Member of an adaptor protein family, that encodes a protein containing a homeobox homology domain, proline rich region and Src-homology 3 (SH3) domain, and are components of the Abi/WAVE complex which regulates actin polymerization. The encoded protein inhibits ectopic metastasis of tumor cells as well as cell migration. This may be accomplished through interaction with p21-activated kinase".	"*ABI3* tumor-suppressive effect and/or cytoskeleton remodeling comes from the reduction of phosphorylation of AKT and GSKβ". *ABI3* expression is lost in follicular thyroid carcinomas" (Moraes et al. 2017). "Overexpression of *ABI3* in metastatic glioma cells decreased cell motility and the metastasis potential in vivo" (Ichigotani et al. 2002). "*ABI3* ectopic expression reduces in vitro and in vivo cell growth properties while inducing senescence" (Latini et al. 2011).	No found
CDK5RAP3	CDK5 Regulatory Subunit Associated Protein 3. "Substrate adapter of E3 ligase complexes mediating ufmylation, the covalent attachment of the ubiquitin-like modifier UFM1 to substrate proteins, and which is involved in various processes, such as ribosome recycling and reticulophagy (also called ER-phagy). Also acts as a regulator of transcription: negatively regulates NF-kappa-B-mediated gene transcription through the control of RELA phosphorylation. Moreover, regulates mitotic G2/M transition checkpoint and mitotic G2 DNA damage checkpoint. Through its interaction with CDKN2A/ARF and MDM2 may induce MDM2-dependent p53/TP53 ubiquitination, stabilization and activation in the nucleus, thereby promoting G1 cell cycle arrest and inhibition of cell proliferation".	"*CDK5RAP3* as a tumor suppressor negatively regulates self-renewal and invasion and is regulated by ERK1/2 signaling in human gastric cancer (Lin et al., 2020). "*CDK5RAP3* is widely overexpressed in hepatocellular carcinoma and that overexpression of *CDK5RAP3* promotes its metastasis through PAK4 activation" (Mak et al., 2011). "CDK5RAP3 works as an enhancer of STAT3-dependent gene expression. We found that *STAT3* transcriptional function is modulated by *CDK5RAP3* in breast cancer cells, and silencing *CDK5RAP3* reduces STAT3-mediated tumorigenic phenotypes including clonogenesis, and migration" (Egusquiaguirre et al., 2020)	"*CDK5RAP3* functions in signaling pathways governing transcriptional regulation and cell cycle progression. *CDK5RAP3* showed significant expressional, prognostic, and clinic-pathologic values in prostate cancer" (Wan et al., 2024). "Alterations in the expression of *CDK5RAP3* can influence the aggressiveness of prostate cancer, and it has been included as a component of a prognostic model that uses cell cycle-related genes to predict patient outcomes" (Liu et al. 2021).
CHEK2	Checkpoint Kinase 2. "Serine/threonine-protein kinase which is required for checkpoint-mediated cell cycle arrest, activation of DNA repair and apoptosis in response to the presence of DNA double-strand breaks. May also negatively regulate cell cycle progression during unperturbed cell cycles. It contains a forkhead-associated protein interaction domain essential for activation in response to DNA damage and is rapidly phosphorylated in response to replication blocks and DNA damage. When activated, the encoded protein is known to inhibit CDC25C phosphatase, preventing entry into mitosis, and has been shown to stabilize the tumor suppressor protein p53, leading to cell cycle arrest in G1. In addition, this protein interacts with and phosphorylates BRCA1, allowing BRCA1 to restore survival after DNA damage".	"Women with the *CHEK2* c.1100delC (p.Thr367fs) pathogenic variant (PV) have an increased risk to develop breast cancer, which further increases in a familial breast cancer setting" (Adank et al., 2013). "*CHEK2**1100delC heterozygosity is associated with 15% to 82% increased risk for at least some cancers (stomach cancer, renal cancer, sarcoma, and prostate cancer) in addition to breast cancer." (Näslund-Koch et al., 2016). "Functional analyses of *CHEK2* missense VUS reveal an association between impaired protein function and increased breast cancer risk." (Boonen et al., 2022). "*PTPN13* rs989902 and *CHEK2* rs738722 are associated with an increased risk of esophageal squamous cell carcinoma in the Chinese Han population (Tu et al., 2023).	"*CHEK2* variants are low-penetrance prostate cancer predisposition alleles that contribute significantly to familial clustering of prostate cancer at the population level." (Seppälä et al., 2003). "*CHEK2* mutations predispose men and women to a range of cancer types, including breast and prostate cancer. The truncating mutations are associated with higher penetrance than the missense mutation ." (Cybulski et al, 2007). "The overall meta-analysis demonstrated that the CHEK2 1100delC mutation (OR 3.29; 95% confidence interval: 1.85-5.85; P = 0.00) and I157T missense mutation (OR 1.80; 95% confidence interval: 1.51-2.14; P = 0.00) was associated with higher risk of Prostate Cancer." (Wang et al., 2015).
ZNF391	Zinc Finger Protein 391. "Transcriptional factor predicted to	"Among the 2999 differentially expressed genes, *ZNF391* and	No found

	enable DNA-binding transcription factor activity, RNA polymerase II-specific and RNA polymerase II transcription regulatory region sequence-specific DNA binding activity. Also it is predicted to be involved in regulation of transcription by RNA polymerase II”.	*MRPS11* were upregulated in uveal melanoma patients” (Zhao et al., 2020).	
ZKSCAN3	Zinc Finger With KRAB And SCAN Domains 3. “Transcriptional factor that Enables DNA-binding transcription repressor activity, RNA polymerase II-specific; RNA polymerase II cis-regulatory region sequence-specific DNA binding activity; and chromatin binding activity. Involved in several processes, including negative regulation of autophagy; negative regulation of cellular senescence; and regulation of DNA-templated transcription. Located in cytoplasm and nucleoplasm”.	“*ZKSCAN3* was initially identified as a driver of colorectal cancer; however, it also plays an important role in cancer cell proliferation, migration, and metastasis in several human malignancies, including colon, bone marrow, prostate, bladder, and cervical cancers.” (Yang et al., 2008; Kim et al., 2016; Yang et al., 2011; Zhang et al., 2012; Kawahara et al., 2016; Lee et al., 2018).	“In vivo studies using orthotopic tumor models indicated that overexpression of *ZKSCAN3* significantly enhanced tumorigenicity. ZKSCAN3, a zinc finger transcription factor, plays a critical role in promoting prostate cancer cell migration” (Zhang et al., 2012). “The positive rates or levels of *ZKSCAN3* expression were significantly higher in carcinoma than in benign prostate tissue or high-grade PIN and in high-grade PIN than in benign tissue prostate cancer lines. *ZKSCAN3* silencing resulted in significant decreases in cell proliferation/ migration/ invasion” (Kawahara et al., 2020).
LAMC2	Laminin Subunit Gamma 2. “It encodes the gamma chain isoform laminin, gamma 2. The gamma 2 chain, formerly thought to be a truncated version of beta chain (B2t), is highly homologous to the gamma 1 chain; however, it lacks domain VI, and domains V, IV and III are shorter. It is specifically localized to epithelial cells in skin, lung, and kidney. The gamma 2 chain together with alpha 3 and beta 3 chains constitute laminin 5 (earlier known as kalinin), which is an integral part of the anchoring filaments that connect epithelial cells to the underlying basement membrane”.	“*LAMC2* mRNA levels are consistently and significantly higher in tumor tissue versus adjacent normal tissue in pancreatic ductal adenocarcinoma patients” (Cave et al., 2022). “LAMC2 promotes the proliferation of cancer cells and induces infiltration of macrophages in non-small cell lung cancer” (Liu et al., 2021).	“ *LAMC2*, along with other laminin-5 encoding genes (*LAMA3* and *LAMB3*), showed evidence of aberrant promoter methylation in prostate cancer samples” (Sathyanarayana et al., 2003). “Certain gene amplifications, being *LAMC2* one of them, are associated with the development of hormone-resistant prostate cancer” (Edwards et al., 2003). “Activation of AKT that up-regulates *MMP-2* and *LAMC2*, induces the invasion and vasculogenic mimicry of human PCa PC-3 cells” (Yeo et al., 2019).
TP63	Tumor Protein P63. “p53 family protein that acts as a sequence specific DNA binding transcriptional activator or repressor. Alternative splicing of this gene and the use of alternative promoters result in multiple transcript variants encoding different isoforms that vary in their functional properties. These isoforms function during skin development and maintenance, adult stem/progenitor cell regulation, heart development and premature aging. Some isoforms have been found to protect the germline by eliminating oocytes or testicular germ cells that have suffered DNA damage”.	“Both major p63 protein isoforms are expressed in triple-negative breast cancers with different tumor characteristics, indicating distinct functional activities of p63 variants in breast cancer” (Coates et al., 2016). “*TP63* functions as a tumor suppressor regulated by GAS5/miR-221-3p signaling axis in human non-small cell lung cancer cells” (Shen et al., 2023). “TP63 and STAT1 mutually suppress each other to regulate the IFNγ signaling by co-occupying and co-regulating their own promoters and enhancers in squamous cell carcinomas. Silencing of *TP63* enhances the anti-tumor efficacy of PD-1 blockade by promoting CD8+ T cell infiltration and functionality” (Jiang et al., 2024).	“*TP63* and *TRIM29* are key transcription regulators and are downregulated in prostate adenocarcinoma. *TP63* regulates the level of enhancer methylation in prostate basal epithelial cells” (Sultanov et al., 2024).” In the transcriptional regulation network, *TP63* and *FOXO1* act as suppressors of prostate cancer lineage plasticity” (Wei et al., 2024). “*TP63* has significantly lower mRNA expression levels in patients with prostate cells with cribiform pattern 4 (CP4) compared to those without” (Sayan et al., 2024). “Tumor protein p63 (*TP63*) and S100 calcium binding protein A14 (*S100A14*) were poorly expressed in the prostate cancer tissues and cells” (Wu et al., 2024).
ZBTB46	Zinc Finger and BTB Domain Containing 46. “Transcriptional factor predicted to enable DNA-binding transcription repressor activity, RNA polymerase II-specific and transcription cis-regulatory region binding activity. It is involved in the regulation of transcription by RNA polymerase II”.	“Tumor-driven, unremitting expression of *SATB1* in activated *ZBTB46* (+) inflammatory dendritic cells that infiltrate ovarian tumors results in an immunosuppressive phenotype characterized by increased secretion of tumor-promoting Galectin-1 and IL-6 (Tesone et al., 2016. “ZBTB46 is essential for survival and proliferation of acute myeloid leukemia cell line but dispensable for normal hematopoiesis (Liu et al., 2020). “ZBTB46-deficient endothelial cells were highly angiogenic, and ZBTB46-deficient bone marrow progenitors upregulated *CEBPB* and diverted the dendritic cell program to immunosuppressive myeloid lineage output, potentially explaining the myeloid lineage skewing phenomenon in cancer” (Kabir et al., 2024).	“Inhibition of the androgen receptor induces a novel tumor promoter, ZBTB46, for prostate cancer metastasis” (Chen et al., 2017). “Leukemia inhibitory factor promotes castration-resistant prostate cancer and neuroendocrine differentiation by activated *ZBTB46*” (Liu et al., 2019). ”ZBTB46 interacted with FOXA2 and HIF1A and increased the abundance of MCTP1 in a hypoxia-dependent manner, which promotes PC3 prostate cancer cell migration and neuroendocrine differentiation” (Liu et al., 2024). “Upregulation of *PCK1* supports cell proliferation and reciprocally increases *ZBTB46* levels to promote the expression of neuroendocrine markers that are conducive to the development of neuroendocrine characteristic castration-resistant prostate cancer” (Wen et al., 2022).

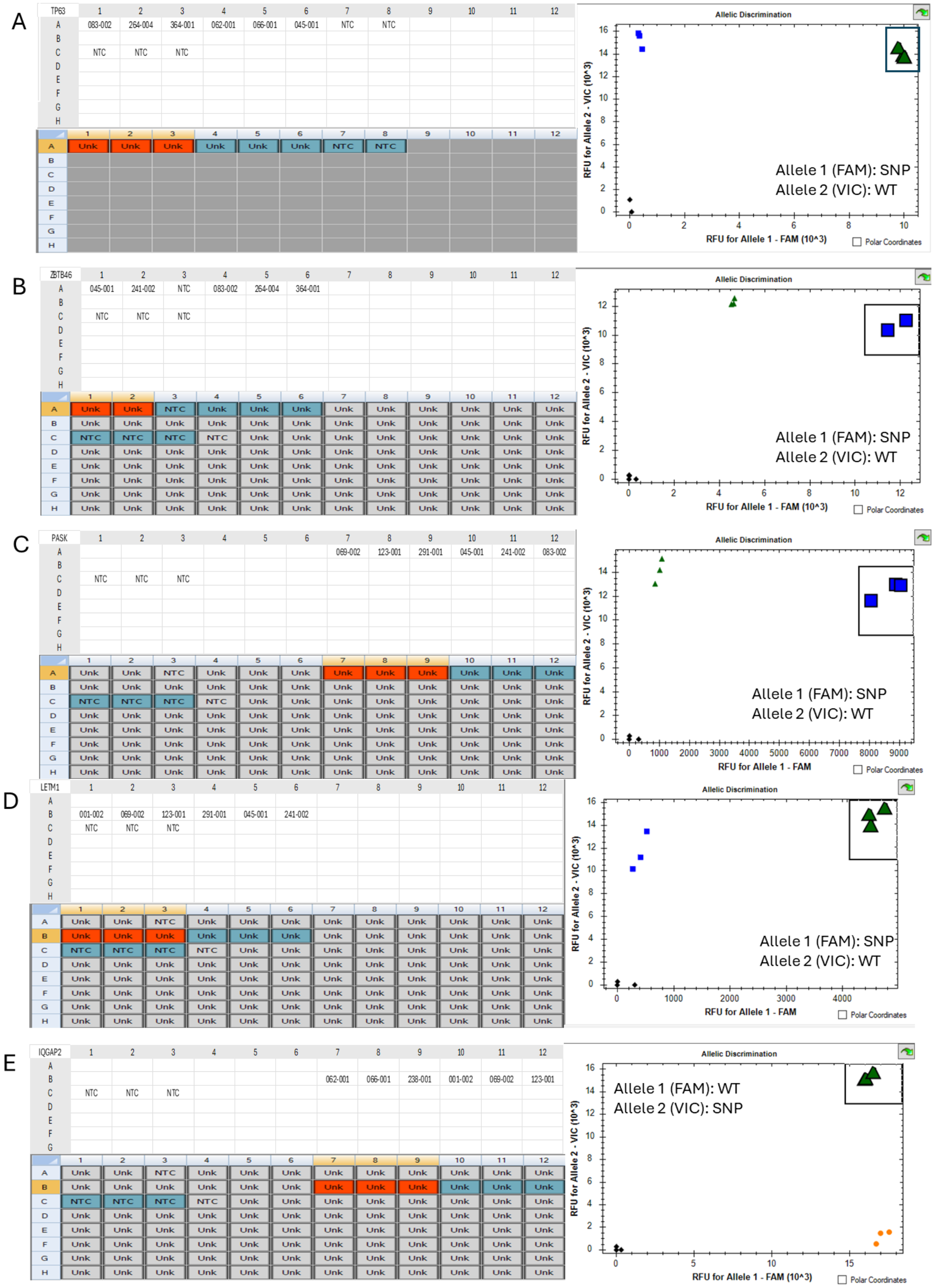
PASK	PAS Domain Containing Serine/Threonine Kinase. "Serine/threonine kinase family that contains two PAS domains. It is involved in energy homeostasis and protein translation. Probably plays a role under changing environmental conditions (oxygen, glucose, nutrition), rather than under standard conditions. Acts as a sensor involved in energy homeostasis, regulates glycogen synthase synthesis by mediating phosphorylation of GYS1, leading to GYS1 inactivation. It may play a role in the regulation of protein translation by phosphorylating EEF1A1, leading to increased translation efficiency".	"The nine-gene signature prognostic model (ARHGEF38-IT1, CCDC15, CPZ, DNASE1L2, NUDT10, PASK, PLCL1, PRR5-ARHGAP8, and SYCE2) that was constructed from 178 survival-related differentially expressed genes, was significantly related to overall survival, clinical characteristics, tumor microenvironment immune cells, tumor mutation burden, and cancer-related pathways in stomach adenocarcinoma" (Ye et al., 2020)."High expression of *PASK* is associated with low risk and better prognosis in ovarian cancer" (Zhu et al., 2023).	"*PASK* expression is upregulated in prostate cancer patients according to urinary exosomal mRNA" (Yu et al., 2024).
TASOR	Transcription Activation Suppressor. "Component of the HUSH complex, a multiprotein complex that mediates epigenetic repression. It enables chromatin binding activity. It is involved in protein localization to heterochromatin and regulation of macromolecule biosynthetic process".	"*TASOR* and *PPHLN1* are transcriptionally up-regulated in most EBV-associated gastric cancer cells" (Zhang et al., 2023). "Overexpression of *TASOR* can substantially reduce the transcription in cancer cells (hence their proliferation) while increasing the renewal of the normal cells in metastatic clear cell renal cell carcinoma" (Iacobas et al., 2020). "TASOR is a key factor in gene silencing, particularly in the repression of L1 transposable elements. A loss of silencing of the repeat elements leads to genome instability and human diseases, including cancer and ageing" (Li et al., 2023).	No found
LETM1	Leucine Zipper And EF-Hand Containing Transmembrane Protein 1. "It encodes a protein that is localized to the inner mitochondrial membrane, which maintains the mitochondrial tubular shapes and is required for normal mitochondrial morphology and cellular viability. It mediates either calcium or potassium/proton antiport, proton-dependent calcium efflux from mitochondrion and also acts as an electroneutral mitochondrial proton/potassium exchanger".	"*LETM1* is a potential cancer stem-like cell marker and predicts poor prognosis in colorectal adenocarcinoma" (Piao et al., 2019). "*LETM1* overexpression is correlated with the clinical features and survival outcome of breast cancer" (Li et al., 2015). "*LETM1* is a marker of cancer stem-like cells and predictor of poor prognosis in esophageal squamous cell carcinoma" (Yang et al., 2018).	"*LETM1* is a potential prognostic biomarker and promotes cell progression in prostate cancer. The expression of *LETM1* was correlated with cancer cell stemness-associated genes, endothelial-mesenchymal transition-related genes, cell cycle regulatory genes, and PI3K/Akt signaling gene expression in prostate cancer" (Piao et al., 2020).
IQGAP2	IQ Motif Containing GTPase Activating Protein 2. "It contains three IQ domains, one calponin homology domain, one Ras-GAP domain and one WW domain. It interacts with components of the cytoskeleton, with cell adhesion molecules, and with several signaling molecules to regulate cell morphology and motility. It also acts as a tumor suppressor and has been found to play a role in regulating innate antiviral responses. It binds to activated CDC42 and RAC1 but does not seem to stimulate their GTPase activity. It associates with calmodulin".	"Increased IQGAP1 and/or decreased IQGAP2 contribute to the pathogenesis of human hepatocellular carcinoma. Furthermore, downregulation of *IQGAP2* occurs independently of hypermethylation of the *IQGAP2* promoter" (White et al., 2010)."*IQGAP2* works as a tumor suppressor in hepatocellular, prostate, and gastric carcinomas" (Smith et al., 2015). "*IQGAP2* mRNA expression is correlated with the expression of immunosuppressive genes and leukocyte infiltration in diffuse large B-cell lymphoma" (Tang et al., 2021).	"IQGAP2 may suppress PC tumorigenesis, at least in part, by up-regulation of E-cadherin. Mechanistically, overexpression of IQGAP2 significantly reduced AKT activation in DU145 cells and inhibition of AKT activation upregulated E-cadherin, suggesting that IQGAP2 increases E-cadherin expression by inhibiting AKT activation. Taken together, we demonstrate here that IQGAP2 is a candidate tumour suppressor of prostate cancer" (Xie et al., 2012). "*IQGAP2* mRNA expression was significantly elevated particularly in low-grade (primary Gleason score ≤3) PCs; these changes separate PC from normal tissues with area under curve values of 0.7-0.8. Significant reductions in IQGAP2 mRNA levels and gene copy number occurred in more than 70 metastases compared to at least 230 local PCs. This duo-alteration in *IQGAP2* expression supports *IQGAP2* elevation suppressing and its downregulation facilitating PC progression" (Xie et al., 2019).

* The gene functions are directly sourced from Gene Cards.

† The justifications for the association with cancer, or specifically PCa, are direct quotes taken from the cited publications.

Appendix 3 – TaqMan™ SNP Genotyping Assay validation

Plate maps and allelic discrimination scatter plots of the high-risk families' index patients used as positive and negative controls for each TaqMan™ SNP Genotyping Assay validation. *TP63* rs190865056; (A), *ZBTB46* rs34785134 (B), *PASK* rs35129131 (C), *LETM1* rs62623389 (D), and *IQGAP2* rs34592828 (E). The orange boxes indicate the samples that are heterozygous for the studied variant in the plate map. The black rectangle in the allelic discrimination plot indicates the samples that are heterozygous for the tested variant in the allelic discrimination plot. NTC no-template control, SNP variant allele, WT reference allele.



A

TP63	1	2	3	4	5	6	7	8	9	10	11	12
A	083-002	264-004	364-001	062-001	066-001	045-001	NTC	NTC				
B												
C	NTC	NTC	NTC									
D												
E												
F												
G												
H												

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	NTC	NTC				
B												
C												
D												
E												
F												
G												
H												

B

ZBTB46	1	2	3	4	5	6	7	8	9	10	11	12
A	045-001	241-002	NTC	083-002	264-004	364-001						
B												
C	NTC	NTC	NTC									
D												
E												
F												
G												
H												

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	NTC	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	NTC	NTC	NTC	NTC	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk

C

PASK	1	2	3	4	5	6	7	8	9	10	11	12
A							069-002	123-001	291-001	045-001	241-002	083-002
B												
C	NTC	NTC	NTC									
D												
E												
F												
G												
H												

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	NTC	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	NTC	NTC	NTC	NTC	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk

D

LETM1	1	2	3	4	5	6	7	8	9	10	11	12
A												
B	001-002	069-002	123-001	291-001	045-001	241-002						
C	NTC	NTC	NTC									
D												
E												
F												
G												
H												

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	NTC	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	NTC	NTC	NTC	NTC	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk

E

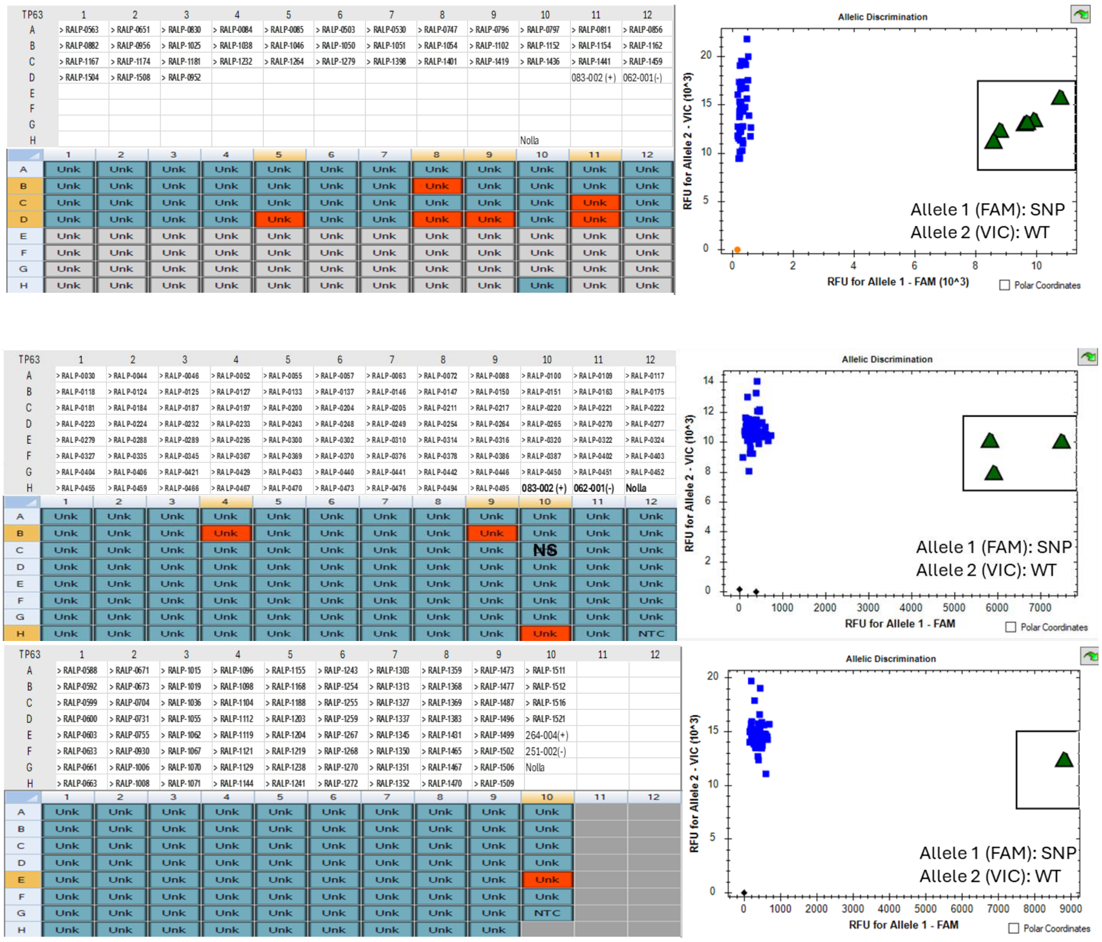
IQGAP2	1	2	3	4	5	6	7	8	9	10	11	12
A												
B							062-001	066-001	238-001	001-002	069-002	123-001
C	NTC	NTC	NTC									
D												
E												
F												
G												

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	NTC	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	NTC	NTC	NTC	NTC	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk

Appendix 4 – Plate maps and allelic discrimination scatter plots of RALP patients with family history of PCa and HBOC

Plate maps and allelic discrimination scatter plots of the RALP patients with a family history of PCa and HBOC (FH+) using TaqMan™ SNP Genotyping Assays. Individuals were genotyped for *TP63* rs190865056 (A), *ZBTB46* rs34785134 (B), *PASK* rs35129131 (C), *LETM1* rs62623389 (D), and *IQGAP2* rs34592828 (E). In the plate map, orange boxes indicate heterozygous individuals, while green boxes represent those homozygous for the studied variant. In the allelic discrimination plot, the black rectangle highlights the heterozygous participants, and the green rectangle indicates the homozygous ones for the tested variant. NS no signal, Nolla no-template control, SNP variant allele, WT reference allele.

A



TP63	1	2	3	4	5	6	7	8	9	10	11	12
A	> RALP-0563	> RALP-0651	> RALP-0830	> RALP-0084	> RALP-0085	> RALP-0503	> RALP-0530	> RALP-0747	> RALP-0796	> RALP-0797	> RALP-0811	> RALP-0856
B	> RALP-0882	> RALP-0956	> RALP-1025	> RALP-1038	> RALP-1046	> RALP-1050	> RALP-1051	> RALP-1054	> RALP-1102	> RALP-1152	> RALP-1154	> RALP-1162
C	> RALP-1167	> RALP-1174	> RALP-1181	> RALP-1232	> RALP-1264	> RALP-1279	> RALP-1398	> RALP-1401	> RALP-1419	> RALP-1436	> RALP-1441	> RALP-1459
D	> RALP-1504	> RALP-1508	> RALP-0952								083-002 (+)	062-001(-)
E												
F												
G												
H										Nolla		

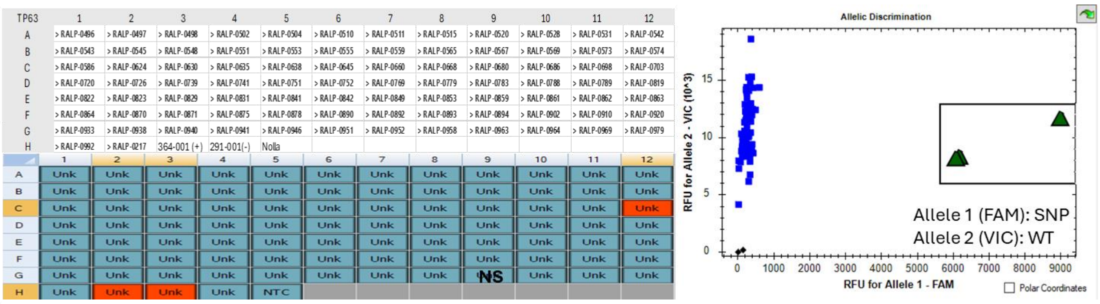
	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk

TP63	1	2	3	4	5	6	7	8	9	10	11	12
A	> RALP-0030	> RALP-0044	> RALP-0046	> RALP-0052	> RALP-0055	> RALP-0057	> RALP-0063	> RALP-0072	> RALP-0088	> RALP-0100	> RALP-0109	> RALP-0117
B	> RALP-0118	> RALP-0124	> RALP-0125	> RALP-0127	> RALP-0133	> RALP-0137	> RALP-0146	> RALP-0147	> RALP-0150	> RALP-0151	> RALP-0163	> RALP-0175
C	> RALP-0181	> RALP-0184	> RALP-0187	> RALP-0197	> RALP-0200	> RALP-0204	> RALP-0205	> RALP-0211	> RALP-0217	> RALP-0220	> RALP-0221	> RALP-0222
D	> RALP-0223	> RALP-0224	> RALP-0232	> RALP-0233	> RALP-0243	> RALP-0248	> RALP-0249	> RALP-0254	> RALP-0264	> RALP-0265	> RALP-0270	> RALP-0277
E	> RALP-0279	> RALP-0288	> RALP-0289	> RALP-0295	> RALP-0300	> RALP-0302	> RALP-0310	> RALP-0314	> RALP-0316	> RALP-0320	> RALP-0322	> RALP-0324
F	> RALP-0327	> RALP-0335	> RALP-0345	> RALP-0367	> RALP-0369	> RALP-0370	> RALP-0376	> RALP-0378	> RALP-0386	> RALP-0387	> RALP-0402	> RALP-0403
G	> RALP-0404	> RALP-0406	> RALP-0421	> RALP-0429	> RALP-0433	> RALP-0440	> RALP-0441	> RALP-0442	> RALP-0446	> RALP-0450	> RALP-0451	> RALP-0452
H	> RALP-0455	> RALP-0459	> RALP-0466	> RALP-0467	> RALP-0470	> RALP-0473	> RALP-0476	> RALP-0494	> RALP-0495	083-002 (+)	062-001(-)	Nolla

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	NS	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	NTC

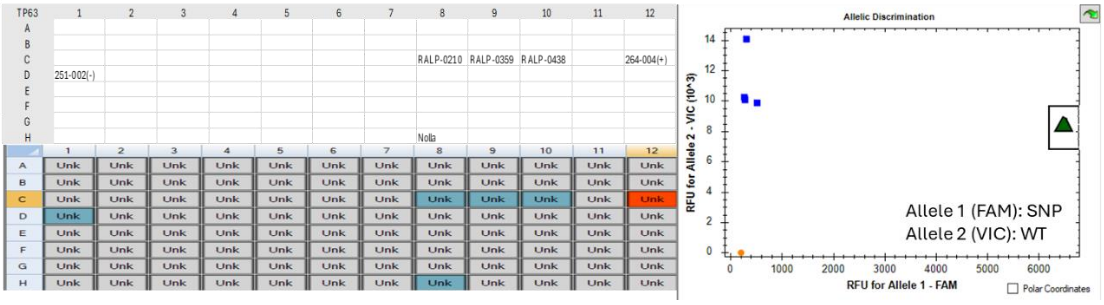
TP63	1	2	3	4	5	6	7	8	9	10	11	12
A	> RALP-0588	> RALP-0671	> RALP-1015	> RALP-1096	> RALP-1155	> RALP-1243	> RALP-1303	> RALP-1359	> RALP-1473	> RALP-1511		
B	> RALP-0592	> RALP-0673	> RALP-1019	> RALP-1098	> RALP-1168	> RALP-1254	> RALP-1313	> RALP-1368	> RALP-1477	> RALP-1512		
C	> RALP-0599	> RALP-0704	> RALP-1036	> RALP-1104	> RALP-1188	> RALP-1255	> RALP-1327	> RALP-1369	> RALP-1487	> RALP-1516		
D	> RALP-0600	> RALP-0731	> RALP-1055	> RALP-1112	> RALP-1203	> RALP-1259	> RALP-1337	> RALP-1383	> RALP-1496	> RALP-1521		
E	> RALP-0603	> RALP-0755	> RALP-1062	> RALP-1119	> RALP-1204	> RALP-1267	> RALP-1345	> RALP-1431	> RALP-1499	264-004(+)		
F	> RALP-0633	> RALP-0930	> RALP-1067	> RALP-1121	> RALP-1219	> RALP-1268	> RALP-1350	> RALP-1465	> RALP-1502	251-002(-)		
G	> RALP-0661	> RALP-1006	> RALP-1070	> RALP-1129	> RALP-1238	> RALP-1270	> RALP-1351	> RALP-1467	> RALP-1506	Nolla		
H	> RALP-0663	> RALP-1008	> RALP-1071	> RALP-1144	> RALP-1241	> RALP-1272	> RALP-1352	> RALP-1470	> RALP-1509			

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	NTC		
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk			



TP63	1	2	3	4	5	6	7	8	9	10	11	12
A	> RALP-0496	> RALP-0497	> RALP-0498	> RALP-0502	> RALP-0504	> RALP-0510	> RALP-0511	> RALP-0515	> RALP-0520	> RALP-0528	> RALP-0531	> RALP-0542
B	> RALP-0543	> RALP-0545	> RALP-0548	> RALP-0551	> RALP-0553	> RALP-0555	> RALP-0559	> RALP-0565	> RALP-0567	> RALP-0569	> RALP-0573	> RALP-0574
C	> RALP-0586	> RALP-0624	> RALP-0630	> RALP-0635	> RALP-0638	> RALP-0645	> RALP-0660	> RALP-0668	> RALP-0680	> RALP-0686	> RALP-0698	> RALP-0703
D	> RALP-0720	> RALP-0726	> RALP-0739	> RALP-0741	> RALP-0751	> RALP-0752	> RALP-0769	> RALP-0779	> RALP-0783	> RALP-0788	> RALP-0789	> RALP-0819
E	> RALP-0822	> RALP-0823	> RALP-0829	> RALP-0831	> RALP-0841	> RALP-0842	> RALP-0849	> RALP-0853	> RALP-0859	> RALP-0861	> RALP-0862	> RALP-0863
F	> RALP-0864	> RALP-0870	> RALP-0871	> RALP-0875	> RALP-0878	> RALP-0890	> RALP-0892	> RALP-0893	> RALP-0894	> RALP-0902	> RALP-0910	> RALP-0920
G	> RALP-0933	> RALP-0938	> RALP-0940	> RALP-0941	> RALP-0946	> RALP-0951	> RALP-0952	> RALP-0958	> RALP-0963	> RALP-0964	> RALP-0969	> RALP-0979
H	> RALP-0992	> RALP-0217	364-001 (+)	291-001(-)	Nolla							

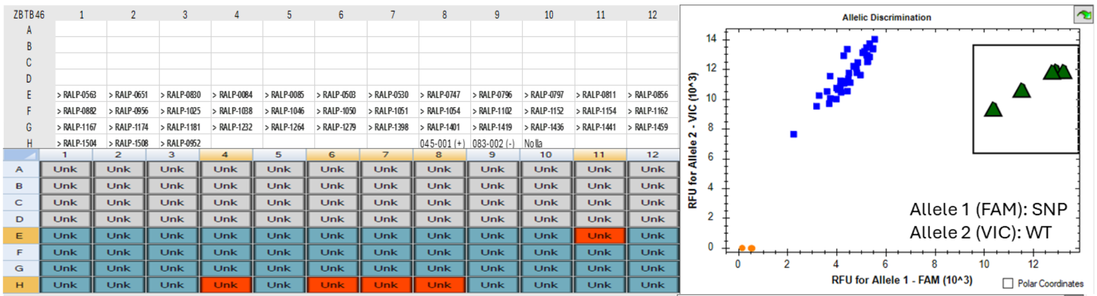
	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	NS	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	NTC							



TP63	1	2	3	4	5	6	7	8	9	10	11	12
A												
B												
C								RALP-0210	RALP-0359	RALP-0438		264-004(+)
D	251-002(-)											
E												
F												
G												
H								Nolla				

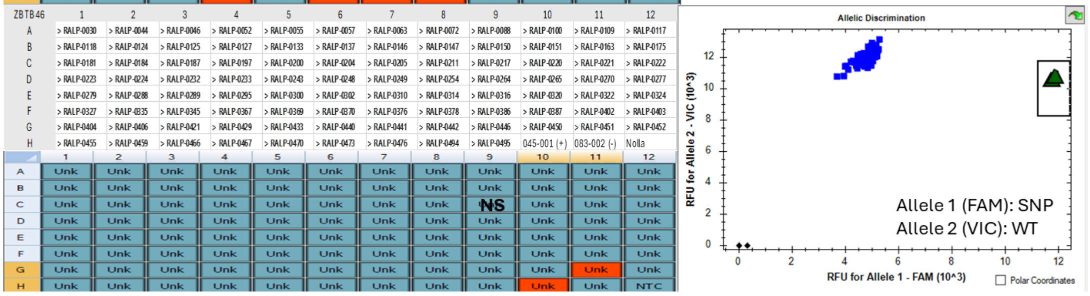
	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk

B



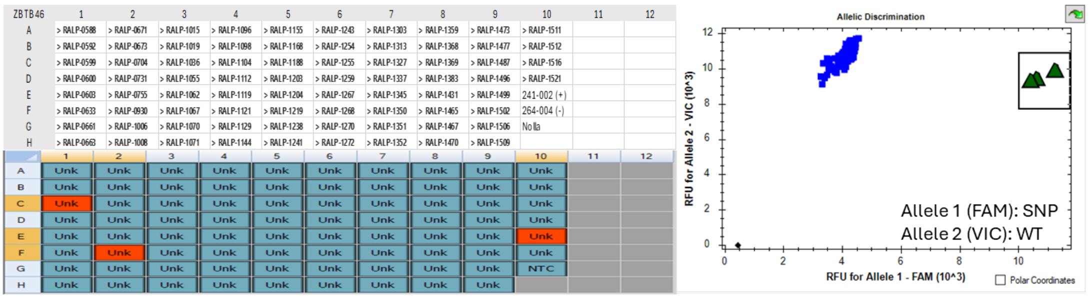
ZBTB46	1	2	3	4	5	6	7	8	9	10	11	12
A												
B												
C												
D												
E	> RALP-0563	> RALP-0651	> RALP-0830	> RALP-0084	> RALP-0085	> RALP-0503	> RALP-0530	> RALP-0747	> RALP-0796	> RALP-0797	> RALP-0811	> RALP-0856
F	> RALP-0882	> RALP-0956	> RALP-1025	> RALP-1038	> RALP-1046	> RALP-1050	> RALP-1051	> RALP-1054	> RALP-1102	> RALP-1152	> RALP-1154	> RALP-1162
G	> RALP-1167	> RALP-1174	> RALP-1181	> RALP-1232	> RALP-1264	> RALP-1279	> RALP-1398	> RALP-1401	> RALP-1419	> RALP-1436	> RALP-1441	> RALP-1459
H	> RALP-1504	> RALP-1508	> RALP-0952					045-001 (+)	083-002 (-)	Nolla		

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk



ZBTB46	1	2	3	4	5	6	7	8	9	10	11	12
A	> RALP-0030	> RALP-0044	> RALP-0046	> RALP-0052	> RALP-0055	> RALP-0057	> RALP-0063	> RALP-0072	> RALP-0088	> RALP-0100	> RALP-0109	> RALP-0117
B	> RALP-0118	> RALP-0124	> RALP-0125	> RALP-0127	> RALP-0133	> RALP-0137	> RALP-0146	> RALP-0147	> RALP-0150	> RALP-0151	> RALP-0163	> RALP-0175
C	> RALP-0181	> RALP-0184	> RALP-0187	> RALP-0197	> RALP-0200	> RALP-0204	> RALP-0205	> RALP-0211	> RALP-0217	> RALP-0220	> RALP-0221	> RALP-0222
D	> RALP-0223	> RALP-0224	> RALP-0232	> RALP-0233	> RALP-0243	> RALP-0248	> RALP-0249	> RALP-0254	> RALP-0264	> RALP-0265	> RALP-0270	> RALP-0277
E	> RALP-0279	> RALP-0288	> RALP-0289	> RALP-0295	> RALP-0300	> RALP-0302	> RALP-0310	> RALP-0314	> RALP-0316	> RALP-0320	> RALP-0322	> RALP-0324
F	> RALP-0327	> RALP-0335	> RALP-0345	> RALP-0367	> RALP-0369	> RALP-0370	> RALP-0376	> RALP-0378	> RALP-0386	> RALP-0387	> RALP-0402	> RALP-0403
G	> RALP-0404	> RALP-0406	> RALP-0421	> RALP-0429	> RALP-0433	> RALP-0440	> RALP-0441	> RALP-0442	> RALP-0446	> RALP-0450	> RALP-0451	> RALP-0452
H	> RALP-0455	> RALP-0459	> RALP-0466	> RALP-0467	> RALP-0470	> RALP-0473	> RALP-0476	> RALP-0494	> RALP-0495	045-001 (+)	083-002 (-)	Nolla

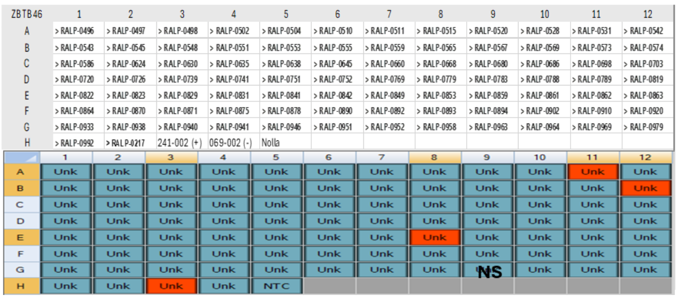
	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	NS	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	NTC



ZBTB46	1	2	3	4	5	6	7	8	9	10	11	12
A	> RALP-0588	> RALP-0671	> RALP-1015	> RALP-1096	> RALP-1155	> RALP-1243	> RALP-1303	> RALP-1359	> RALP-1473	> RALP-1511		
B	> RALP-0592	> RALP-0673	> RALP-1019	> RALP-1098	> RALP-1168	> RALP-1254	> RALP-1313	> RALP-1368	> RALP-1477	> RALP-1512		
C	> RALP-0599	> RALP-0704	> RALP-1036	> RALP-1104	> RALP-1188	> RALP-1255	> RALP-1327	> RALP-1369	> RALP-1487	> RALP-1516		
D	> RALP-0600	> RALP-0731	> RALP-1055	> RALP-1112	> RALP-1203	> RALP-1259	> RALP-1337	> RALP-1383	> RALP-1496	> RALP-1521		
E	> RALP-0603	> RALP-0755	> RALP-1062	> RALP-1119	> RALP-1204	> RALP-1267	> RALP-1345	> RALP-1431	> RALP-1499	241-002 (+)		
F	> RALP-0633	> RALP-0930	> RALP-1067	> RALP-1121	> RALP-1219	> RALP-1268	> RALP-1350	> RALP-1465	> RALP-1502	264-004 (-)		
G	> RALP-0661	> RALP-1006	> RALP-1070	> RALP-1129	> RALP-1238	> RALP-1270	> RALP-1351	> RALP-1467	> RALP-1506	Nolla		
H	> RALP-0663	> RALP-1008	> RALP-1071	> RALP-1144	> RALP-1241	> RALP-1272	> RALP-1352	> RALP-1470	> RALP-1509			

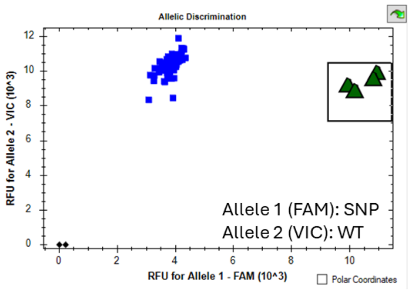
	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	NTC		
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk			

B

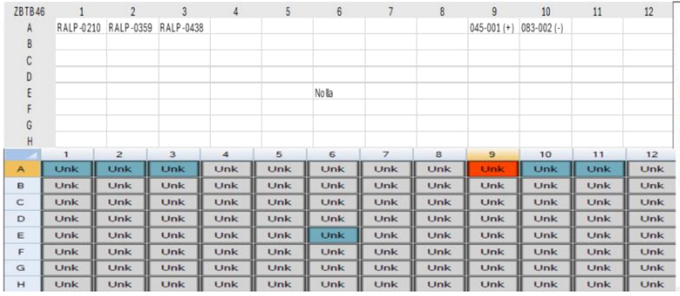


ZBTB46	1	2	3	4	5	6	7	8	9	10	11	12
A	> RALP-0496	> RALP-0497	> RALP-0498	> RALP-0502	> RALP-0504	> RALP-0510	> RALP-0511	> RALP-0515	> RALP-0520	> RALP-0528	> RALP-0531	> RALP-0542
B	> RALP-0543	> RALP-0545	> RALP-0548	> RALP-0551	> RALP-0553	> RALP-0555	> RALP-0559	> RALP-0565	> RALP-0567	> RALP-0569	> RALP-0573	> RALP-0574
C	> RALP-0586	> RALP-0624	> RALP-0630	> RALP-0635	> RALP-0638	> RALP-0645	> RALP-0660	> RALP-0668	> RALP-0680	> RALP-0686	> RALP-0698	> RALP-0703
D	> RALP-0720	> RALP-0726	> RALP-0739	> RALP-0741	> RALP-0751	> RALP-0752	> RALP-0769	> RALP-0779	> RALP-0783	> RALP-0788	> RALP-0789	> RALP-0819
E	> RALP-0822	> RALP-0823	> RALP-0829	> RALP-0831	> RALP-0841	> RALP-0842	> RALP-0849	> RALP-0853	> RALP-0859	> RALP-0861	> RALP-0862	> RALP-0863
F	> RALP-0864	> RALP-0870	> RALP-0871	> RALP-0875	> RALP-0878	> RALP-0890	> RALP-0892	> RALP-0893	> RALP-0894	> RALP-0902	> RALP-0910	> RALP-0920
G	> RALP-0933	> RALP-0938	> RALP-0940	> RALP-0941	> RALP-0946	> RALP-0951	> RALP-0952	> RALP-0958	> RALP-0963	> RALP-0964	> RALP-0969	> RALP-0979
H	> RALP-0992	> RALP-0217	241-002 (+)	069-002 (-)	Nolla							

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	NS	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	NTC							

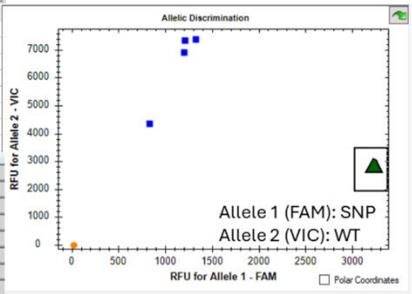


Allele 1 (FAM): SNP
Allele 2 (VIC): WT



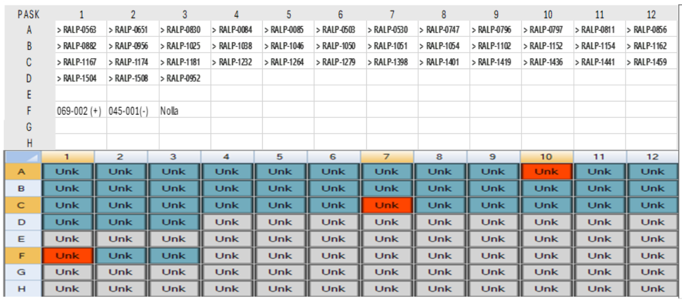
ZBTB46	1	2	3	4	5	6	7	8	9	10	11	12
A	RALP-0210	RALP-0359	RALP-0438						045-001 (+)	083-002 (-)		
B												
C												
D												
E						Nolla						
F												
G												
H												

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk



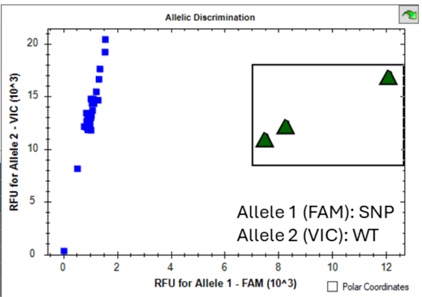
Allele 1 (FAM): SNP
Allele 2 (VIC): WT

C

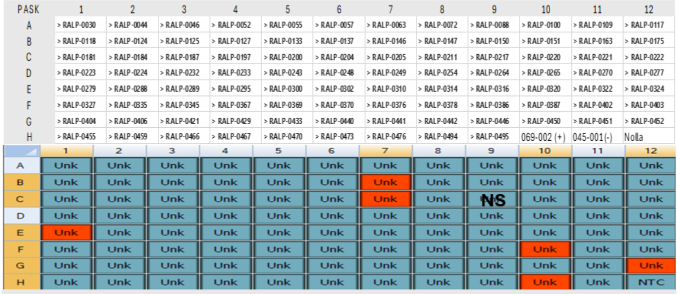


PASK	1	2	3	4	5	6	7	8	9	10	11	12
A	> RALP-0563	> RALP-0651	> RALP-0830	> RALP-0084	> RALP-0085	> RALP-0503	> RALP-0530	> RALP-0747	> RALP-0796	> RALP-0797	> RALP-0811	> RALP-0856
B	> RALP-0882	> RALP-0956	> RALP-1025	> RALP-1038	> RALP-1046	> RALP-1050	> RALP-1051	> RALP-1054	> RALP-1102	> RALP-1152	> RALP-1154	> RALP-1162
C	> RALP-1167	> RALP-1174	> RALP-1181	> RALP-1232	> RALP-1264	> RALP-1279	> RALP-1398	> RALP-1401	> RALP-1419	> RALP-1436	> RALP-1441	> RALP-1459
D	> RALP-1504	> RALP-1508	> RALP-0952									
E												
F	069-002 (+)	045-001(-)	Nolla									
G												
H												

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk

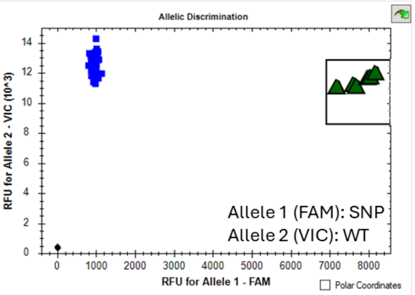


Allele 1 (FAM): SNP
Allele 2 (VIC): WT

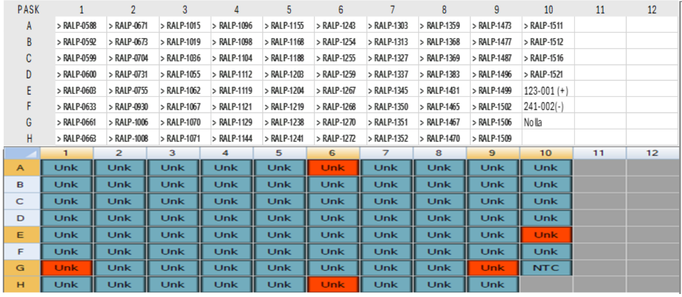


PASK	1	2	3	4	5	6	7	8	9	10	11	12
A	> RALP-0030	> RALP-0044	> RALP-0046	> RALP-0052	> RALP-0055	> RALP-0057	> RALP-0063	> RALP-0072	> RALP-0088	> RALP-0100	> RALP-0109	> RALP-0117
B	> RALP-0118	> RALP-0124	> RALP-0125	> RALP-0127	> RALP-0133	> RALP-0137	> RALP-0146	> RALP-0147	> RALP-0150	> RALP-0151	> RALP-0163	> RALP-0175
C	> RALP-0181	> RALP-0184	> RALP-0187	> RALP-0197	> RALP-0200	> RALP-0204	> RALP-0205	> RALP-0211	> RALP-0217	> RALP-0220	> RALP-0221	> RALP-0222
D	> RALP-0223	> RALP-0224	> RALP-0232	> RALP-0233	> RALP-0243	> RALP-0248	> RALP-0249	> RALP-0254	> RALP-0264	> RALP-0265	> RALP-0270	> RALP-0277
E	> RALP-0279	> RALP-0288	> RALP-0289	> RALP-0295	> RALP-0300	> RALP-0302	> RALP-0310	> RALP-0314	> RALP-0316	> RALP-0320	> RALP-0322	> RALP-0324
F	> RALP-0327	> RALP-0335	> RALP-0345	> RALP-0367	> RALP-0369	> RALP-0370	> RALP-0376	> RALP-0378	> RALP-0386	> RALP-0387	> RALP-0402	> RALP-0403
G	> RALP-0404	> RALP-0406	> RALP-0421	> RALP-0429	> RALP-0433	> RALP-0440	> RALP-0441	> RALP-0442	> RALP-0446	> RALP-0450	> RALP-0451	> RALP-0452
H	> RALP-0455	> RALP-0459	> RALP-0466	> RALP-0467	> RALP-0470	> RALP-0473	> RALP-0476	> RALP-0494	> RALP-0495	069-002 (+)	045-001(-)	Nolla

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	NS	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	NTC

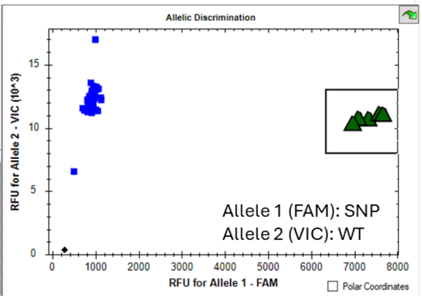


Allele 1 (FAM): SNP
Allele 2 (VIC): WT

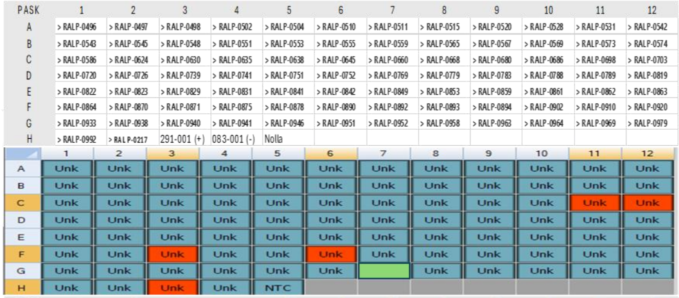


PASK	1	2	3	4	5	6	7	8	9	10	11	12
A	> RALP-0588	> RALP-0671	> RALP-1015	> RALP-1096	> RALP-1155	> RALP-1243	> RALP-1303	> RALP-1359	> RALP-1473	> RALP-1511		
B	> RALP-0592	> RALP-0673	> RALP-1019	> RALP-1098	> RALP-1168	> RALP-1254	> RALP-1313	> RALP-1368	> RALP-1477	> RALP-1512		
C	> RALP-0599	> RALP-0704	> RALP-1036	> RALP-1104	> RALP-1188	> RALP-1255	> RALP-1327	> RALP-1369	> RALP-1487	> RALP-1516		
D	> RALP-0600	> RALP-0731	> RALP-1055	> RALP-1112	> RALP-1203	> RALP-1259	> RALP-1337	> RALP-1383	> RALP-1496	> RALP-1521		
E	> RALP-0603	> RALP-0755	> RALP-1062	> RALP-1119	> RALP-1204	> RALP-1267	> RALP-1345	> RALP-1431	> RALP-1499	123-001 (+)		
F	> RALP-0633	> RALP-0930	> RALP-1067	> RALP-1121	> RALP-1219	> RALP-1268	> RALP-1350	> RALP-1465	> RALP-1502	241-002(-)		
G	> RALP-0661	> RALP-1006	> RALP-1070	> RALP-1129	> RALP-1238	> RALP-1270	> RALP-1351	> RALP-1467	> RALP-1506	Nolla		
H	> RALP-0663	> RALP-1008	> RALP-1071	> RALP-1144	> RALP-1241	> RALP-1272	> RALP-1352	> RALP-1470	> RALP-1509			

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	NTC		
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk			

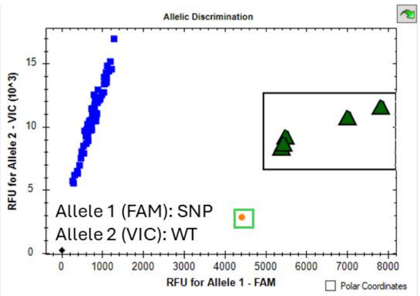


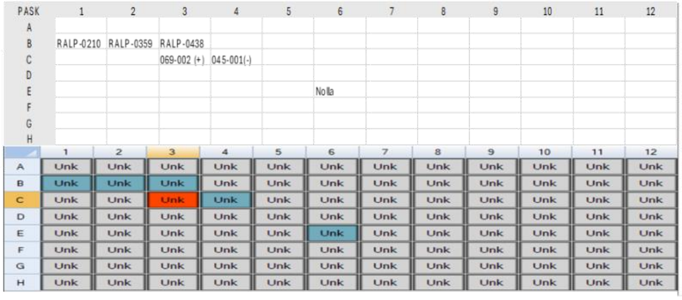
Allele 1 (FAM): SNP
Allele 2 (VIC): WT



PASK	1	2	3	4	5	6	7	8	9	10	11	12
A	> RALP-0496	> RALP-0497	> RALP-0498	> RALP-0502	> RALP-0504	> RALP-0510	> RALP-0511	> RALP-0515	> RALP-0520	> RALP-0528	> RALP-0531	> RALP-0542
B	> RALP-0543	> RALP-0545	> RALP-0548	> RALP-0551	> RALP-0553	> RALP-0555	> RALP-0559	> RALP-0565	> RALP-0567	> RALP-0569	> RALP-0573	> RALP-0574
C	> RALP-0586	> RALP-0624	> RALP-0630	> RALP-0635	> RALP-0638	> RALP-0645	> RALP-0660	> RALP-0668	> RALP-0680	> RALP-0686	> RALP-0698	> RALP-0703
D	> RALP-0720	> RALP-0726	> RALP-0739	> RALP-0741	> RALP-0751	> RALP-0752	> RALP-0769	> RALP-0779	> RALP-0783	> RALP-0788	> RALP-0789	> RALP-0819
E	> RALP-0822	> RALP-0823	> RALP-0829	> RALP-0831	> RALP-0841	> RALP-0842	> RALP-0849	> RALP-0853	> RALP-0859	> RALP-0861	> RALP-0862	> RALP-0863
F	> RALP-0864	> RALP-0870	> RALP-0871	> RALP-0875	> RALP-0878	> RALP-0890	> RALP-0892	> RALP-0893	> RALP-0894	> RALP-0902	> RALP-0910	> RALP-0920
G	> RALP-0933	> RALP-0938	> RALP-0940	> RALP-0941	> RALP-0946	> RALP-0951	> RALP-0952	> RALP-0958	> RALP-0963	> RALP-0964	> RALP-0969	> RALP-0979
H	> RALP-0992	> RALP-0217	291-001 (+)	083-001 (-)	Nolla							

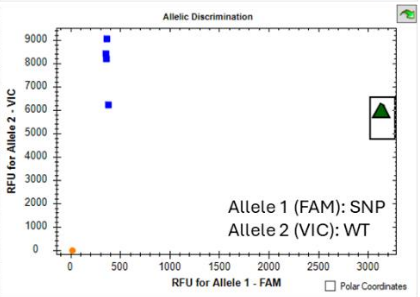
	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk		Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	NTC							



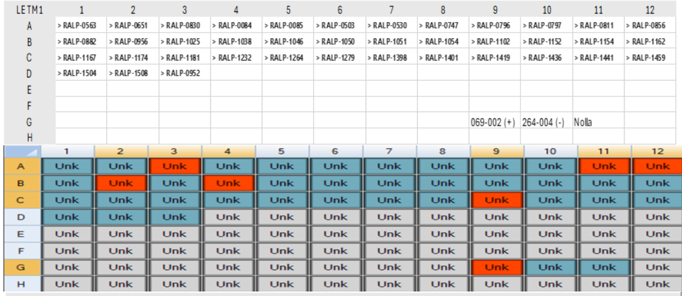


PASK	1	2	3	4	5	6	7	8	9	10	11	12
A												
B	RALP-0210	RALP-0359	RALP-0438									
C			069-002 (+)	045-001(-)								
D												
E						Nolla						
F												
G												
H												

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk

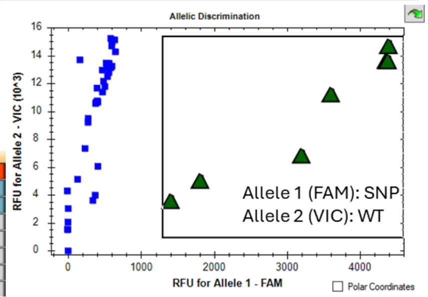


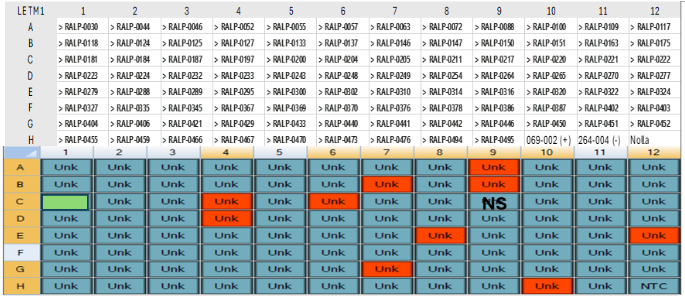
D



LETM1	1	2	3	4	5	6	7	8	9	10	11	12
A	> RALP-0563	> RALP-0651	> RALP-0830	> RALP-0084	> RALP-0085	> RALP-0503	> RALP-0530	> RALP-0747	> RALP-0796	> RALP-0797	> RALP-0811	> RALP-0856
B	> RALP-0882	> RALP-0956	> RALP-1025	> RALP-1038	> RALP-1046	> RALP-1050	> RALP-1051	> RALP-1054	> RALP-1102	> RALP-1152	> RALP-1154	> RALP-1162
C	> RALP-1167	> RALP-1174	> RALP-1181	> RALP-1232	> RALP-1264	> RALP-1279	> RALP-1398	> RALP-1401	> RALP-1419	> RALP-1436	> RALP-1441	> RALP-1459
D	> RALP-1504	> RALP-1508	> RALP-0952									
E												
F												
G									069-002 (+)	264-004 (-)	Nolla	
H												

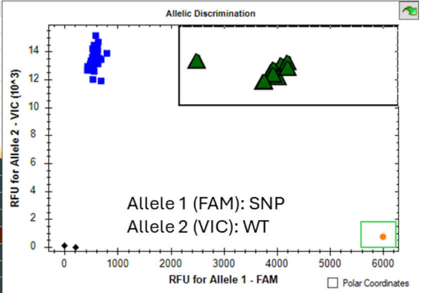
	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk

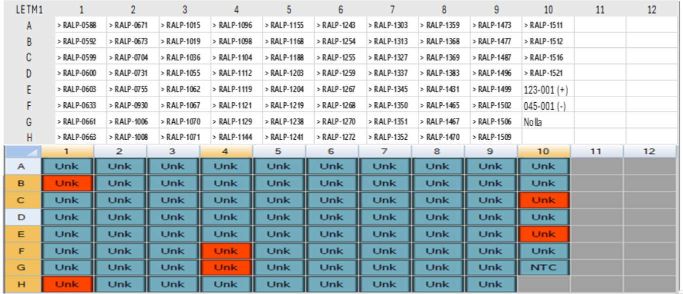




LETM1	1	2	3	4	5	6	7	8	9	10	11	12
A	> RALP-0030	> RALP-0044	> RALP-0046	> RALP-0052	> RALP-0055	> RALP-0057	> RALP-0063	> RALP-0072	> RALP-0088	> RALP-0100	> RALP-0109	> RALP-0117
B	> RALP-0118	> RALP-0124	> RALP-0125	> RALP-0127	> RALP-0133	> RALP-0137	> RALP-0146	> RALP-0147	> RALP-0150	> RALP-0151	> RALP-0163	> RALP-0175
C	> RALP-0181	> RALP-0184	> RALP-0187	> RALP-0197	> RALP-0200	> RALP-0204	> RALP-0205	> RALP-0211	> RALP-0217	> RALP-0220	> RALP-0221	> RALP-0222
D	> RALP-0223	> RALP-0224	> RALP-0232	> RALP-0233	> RALP-0243	> RALP-0248	> RALP-0249	> RALP-0254	> RALP-0264	> RALP-0265	> RALP-0270	> RALP-0277
E	> RALP-0279	> RALP-0288	> RALP-0289	> RALP-0295	> RALP-0300	> RALP-0302	> RALP-0310	> RALP-0314	> RALP-0316	> RALP-0320	> RALP-0322	> RALP-0324
F	> RALP-0327	> RALP-0335	> RALP-0345	> RALP-0367	> RALP-0369	> RALP-0370	> RALP-0376	> RALP-0378	> RALP-0386	> RALP-0387	> RALP-0402	> RALP-0403
G	> RALP-0404	> RALP-0406	> RALP-0421	> RALP-0429	> RALP-0433	> RALP-0440	> RALP-0441	> RALP-0442	> RALP-0446	> RALP-0450	> RALP-0451	> RALP-0452
H	> RALP-0455	> RALP-0459	> RALP-0466	> RALP-0467	> RALP-0470	> RALP-0473	> RALP-0476	> RALP-0494	> RALP-0495	069-002 (+)	264-004 (-)	Nolla

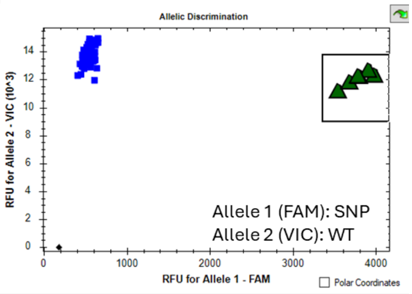
	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C		Unk	Unk	Unk	Unk	Unk	Unk	Unk	NS	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	NTC

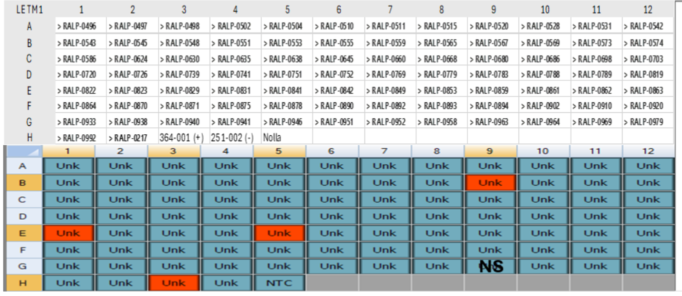




LETM1	1	2	3	4	5	6	7	8	9	10	11	12
A	> RALP-0588	> RALP-0671	> RALP-1015	> RALP-1096	> RALP-1155	> RALP-1243	> RALP-1303	> RALP-1359	> RALP-1473	> RALP-1511		
B	> RALP-0592	> RALP-0673	> RALP-1019	> RALP-1098	> RALP-1168	> RALP-1254	> RALP-1313	> RALP-1368	> RALP-1477	> RALP-1512		
C	> RALP-0599	> RALP-0704	> RALP-1036	> RALP-1104	> RALP-1188	> RALP-1255	> RALP-1327	> RALP-1369	> RALP-1487	> RALP-1516		
D	> RALP-0600	> RALP-0731	> RALP-1055	> RALP-1112	> RALP-1203	> RALP-1259	> RALP-1337	> RALP-1383	> RALP-1496	> RALP-1521		
E	> RALP-0603	> RALP-0755	> RALP-1062	> RALP-1119	> RALP-1204	> RALP-1267	> RALP-1345	> RALP-1431	> RALP-1499	123-001 (+)		
F	> RALP-0633	> RALP-0930	> RALP-1067	> RALP-1121	> RALP-1219	> RALP-1268	> RALP-1350	> RALP-1465	> RALP-1502	045-001 (-)		
G	> RALP-0661	> RALP-1006	> RALP-1070	> RALP-1129	> RALP-1238	> RALP-1270	> RALP-1351	> RALP-1467	> RALP-1506	Nolla		
H	> RALP-0663	> RALP-1008	> RALP-1071	> RALP-1144	> RALP-1241	> RALP-1272	> RALP-1352	> RALP-1470	> RALP-1509			

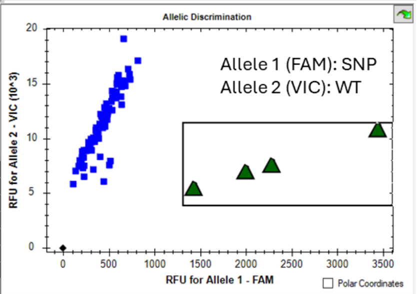
	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	NTC		
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk			

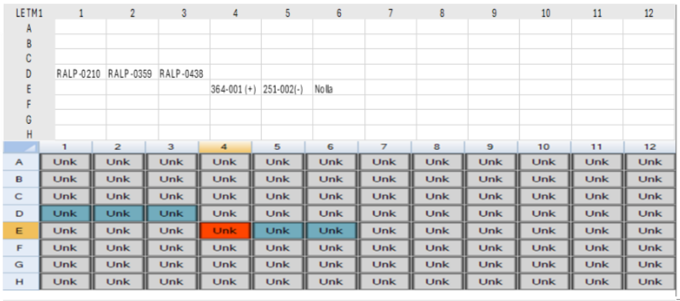




LETM1	1	2	3	4	5	6	7	8	9	10	11	12
A	> RALP-0496	> RALP-0497	> RALP-0498	> RALP-0502	> RALP-0504	> RALP-0510	> RALP-0511	> RALP-0515	> RALP-0520	> RALP-0528	> RALP-0531	> RALP-0542
B	> RALP-0543	> RALP-0545	> RALP-0548	> RALP-0551	> RALP-0553	> RALP-0555	> RALP-0559	> RALP-0565	> RALP-0567	> RALP-0569	> RALP-0573	> RALP-0574
C	> RALP-0586	> RALP-0624	> RALP-0630	> RALP-0635	> RALP-0638	> RALP-0645	> RALP-0660	> RALP-0668	> RALP-0680	> RALP-0686	> RALP-0698	> RALP-0703
D	> RALP-0720	> RALP-0726	> RALP-0739	> RALP-0741	> RALP-0751	> RALP-0752	> RALP-0769	> RALP-0779	> RALP-0783	> RALP-0788	> RALP-0789	> RALP-0819
E	> RALP-0822	> RALP-0823	> RALP-0829	> RALP-0831	> RALP-0841	> RALP-0842	> RALP-0849	> RALP-0853	> RALP-0859	> RALP-0861	> RALP-0862	> RALP-0863
F	> RALP-0864	> RALP-0870	> RALP-0871	> RALP-0875	> RALP-0878	> RALP-0890	> RALP-0892	> RALP-0893	> RALP-0894	> RALP-0902	> RALP-0910	> RALP-0920
G	> RALP-0933	> RALP-0938	> RALP-0940	> RALP-0941	> RALP-0946	> RALP-0951	> RALP-0952	> RALP-0958	> RALP-0963	> RALP-0964	> RALP-0969	> RALP-0979
H	> RALP-0992	> RALP-0217	364-001 (+)	251-002 (-)	Nolla							

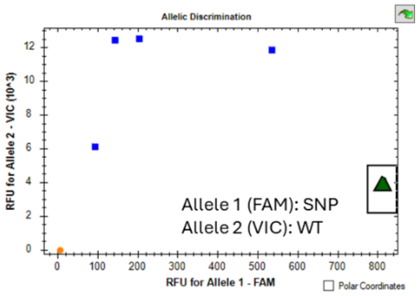
	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	NS	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	NTC							



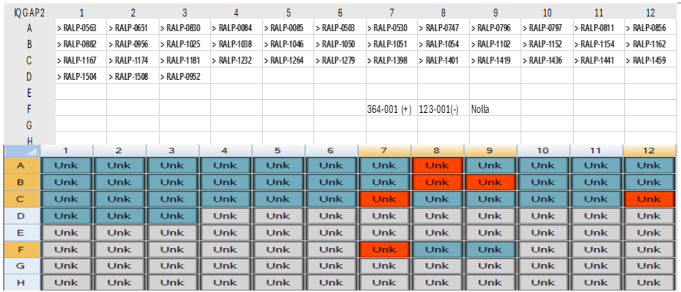


LETM1	1	2	3	4	5	6	7	8	9	10	11	12
A												
B												
C												
D	RALP-0210	RALP-0359	RALP-0438									
E				364-001 (+)	251-002(-)	Nolla						
F												
G												
H												

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk

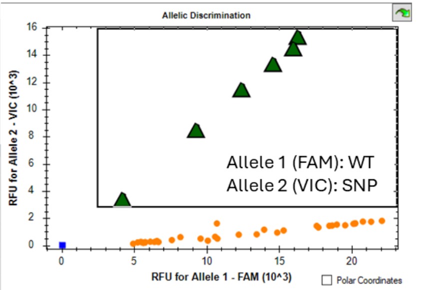


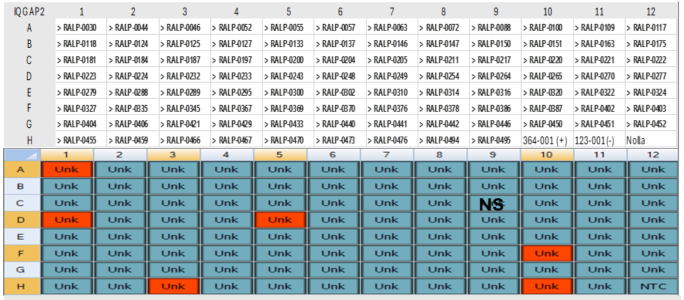
E



IQGAP2	1	2	3	4	5	6	7	8	9	10	11	12
A	> RALP-0563	> RALP-0651	> RALP-0830	> RALP-0084	> RALP-0085	> RALP-0503	> RALP-0530	> RALP-0747	> RALP-0796	> RALP-0797	> RALP-0811	> RALP-0856
B	> RALP-0882	> RALP-0956	> RALP-1025	> RALP-1038	> RALP-1046	> RALP-1050	> RALP-1051	> RALP-1054	> RALP-1102	> RALP-1152	> RALP-1154	> RALP-1162
C	> RALP-1167	> RALP-1174	> RALP-1181	> RALP-1232	> RALP-1264	> RALP-1279	> RALP-1398	> RALP-1401	> RALP-1419	> RALP-1436	> RALP-1441	> RALP-1459
D	> RALP-1504	> RALP-1508	> RALP-0952									
E												
F							364-001 (+)	123-001(-)	Nolla			
G												
H												

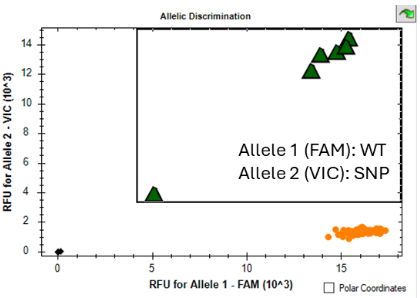
	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk

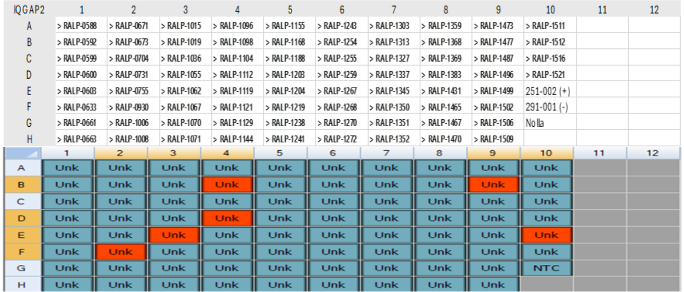




IQGAP2	1	2	3	4	5	6	7	8	9	10	11	12
A	> RALP-0030	> RALP-0044	> RALP-0046	> RALP-0052	> RALP-0055	> RALP-0057	> RALP-0063	> RALP-0072	> RALP-0088	> RALP-0100	> RALP-0109	> RALP-0117
B	> RALP-0118	> RALP-0124	> RALP-0125	> RALP-0127	> RALP-0133	> RALP-0137	> RALP-0146	> RALP-0147	> RALP-0150	> RALP-0151	> RALP-0163	> RALP-0175
C	> RALP-0181	> RALP-0184	> RALP-0187	> RALP-0197	> RALP-0200	> RALP-0204	> RALP-0205	> RALP-0211	> RALP-0217	> RALP-0220	> RALP-0221	> RALP-0222
D	> RALP-0223	> RALP-0224	> RALP-0232	> RALP-0233	> RALP-0243	> RALP-0248	> RALP-0249	> RALP-0254	> RALP-0264	> RALP-0265	> RALP-0270	> RALP-0277
E	> RALP-0279	> RALP-0288	> RALP-0289	> RALP-0295	> RALP-0300	> RALP-0302	> RALP-0310	> RALP-0314	> RALP-0316	> RALP-0320	> RALP-0322	> RALP-0324
F	> RALP-0327	> RALP-0335	> RALP-0345	> RALP-0367	> RALP-0369	> RALP-0370	> RALP-0376	> RALP-0378	> RALP-0386	> RALP-0387	> RALP-0402	> RALP-0403
G	> RALP-0404	> RALP-0406	> RALP-0421	> RALP-0429	> RALP-0433	> RALP-0440	> RALP-0441	> RALP-0442	> RALP-0446	> RALP-0450	> RALP-0451	> RALP-0452
H	> RALP-0455	> RALP-0459	> RALP-0466	> RALP-0467	> RALP-0470	> RALP-0473	> RALP-0476	> RALP-0494	> RALP-0495	364-001 (+)	123-001(-)	Nolla

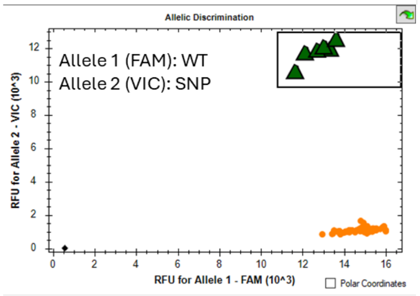
	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	NS	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	NTC

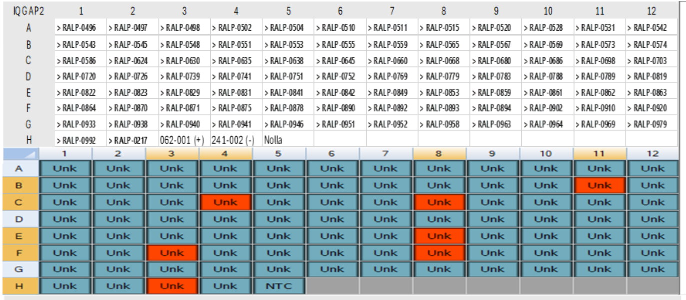




IQGAP2	1	2	3	4	5	6	7	8	9	10	11	12
A	> RALP-0588	> RALP-0671	> RALP-1015	> RALP-1096	> RALP-1155	> RALP-1243	> RALP-1303	> RALP-1359	> RALP-1473	> RALP-1511		
B	> RALP-0592	> RALP-0673	> RALP-1019	> RALP-1098	> RALP-1168	> RALP-1254	> RALP-1313	> RALP-1368	> RALP-1477	> RALP-1512		
C	> RALP-0599	> RALP-0704	> RALP-1036	> RALP-1104	> RALP-1188	> RALP-1255	> RALP-1327	> RALP-1369	> RALP-1487	> RALP-1516		
D	> RALP-0600	> RALP-0731	> RALP-1055	> RALP-1112	> RALP-1203	> RALP-1259	> RALP-1337	> RALP-1383	> RALP-1496	> RALP-1521		
E	> RALP-0603	> RALP-0755	> RALP-1062	> RALP-1119	> RALP-1204	> RALP-1267	> RALP-1345	> RALP-1431	> RALP-1499	251-002 (+)		
F	> RALP-0633	> RALP-0930	> RALP-1067	> RALP-1121	> RALP-1219	> RALP-1268	> RALP-1350	> RALP-1465	> RALP-1502	291-001 (-)		
G	> RALP-0661	> RALP-1006	> RALP-1070	> RALP-1129	> RALP-1238	> RALP-1270	> RALP-1351	> RALP-1467	> RALP-1506	No lla		
H	> RALP-0663	> RALP-1008	> RALP-1071	> RALP-1144	> RALP-1241	> RALP-1272	> RALP-1352	> RALP-1470	> RALP-1509			

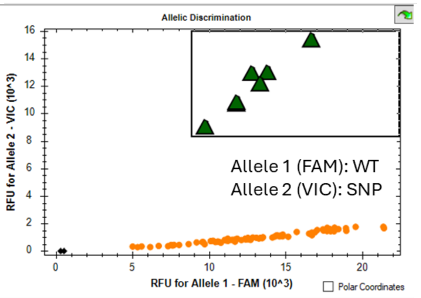
	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk		
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	NTC		
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk			

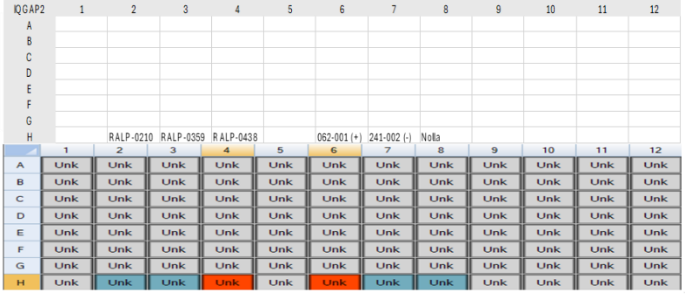




IQGAP2	1	2	3	4	5	6	7	8	9	10	11	12
A	> RALP-0496	> RALP-0497	> RALP-0498	> RALP-0502	> RALP-0504	> RALP-0510	> RALP-0511	> RALP-0515	> RALP-0520	> RALP-0528	> RALP-0531	> RALP-0542
B	> RALP-0543	> RALP-0545	> RALP-0548	> RALP-0551	> RALP-0553	> RALP-0555	> RALP-0559	> RALP-0565	> RALP-0567	> RALP-0569	> RALP-0573	> RALP-0574
C	> RALP-0586	> RALP-0624	> RALP-0630	> RALP-0635	> RALP-0638	> RALP-0645	> RALP-0660	> RALP-0668	> RALP-0680	> RALP-0686	> RALP-0698	> RALP-0703
D	> RALP-0720	> RALP-0726	> RALP-0739	> RALP-0741	> RALP-0751	> RALP-0752	> RALP-0769	> RALP-0779	> RALP-0783	> RALP-0788	> RALP-0789	> RALP-0819
E	> RALP-0822	> RALP-0823	> RALP-0829	> RALP-0831	> RALP-0841	> RALP-0842	> RALP-0849	> RALP-0853	> RALP-0859	> RALP-0861	> RALP-0862	> RALP-0863
F	> RALP-0864	> RALP-0870	> RALP-0871	> RALP-0875	> RALP-0878	> RALP-0890	> RALP-0892	> RALP-0893	> RALP-0894	> RALP-0902	> RALP-0910	> RALP-0920
G	> RALP-0933	> RALP-0938	> RALP-0940	> RALP-0941	> RALP-0946	> RALP-0951	> RALP-0952	> RALP-0958	> RALP-0963	> RALP-0964	> RALP-0969	> RALP-0979
H	> RALP-0992	> RALP-0217	062-001 (+)	241-002 (-)	Nolla							

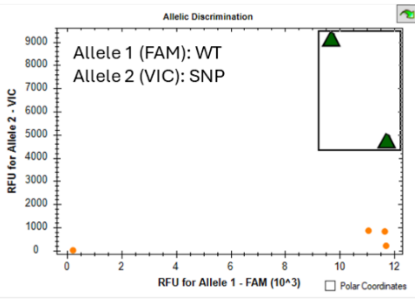
	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	NTC							





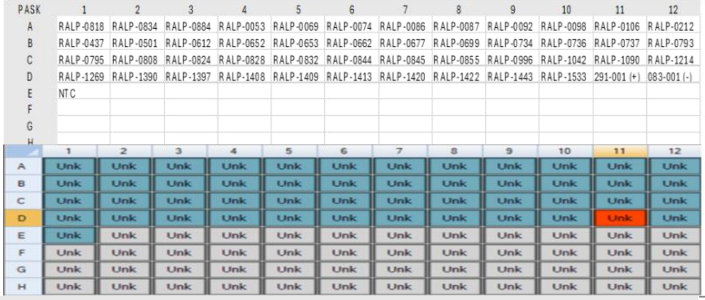
IQGAP2	1	2	3	4	5	6	7	8	9	10	11	12
A												
B												
C												
D												
E												
F												
G												
H		RALP-0210	RALP-0359	RALP-0438		062-001 (+)	241-002 (-)	Nolla				

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk



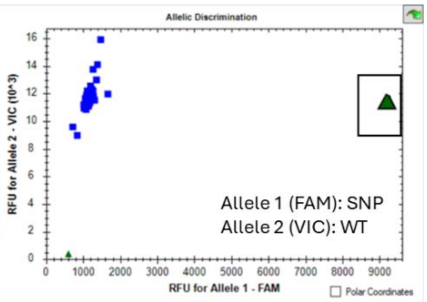
Appendix 5 – Plate maps and allelic discrimination scatter plots of RALP patients without family history of PCa and HBOC

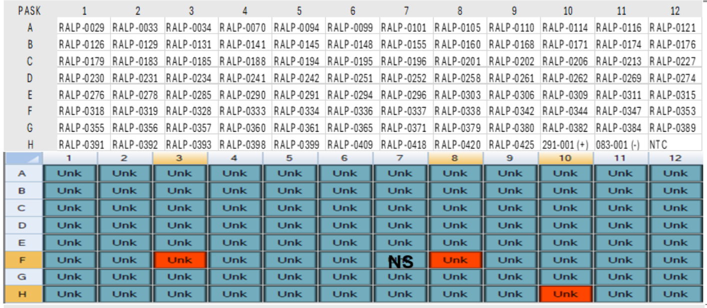
Plate maps and allelic discrimination scatter plots of the RALP patients without a family history of PCa, and HBOC (FH-) using TaqMan™ SNP Genotyping Assay for *PASK* rs35129131 variant. In the plate map, orange boxes indicate heterozygous individuals for the studied variant. In the allelic discrimination plot, the black rectangle highlights the heterozygous individuals for the tested variant. NS no signal, NTC no-template control, SNP variant allele, WT reference allele.



PASK	1	2	3	4	5	6	7	8	9	10	11	12
A	RALP-0818	RALP-0834	RALP-0884	RALP-0053	RALP-0069	RALP-0074	RALP-0086	RALP-0087	RALP-0092	RALP-0098	RALP-0106	RALP-0212
B	RALP-0437	RALP-0501	RALP-0612	RALP-0652	RALP-0653	RALP-0662	RALP-0677	RALP-0699	RALP-0734	RALP-0736	RALP-0737	RALP-0793
C	RALP-0795	RALP-0808	RALP-0824	RALP-0828	RALP-0832	RALP-0844	RALP-0845	RALP-0855	RALP-0996	RALP-1042	RALP-1090	RALP-1214
D	RALP-1269	RALP-1390	RALP-1397	RALP-1408	RALP-1409	RALP-1413	RALP-1420	RALP-1422	RALP-1443	RALP-1533	291-001 (+)	083-001 (-)
E	NTC											
F												
G												
H												

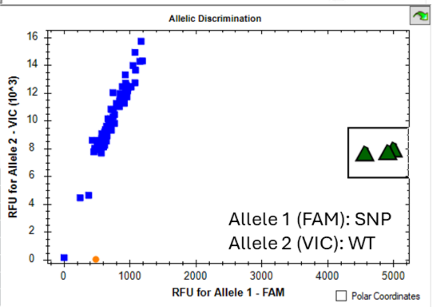
	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk

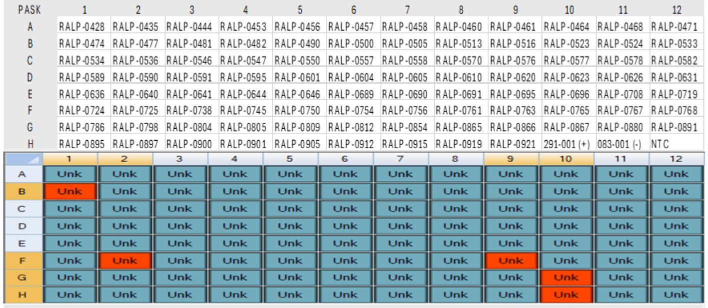




PASK	1	2	3	4	5	6	7	8	9	10	11	12
A	RALP-0029	RALP-0033	RALP-0034	RALP-0070	RALP-0094	RALP-0099	RALP-0101	RALP-0105	RALP-0110	RALP-0114	RALP-0116	RALP-0121
B	RALP-0126	RALP-0129	RALP-0131	RALP-0141	RALP-0145	RALP-0148	RALP-0155	RALP-0160	RALP-0168	RALP-0171	RALP-0174	RALP-0176
C	RALP-0179	RALP-0183	RALP-0185	RALP-0188	RALP-0194	RALP-0195	RALP-0196	RALP-0201	RALP-0202	RALP-0206	RALP-0213	RALP-0227
D	RALP-0230	RALP-0231	RALP-0234	RALP-0241	RALP-0242	RALP-0251	RALP-0252	RALP-0258	RALP-0261	RALP-0262	RALP-0269	RALP-0274
E	RALP-0276	RALP-0278	RALP-0285	RALP-0290	RALP-0291	RALP-0294	RALP-0296	RALP-0303	RALP-0306	RALP-0309	RALP-0311	RALP-0315
F	RALP-0318	RALP-0319	RALP-0328	RALP-0333	RALP-0334	RALP-0336	RALP-0337	RALP-0338	RALP-0342	RALP-0344	RALP-0347	RALP-0353
G	RALP-0355	RALP-0356	RALP-0357	RALP-0360	RALP-0361	RALP-0365	RALP-0371	RALP-0379	RALP-0380	RALP-0382	RALP-0384	RALP-0389
H	RALP-0391	RALP-0392	RALP-0393	RALP-0398	RALP-0399	RALP-0409	RALP-0418	RALP-0420	RALP-0425	291-001 (+)	083-001 (-)	NTC

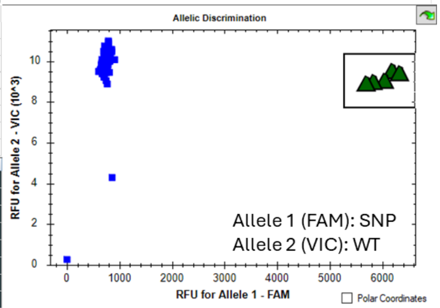
	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	NS	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk

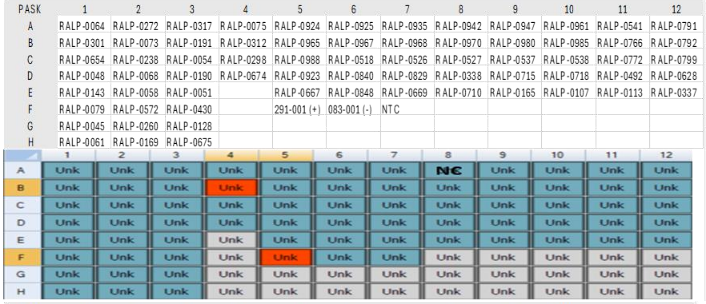




PASK	1	2	3	4	5	6	7	8	9	10	11	12
A	RALP-0428	RALP-0435	RALP-0444	RALP-0453	RALP-0456	RALP-0457	RALP-0458	RALP-0460	RALP-0461	RALP-0464	RALP-0468	RALP-0471
B	RALP-0474	RALP-0477	RALP-0481	RALP-0482	RALP-0490	RALP-0500	RALP-0505	RALP-0513	RALP-0516	RALP-0523	RALP-0524	RALP-0533
C	RALP-0534	RALP-0536	RALP-0546	RALP-0547	RALP-0550	RALP-0557	RALP-0558	RALP-0570	RALP-0576	RALP-0577	RALP-0578	RALP-0582
D	RALP-0589	RALP-0590	RALP-0591	RALP-0595	RALP-0601	RALP-0604	RALP-0605	RALP-0610	RALP-0620	RALP-0623	RALP-0626	RALP-0631
E	RALP-0636	RALP-0640	RALP-0641	RALP-0644	RALP-0646	RALP-0689	RALP-0690	RALP-0691	RALP-0695	RALP-0696	RALP-0708	RALP-0719
F	RALP-0724	RALP-0725	RALP-0738	RALP-0745	RALP-0750	RALP-0754	RALP-0756	RALP-0761	RALP-0763	RALP-0765	RALP-0767	RALP-0768
G	RALP-0786	RALP-0798	RALP-0804	RALP-0805	RALP-0809	RALP-0812	RALP-0854	RALP-0865	RALP-0866	RALP-0867	RALP-0880	RALP-0891
H	RALP-0895	RALP-0897	RALP-0900	RALP-0901	RALP-0905	RALP-0912	RALP-0915	RALP-0919	RALP-0921	291-001 (+)	083-001 (-)	NTC

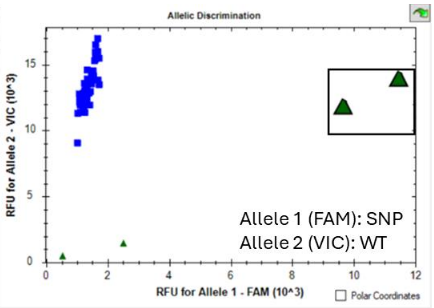
	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk

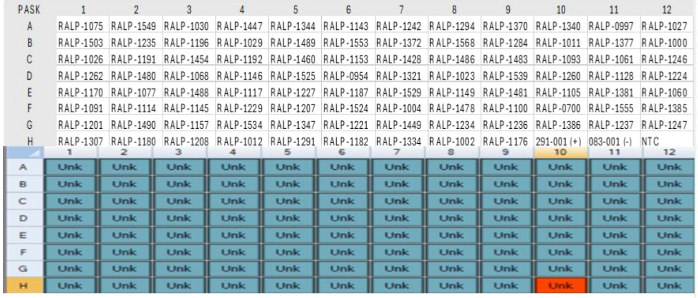




PASK	1	2	3	4	5	6	7	8	9	10	11	12
A	RALP-0064	RALP-0272	RALP-0317	RALP-0075	RALP-0924	RALP-0925	RALP-0935	RALP-0942	RALP-0947	RALP-0961	RALP-0541	RALP-0791
B	RALP-0301	RALP-0073	RALP-0191	RALP-0312	RALP-0965	RALP-0967	RALP-0968	RALP-0970	RALP-0980	RALP-0985	RALP-0766	RALP-0792
C	RALP-0654	RALP-0238	RALP-0054	RALP-0298	RALP-0988	RALP-0518	RALP-0526	RALP-0527	RALP-0537	RALP-0538	RALP-0772	RALP-0799
D	RALP-0048	RALP-0068	RALP-0190	RALP-0674	RALP-0923	RALP-0840	RALP-0829	RALP-0338	RALP-0715	RALP-0718	RALP-0492	RALP-0628
E	RALP-0143	RALP-0058	RALP-0051		RALP-0667	RALP-0848	RALP-0669	RALP-0710	RALP-0165	RALP-0107	RALP-0113	RALP-0337
F	RALP-0079	RALP-0572	RALP-0430		291-001 (+)	083-001 (-)	NTC					
G	RALP-0045	RALP-0260	RALP-0128									
H	RALP-0061	RALP-0169	RALP-0675									

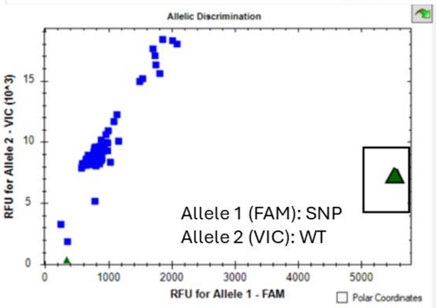
	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	NC	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk





PASK	1	2	3	4	5	6	7	8	9	10	11	12
A	RALP-1075	RALP-1549	RALP-1030	RALP-1447	RALP-1344	RALP-1143	RALP-1242	RALP-1294	RALP-1370	RALP-1340	RALP-0997	RALP-1027
B	RALP-1503	RALP-1235	RALP-1196	RALP-1029	RALP-1489	RALP-1553	RALP-1372	RALP-1568	RALP-1284	RALP-1011	RALP-1377	RALP-1000
C	RALP-1026	RALP-1191	RALP-1454	RALP-1192	RALP-1460	RALP-1153	RALP-1428	RALP-1486	RALP-1483	RALP-1093	RALP-1061	RALP-1246
D	RALP-1262	RALP-1480	RALP-1068	RALP-1146	RALP-1525	RALP-0954	RALP-1321	RALP-1023	RALP-1539	RALP-1260	RALP-1128	RALP-1224
E	RALP-1170	RALP-1077	RALP-1488	RALP-1117	RALP-1227	RALP-1187	RALP-1529	RALP-1149	RALP-1481	RALP-1105	RALP-1381	RALP-1060
F	RALP-1091	RALP-1114	RALP-1145	RALP-1229	RALP-1207	RALP-1524	RALP-1004	RALP-1478	RALP-1100	RALP-0700	RALP-1555	RALP-1385
G	RALP-1201	RALP-1490	RALP-1157	RALP-1534	RALP-1347	RALP-1221	RALP-1449	RALP-1234	RALP-1236	RALP-1386	RALP-1237	RALP-1247
H	RALP-1307	RALP-1180	RALP-1208	RALP-1012	RALP-1291	RALP-1182	RALP-1334	RALP-1002	RALP-1176	291-001 (+)	083-001 (-)	NTC

	1	2	3	4	5	6	7	8	9	10	11	12
A	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
B	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
C	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
D	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
E	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
F	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
G	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
H	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk



Appendix 6 – Genotypes of RALP patients with family history of PCa and HBOC

Genotypes of the studied variants in the RALP patients with family history of PCa and HBOC. 0/0 homozygous reference, 0/1 heterozygous variant, 1/1 homozygous variant.

Individual ID	***TP63***	***ZBTB46***	***PASK***	***LETM1***	***IQGAP2***
	rs190865056	**rs34785134**	**rs35129131**	**rs62623389**	**rs34592828**
RALP-0030	0/0	0/0	0/0	0/0	0/1
RALP-0044	0/0	0/0	0/0	0/0	0/0
RALP-0046	0/0	0/0	0/0	0/0	0/0
RALP-0052	0/0	0/0	0/0	0/0	0/0
RALP-0055	0/0	0/0	0/0	0/0	0/0
RALP-0057	0/0	0/0	0/0	0/0	0/0
RALP-0063	0/0	0/0	0/0	0/0	0/0
RALP-0072	0/0	0/0	0/0	0/0	0/0
RALP-0084	0/0	0/0	0/0	0/0	0/0
RALP-0085	0/0	0/0	0/0	0/0	0/0
RALP-0088	0/0	0/0	0/0	0/1	0/0
RALP-0100	0/0	0/0	0/0	0/0	0/0
RALP-0109	0/0	0/0	0/0	0/0	0/0
RALP-0117	0/0	0/0	0/0	0/0	0/0
RALP-0118	0/0	0/0	0/0	0/0	0/0
RALP-0124	0/0	0/0	0/0	0/0	0/0
RALP-0125	0/0	0/0	0/0	0/0	0/0
RALP-0127	0/1	0/0	0/0	0/0	0/0
RALP-0133	0/0	0/0	0/0	0/0	0/0
RALP-0137	0/0	0/0	0/0	0/0	0/0
RALP-0146	0/0	0/0	0/1	0/1	0/0
RALP-0147	0/0	0/0	0/0	0/0	0/0
RALP-0150	0/1	0/0	0/0	0/1	0/0
RALP-0151	0/0	0/0	0/0	0/0	0/0
RALP-0163	0/0	0/0	0/0	0/0	0/0
RALP-0175	0/0	0/0	0/0	0/0	0/0
RALP-0181	0/0	0/0	0/0	1/1	0/0
RALP-0184	0/0	0/0	0/0	0/0	0/0
RALP-0187	0/0	0/0	0/0	0/0	0/0
RALP-0197	0/0	0/0	0/0	0/1	0/0
RALP-0200	0/0	0/0	0/0	0/0	0/0
RALP-0204	0/0	0/0	0/0	0/1	0/0
RALP-0205	0/0	0/0	0/1	0/0	0/0
RALP-0210	0/0	0/0	0/0	0/0	0/1
RALP-0211	0/0	0/0	0/0	0/0	0/0
RALP-0217	0/1	0/0	0/0	0/0	0/0
RALP-0220	0/0	0/0	0/0	0/0	0/0
RALP-0221	0/0	0/0	0/0	0/0	0/0
RALP-0222	0/0	0/0	0/0	0/0	0/0
RALP-0223	0/0	0/0	0/0	0/0	0/1

RALP-0224	0/0	0/0	0/0	0/0	0/0
RALP-0232	0/0	0/0	0/0	0/0	0/0
RALP-0233	0/0	0/0	0/0	0/1	0/0
RALP-0243	0/0	0/0	0/0	0/0	0/1
RALP-0248	0/0	0/0	0/0	0/0	0/0
RALP-0249	0/0	0/0	0/0	0/0	0/0
RALP-0254	0/0	0/0	0/0	0/0	0/0
RALP-0264	0/0	0/0	0/0	0/0	0/0
RALP-0265	0/0	0/0	0/0	0/0	0/0
RALP-0270	0/0	0/0	0/0	0/0	0/0
RALP-0277	0/0	0/0	0/0	0/0	0/0
RALP-0279	0/0	0/0	0/1	0/0	0/0
RALP-0288	0/0	0/0	0/0	0/0	0/0
RALP-0289	0/0	0/0	0/0	0/0	0/0
RALP-0295	0/0	0/0	0/0	0/0	0/0
RALP-0300	0/0	0/0	0/0	0/0	0/0
RALP-0302	0/0	0/0	0/0	0/0	0/0
RALP-0310	0/0	0/0	0/0	0/0	0/0
RALP-0314	0/0	0/0	0/0	0/1	0/0
RALP-0316	0/0	0/0	0/0	0/0	0/0
RALP-0320	0/0	0/0	0/0	0/0	0/0
RALP-0322	0/0	0/0	0/0	0/0	0/0
RALP-0324	0/0	0/0	0/0	0/1	0/0
RALP-0327	0/0	0/0	0/0	0/0	0/0
RALP-0335	0/0	0/0	0/0	0/0	0/0
RALP-0345	0/0	0/0	0/0	0/0	0/0
RALP-0367	0/0	0/0	0/0	0/0	0/0
RALP-0369	0/0	0/0	0/0	0/0	0/0
RALP-0370	0/0	0/0	0/0	0/0	0/0
RALP-0376	0/0	0/0	0/0	0/0	0/0
RALP-0378	0/0	0/0	0/0	0/0	0/0
RALP-0386	0/0	0/0	0/0	0/0	0/0
RALP-0387	0/0	0/0	0/1	0/0	0/1
RALP-0402	0/0	0/0	0/0	0/0	0/0
RALP-0403	0/0	0/0	0/0	0/0	0/0
RALP-0404	0/0	0/0	0/0	0/0	0/0
RALP-0406	0/0	0/0	0/0	0/0	0/0
RALP-0421	0/0	0/0	0/0	0/0	0/0
RALP-0429	0/0	0/0	0/0	0/0	0/0
RALP-0433	0/0	0/0	0/0	0/0	0/0
RALP-0438	0/0	0/0	0/0	0/0	0/0
RALP-0440	0/0	0/0	0/0	0/0	0/0
RALP-0441	0/0	0/0	0/0	0/1	0/0
RALP-0442	0/0	0/0	0/0	0/0	0/0
RALP-0446	0/0	0/0	0/0	0/0	0/0
RALP-0450	0/0	0/0	0/0	0/0	0/0
RALP-0451	0/0	0/1	0/0	0/0	0/0
RALP-0452	0/0	0/0	0/1	0/0	0/0

RALP-0455	0/0	0/0	0/0	0/0	0/0
RALP-0459	0/0	0/0	0/0	0/0	0/0
RALP-0466	0/0	0/0	0/0	0/0	0/1
RALP-0467	0/0	0/0	0/0	0/0	0/0
RALP-0470	0/0	0/0	0/0	0/0	0/0
RALP-0473	0/0	0/0	0/0	0/0	0/0
RALP-0476	0/0	0/0	0/0	0/0	0/0
RALP-0494	0/0	0/0	0/0	0/0	0/0
RALP-0495	0/0	0/0	0/0	0/0	0/0
RALP-0496	0/0	0/0	0/0	0/0	0/0
RALP-0497	0/0	0/0	0/0	0/0	0/0
RALP-0498	0/0	0/0	0/0	0/0	0/0
RALP-0502	0/0	0/0	0/0	0/0	0/0
RALP-0503	0/0	0/0	0/0	0/0	0/0
RALP-0504	0/0	0/0	0/0	0/0	0/0
RALP-0510	0/0	0/0	0/0	0/0	0/0
RALP-0511	0/0	0/0	0/0	0/0	0/0
RALP-0515	0/0	0/0	0/0	0/0	0/0
RALP-0520	0/0	0/0	0/0	0/0	0/0
RALP-0528	0/0	0/0	0/0	0/0	0/0
RALP-0530	0/0	0/0	0/0	0/0	0/0
RALP-0531	0/0	0/1	0/0	0/0	0/0
RALP-0542	0/0	0/0	0/0	0/0	0/0
RALP-0543	0/0	0/0	0/0	0/0	0/0
RALP-0545	0/0	0/0	0/0	0/0	0/0
RALP-0548	0/0	0/0	0/0	0/0	0/0
RALP-0551	0/0	0/0	0/0	0/0	0/0
RALP-0553	0/0	0/0	0/0	0/0	0/0
RALP-0555	0/0	0/0	0/0	0/0	0/0
RALP-0559	0/0	0/0	0/0	0/0	0/0
RALP-0563	0/0	0/0	0/0	0/0	0/0
RALP-0565	0/0	0/0	0/0	0/0	0/0
RALP-0567	0/0	0/0	0/0	0/1	0/0
RALP-0569	0/0	0/0	0/0	0/0	0/0
RALP-0573	0/0	0/0	0/0	0/0	0/1
RALP-0574	0/0	0/1	0/0	0/0	0/0
RALP-0586	0/0	0/0	0/0	0/0	0/0
RALP-0588	0/0	0/0	0/0	0/0	0/0
RALP-0592	0/0	0/0	0/0	0/1	0/0
RALP-0599	0/0	0/1	0/0	0/0	0/0
RALP-0600	0/0	0/0	0/0	0/0	0/0
RALP-0603	0/0	0/0	0/0	0/0	0/0
RALP-0624	0/0	0/0	0/0	0/0	0/0
RALP-0630	0/0	0/0	0/0	0/0	0/0
RALP-0633	0/0	0/0	0/0	0/0	0/0
RALP-0635	0/0	0/0	0/0	0/0	0/1
RALP-0638	0/0	0/0	0/0	0/0	0/0
RALP-0645	0/0	0/0	0/0	0/0	0/0

RALP-0651	0/0	0/0	0/0	0/0	0/0
RALP-0660	0/0	0/0	0/0	0/0	0/0
RALP-0661	0/0	0/0	0/1	0/0	0/0
RALP-0663	0/0	0/0	0/0	0/1	0/0
RALP-0668	0/0	0/0	0/0	0/0	0/1
RALP-0671	0/0	0/0	0/0	0/0	0/0
RALP-0673	0/0	0/0	0/0	0/0	0/0
RALP-0680	0/0	0/0	0/0	0/0	0/0
RALP-0686	0/0	0/0	0/0	0/0	0/0
RALP-0698	0/0	0/0	0/1	0/0	0/0
RALP-0703	0/1	0/0	0/1	0/0	0/0
RALP-0704	0/0	0/0	0/0	0/0	0/0
RALP-0720	0/0	0/0	0/0	0/0	0/0
RALP-0726	0/0	0/0	0/0	0/0	0/0
RALP-0731	0/0	0/0	0/0	0/0	0/0
RALP-0739	0/0	0/0	0/0	0/0	0/0
RALP-0741	0/0	0/0	0/0	0/0	0/0
RALP-0747	0/0	0/0	0/0	0/0	0/1
RALP-0751	0/0	0/0	0/0	0/0	0/0
RALP-0752	0/0	0/0	0/0	0/0	0/0
RALP-0755	0/0	0/0	0/0	0/0	0/0
RALP-0769	0/0	0/0	0/0	0/0	0/0
RALP-0779	0/0	0/0	0/0	0/0	0/0
RALP-0783	0/0	0/0	0/0	0/0	0/0
RALP-0788	0/0	0/0	0/0	0/0	0/0
RALP-0789	0/0	0/0	0/0	0/0	0/0
RALP-0796	0/0	0/0	0/0	0/0	0/0
RALP-0797	0/0	0/0	0/1	0/0	0/0
RALP-0811	0/0	0/1	0/0	0/1	0/0
RALP-0819	0/0	0/0	0/0	0/0	0/0
RALP-0822	0/0	0/0	0/0	0/1	0/0
RALP-0823	0/0	0/0	0/0	0/0	0/0
RALP-0829	0/0	0/0	0/0	0/0	0/0
RALP-0830	0/0	0/0	0/0	0/1	0/0
RALP-0831	0/0	0/0	0/0	0/0	0/0
RALP-0841	0/0	0/0	0/0	0/1	0/0
RALP-0842	0/0	0/0	0/0	0/0	0/0
RALP-0849	0/0	0/0	0/0	0/0	0/0
RALP-0853	0/0	0/1	0/0	0/0	0/1
RALP-0856	0/0	0/0	0/0	0/1	0/0
RALP-0859	0/0	0/0	0/0	0/0	0/0
RALP-0861	0/0	0/0	0/0	0/0	0/0
RALP-0862	0/0	0/0	0/0	0/0	0/0
RALP-0863	0/0	0/0	0/0	0/0	0/0
RALP-0864	0/0	0/0	0/0	0/0	0/0
RALP-0870	0/0	0/0	0/0	0/0	0/0
RALP-0871	0/0	0/0	0/1	0/0	0/1
RALP-0875	0/0	0/0	0/0	0/0	0/0

RALP-0878	0/0	0/0	0/0	0/0	0/0
RALP-0882	0/0	0/0	0/0	0/0	0/0
RALP-0890	0/0	0/0	0/1	0/0	0/0
RALP-0892	0/0	0/0	0/0	0/0	0/0
RALP-0893	0/0	0/0	0/0	0/0	0/1
RALP-0894	0/0	0/0	0/0	0/0	0/0
RALP-0902	0/0	0/0	0/0	0/0	0/0
RALP-0910	0/0	0/0	0/0	0/0	0/0
RALP-0920	0/0	0/0	0/0	0/0	0/0
RALP-0930	0/0	0/1	0/0	0/0	0/1
RALP-0933	0/0	0/0	0/0	0/0	0/0
RALP-0938	0/0	0/0	0/0	0/0	0/0
RALP-0940	0/0	0/0	0/0	0/0	0/0
RALP-0941	0/0	0/0	0/0	0/0	0/0
RALP-0946	0/0	0/0	0/0	0/0	0/0
RALP-0951	0/0	0/0	0/0	0/0	0/0
RALP-0952	0/0	0/0	1/1	0/0	0/0
RALP-0956	0/0	0/0	0/0	0/1	0/0
RALP-0958	0/0	0/0	0/0	0/0	0/0
RALP-0963	0/0	0/0	0/0	0/0	0/0
RALP-0964	0/0	0/0	0/0	0/0	0/0
RALP-0969	0/0	0/0	0/0	0/0	0/0
RALP-0979	0/0	0/0	0/0	0/0	0/0
RALP-0992	0/0	0/0	0/0	0/0	0/0
RALP-1006	0/0	0/0	0/0	0/0	0/0
RALP-1008	0/0	0/0	0/0	0/0	0/0
RALP-1015	0/0	0/0	0/0	0/0	0/0
RALP-1019	0/0	0/0	0/0	0/0	0/0
RALP-1025	0/0	0/0	0/0	0/0	0/0
RALP-1036	0/0	0/0	0/0	0/0	0/0
RALP-1038	0/0	0/0	0/0	0/1	0/0
RALP-1046	0/0	0/0	0/0	0/0	0/0
RALP-1050	0/0	0/0	0/0	0/0	0/0
RALP-1051	0/0	0/0	0/0	0/0	0/0
RALP-1054	0/1	0/0	0/0	0/0	0/1
RALP-1055	0/0	0/0	0/0	0/0	0/0
RALP-1062	0/0	0/0	0/0	0/0	0/1
RALP-1067	0/0	0/0	0/0	0/0	0/0
RALP-1070	0/0	0/0	0/0	0/0	0/0
RALP-1071	0/0	0/0	0/0	0/0	0/0
RALP-1096	0/0	0/0	0/0	0/0	0/0
RALP-1098	0/0	0/0	0/0	0/0	0/1
RALP-1102	0/0	0/0	0/0	0/0	0/1
RALP-1104	0/0	0/0	0/0	0/0	0/0
RALP-1112	0/0	0/0	0/0	0/0	0/1
RALP-1119	0/0	0/0	0/0	0/1	0/0
RALP-1121	0/0	0/0	0/0	0/1	0/0
RALP-1129	0/0	0/0	0/0	0/0	0/0

RALP-1144	0/0	0/0	0/0	0/0	0/0
RALP-1152	0/0	0/0	0/0	0/0	0/0
RALP-1154	0/0	0/0	0/0	0/0	0/0
RALP-1155	0/0	0/0	0/0	0/0	0/0
RALP-1162	0/0	0/0	0/0	0/0	0/0
RALP-1167	0/0	0/0	0/0	0/0	0/0
RALP-1168	0/0	0/0	0/0	0/0	0/0
RALP-1174	0/0	0/0	0/0	0/0	0/0
RALP-1181	0/0	0/0	0/0	0/0	0/0
RALP-1188	0/0	0/0	0/0	0/0	0/0
RALP-1203	0/0	0/0	0/0	0/0	0/0
RALP-1204	0/0	0/0	0/0	0/0	0/0
RALP-1219	0/0	0/0	0/0	0/0	0/0
RALP-1232	0/0	0/0	0/0	0/0	0/0
RALP-1238	0/0	0/0	0/0	0/0	0/0
RALP-1241	0/0	0/0	0/0	0/0	0/0
RALP-1243	0/0	0/0	0/1	0/0	0/0
RALP-1254	0/0	0/0	0/0	0/0	0/0
RALP-1255	0/0	0/0	0/0	0/0	0/0
RALP-1259	0/0	0/0	0/0	0/0	0/0
RALP-1264	0/0	0/0	0/0	0/0	0/0
RALP-1267	0/0	0/0	0/0	0/0	0/0
RALP-1268	0/0	0/0	0/0	0/0	0/0
RALP-1270	0/0	0/0	0/0	0/0	0/0
RALP-1272	0/0	0/0	0/1	0/0	0/0
RALP-1279	0/0	0/0	0/0	0/0	0/0
RALP-1303	0/0	0/0	0/0	0/0	0/0
RALP-1313	0/0	0/0	0/0	0/0	0/0
RALP-1327	0/0	0/0	0/0	0/0	0/0
RALP-1337	0/0	0/0	0/0	0/0	0/0
RALP-1345	0/0	0/0	0/0	0/0	0/0
RALP-1350	0/0	0/0	0/0	0/0	0/0
RALP-1351	0/0	0/0	0/0	0/0	0/0
RALP-1352	0/0	0/0	0/0	0/0	0/0
RALP-1359	0/0	0/0	0/0	0/0	0/0
RALP-1368	0/0	0/0	0/0	0/0	0/0
RALP-1369	0/0	0/0	0/0	0/0	0/0
RALP-1383	0/0	0/0	0/0	0/0	0/0
RALP-1398	0/0	0/0	0/1	0/0	0/1
RALP-1401	0/0	0/0	0/0	0/0	0/0
RALP-1419	0/0	0/0	0/0	0/1	0/0
RALP-1431	0/0	0/0	0/0	0/0	0/0
RALP-1436	0/0	0/0	0/0	0/0	0/0
RALP-1441	0/1	0/0	0/0	0/0	0/0
RALP-1459	0/0	0/0	0/0	0/0	0/1
RALP-1465	0/0	0/0	0/0	0/0	0/0
RALP-1467	0/0	0/0	0/0	0/0	0/0
RALP-1470	0/0	0/0	0/0	0/0	0/0

RALP-1473	0/0	0/0	0/0	0/0	0/0
RALP-1477	0/0	0/0	0/0	0/0	0/1
RALP-1487	0/0	0/0	0/0	0/0	0/0
RALP-1496	0/0	0/0	0/0	0/0	0/0
RALP-1499	0/0	0/0	0/0	0/0	0/0
RALP-1502	0/0	0/0	0/0	0/0	0/0
RALP-1504	0/0	0/0	0/0	0/0	0/0
RALP-1506	0/0	0/0	0/1	0/0	0/0
RALP-1508	0/0	0/0	0/0	0/0	0/0
RALP-1509	0/0	0/0	0/0	0/0	0/0
RALP-1511	0/0	0/0	0/0	0/0	0/0
RALP-1512	0/0	0/0	0/0	0/0	0/0
RALP-1516	0/0	0/0	0/0	0/1	0/0
RALP-1521	0/0	0/0	0/0	0/0	0/0

Appendix 7 – Genotypes of RALP patients without family history of PCa and HBOC

PASK rs35129131 genotype in RALP patients without family history of PCa and HBOC. 0/0 homozygous reference, 0/1 heterozygous variant, 1/1 homozygous variant.

Genotype	Individual ID
0/0	RALP-0029, RALP-0033, RALP-0034, RALP-0045, RALP-0051, RALP-0053, RALP-0058, RALP-0061, RALP-0064, RALP-0068, RALP-0069, RALP-0070, RALP-0073, RALP-0074, RALP-0075, RALP-0079, RALP-0086, RALP-0087, RALP-0092, RALP-0094, RALP-0098, RALP-0099, RALP-0101, RALP-0105, RALP-0106, RALP-0107, RALP-0110, RALP-0113, RALP-0114, RALP-0121, RALP-0126, RALP-0128, RALP-0129, RALP-0131, RALP-0141, RALP-0145, RALP-0148, RALP-0155, RALP-0160, RALP-0165, RALP-0168, RALP-0169, RALP-0171, RALP-0183, RALP-0188, RALP-0190, RALP-0191, RALP-0195, RALP-0196, RALP-0201, RALP-0202, RALP-0212, RALP-0213, RALP-0227, RALP-0230, RALP-0231, RALP-0234, RALP-0242, RALP-0258, RALP-0261, RALP-0262, RALP-0269, RALP-0272, RALP-0274, RALP-0276, RALP-0278, RALP-0285, RALP-0294, RALP-0296, RALP-0298, RALP-0306, RALP-0309, RALP-0312, RALP-0317, RALP-0318, RALP-0319, RALP-0333, RALP-0336, RALP-0342, RALP-0344, RALP-0353, RALP-0355, RALP-0356, RALP-0357, RALP-0360, RALP-0361, RALP-0365, RALP-0371, RALP-0379, RALP-0380, RALP-0382, RALP-0384, RALP-0389, RALP-0391, RALP-0392, RALP-0393, RALP-0398, RALP-0399, RALP-0409, RALP-0420, RALP-0428, RALP-0430, RALP-0435, RALP-0437, RALP-0453, RALP-0456, RALP-0457, RALP-0458, RALP-0460, RALP-0461, RALP-0464, RALP-0468, RALP-0471, RALP-0477, RALP-0481, RALP-0482, RALP-0500, RALP-0501, RALP-0505, RALP-0513, RALP-0516, RALP-0518, RALP-0524, RALP-0526, RALP-0533, RALP-0538, RALP-0541, RALP-0546, RALP-0547, RALP-0550, RALP-0557, RALP-0558, RALP-0570, RALP-0572, RALP-0576, RALP-0577, RALP-0578, RALP-0582, RALP-0589, RALP-0590, RALP-0591, RALP-0595, RALP-0604, RALP-0610, RALP-0612, RALP-0620, RALP-0623, RALP-0626, RALP-0628, RALP-0631, RALP-0636, RALP-0640, RALP-0641, RALP-0644, RALP-0646, RALP-0652, RALP-0653, RALP-0654, RALP-0667, RALP-0669, RALP-0674, RALP-0675, RALP-0691, RALP-0695, RALP-0699, RALP-0715, RALP-0718, RALP-0719, RALP-0724, RALP-0734, RALP-0736, RALP-0737, RALP-0745, RALP-0750, RALP-0754, RALP-0756, RALP-0761, RALP-0765, RALP-0766, RALP-0768, RALP-0772, RALP-0791, RALP-0792, RALP-0795, RALP-0799, RALP-0805, RALP-0809, RALP-0818, RALP-0824, RALP-0832, RALP-0838, RALP-0844, RALP-0845, RALP-0854, RALP-0855, RALP-0865, RALP-0880, RALP-0895, RALP-0900, RALP-0901, RALP-0915, RALP-0919, RALP-0921, RALP-0923, RALP-0925, RALP-0935, RALP-0942, RALP-0947, RALP-0954, RALP-0965, RALP-0967, RALP-0968, RALP-0970, RALP-0980, RALP-0985, RALP-0988, RALP-0996, RALP-0997, RALP-1000, RALP-1004, RALP-1011, RALP-1012, RALP-1023, RALP-1026, RALP-1027, RALP-1030, RALP-1060, RALP-1061, RALP-1075, RALP-1077, RALP-1090, RALP-1091, RALP-1093, RALP-1100,

	RALP-1117, RALP-1128, RALP-1145, RALP-1149, RALP-1157, RALP-1170, RALP-1176, RALP-1182, RALP-1187, RALP-1191, RALP-1192, RALP-1201, RALP-1207, RALP-1208, RALP-1214, RALP-1224, RALP-1227, RALP-1229, RALP-1235, RALP-1236, RALP-1242, RALP-1244, RALP-1247, RALP-1260, RALP-1262, RALP-1269, RALP-1284, RALP-1291, RALP-1294, RALP-1307, RALP-1340, RALP-1344, RALP-1347, RALP-1372, RALP-1377, RALP-1381, RALP-1385, RALP-1386, RALP-1397, RALP-1409, RALP-1420, RALP-1422, RALP-1443, RALP-1447, RALP-1449, RALP-1454, RALP-1478, RALP-1480, RALP-1481, RALP-1483, RALP-1486, RALP-1488, RALP-1490, RALP-1503, RALP-1524, RALP-1525
0/1	RALP-0328, RALP-0338, RALP-0474, RALP-0725, RALP-0763, RALP-0867
1/1	-