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Case Report

Genetic Susceptibility due to Moderate Breast Cancer Risk Gene CHEK2 - A Case Report

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Abstract

Today we are increasingly interested in finding out the hereditary variants of moderate risk from a cancer patient. Multigene next generation sequencing (NGS) panel technology, massive parallel sequencing, can efficiently and economically analyze genes in 3 to 6 weeks. There are agreed criteria based on which to suspect hereditary breast cancer and thus to make a referral to clinical genetic unit. The topic research subject is to investigate the cancer risk associated with moderate risk genes. Appropriate follow-up recommendations for persons with moderate genetic susceptibility pathogenic variants to breast cancer are updated regularly as scientific research is published. This is a case report on two *CHEK2* families in which pathogenic variant in *CHEK2* gene does not alone explain the breast cancer risk of the patients. *This is also a mini* review of genetic susceptibility of *CHEK2* moderate breast cancer gene.

INTRODUCTION

In Finland, a woman's risk of developing breast cancer during her life is approximately 13%, and for ovarian cancer less than 2% (2012-2016) [1]. Currently approximately 20 genes are known, with scientific results to have strong evidence with a significantly increased risk for hereditary breast cancer [2,3]. Cancer risk for breast and ovarian cancer is very high with pathogenic variants (PVs) in *BRCA1* and *BRCA2* genes [4] (Table 1), [5-13]. *4-6 % of all breast cancer patients have a pathogenetic variant in CHEK2, PALP2* or *ATM* genes [14], which are in general associated with moderate risk for breast cancer [5] (Table 1). Truncated variants in genes *CHEK2* and *ATM* associates with estrogen receptor positive breast cancer whereas in *PALB2* odds ratio is higher for estrogen receptor negative breast cancer than estrogen positive breast cancer [6]. *BRCA1*, *RAD51C and RAD51D* are more often associated with triplenegative breast cancer [6]. Also, rare (prevalence in the population<1/1000) missense variants in *CHEK2* gene are associated with breast cancer risk independent of the location of the mutation [6]. However, there are also known missense variants in the *CHEK2* gene that do not significantly increase the risk of breast cancer, such as c.538C>T and I157T [15]. According to current understanding *PVs* in *CHEK2* does not associate with ovarian cancer [7].

Identifying Hereditary Breast ± Ovarian Cancer

Suspicion of hereditary breast ± ovarian cancer syndrome arises, when the patient has the following characteristics: an early age of onset compared to average cancer patient, specific type of histological pattern such as medullary, breast and ovarian cancer in same patient and triple-negative or bilateral breast cancer and multiple close relatives with cancers of the syndrome (2 or more breast cancers in 1st or 2nd degree relatives) [7,16]. By evaluating the family history of diagnosed cancer cases and diagnostic gene test results of the cancer patient, clinical geneticist can identify families of hereditary breast ± ovarian cancer with high and moderate risk. Identifying the families with increased risk for breast ± ovarian cancer allows clinicians to improve the prognosis of breast and ovarian cancer patients and their relatives with genetic cancer susceptibility proven by either pedigree and / or genetic examination (Table 2 [7,16,17]). Before testing individuals, informed consent should be requested after adequate information and counseling provided [18]. American Society of Clinical Oncology (ASCO) recommends genetic testing if there is an appropriate genetic tests that for the situation [19].

Basic Cancer Genetics

In both hereditary and sporadic cancer normal genome regulation is impaired [20]. Cancer susceptibility is caused by both inherited germline gene mutations and also somatic gene mutations are needed to tumorigeneses [21]. Current understanding is that approximately four to seven mutations in key driver genes is sufficient to cause cancer [22]. Cancer risk is also influenced by protective genes. Some individuals who inherited a cancer mutation will never develop cancer in their lifetime.

Almost always, hereditary genetic defect is located in tumor suppressor genes. According to Knudson's two-hit theory, two "hits" must occur at the cellular level in a person's tumor suppressor gene, i.e., a genetic defect, one in each alleles of genes, before tumor genesis [21]. In hereditary cancer, one genetic defect is inherited and present since birth.

Genetic susceptibility is a continuum as there are low-risk variants, moderate-risk variants, and high-risk variants. Traditionally high-risk variants are those that are referred to

Table 1: Breast ± Ovarian Cancer Risk on Different Types of Cancer Syndromes.

	BRCA1/2-associated hereditary breast and ovarian cancer	*CHEK2-associated hereditary breast cancer*	*ATM-associated hereditary breast cancer*	*PALB2*-associated hereditary breast and ovarian cancer	*RAD51C/D*-associated hereditary ovarian cancer
Lifetime risk for breast cancer	50 – 70 % [12]	20 – 40 %, in some families ≥ 40 % [6][7][11]	15 – 40 %, in some high-risk variants such as 7271T>G, 50 - 60 % at 80 years [6][7][13]	44 % at 70 years [5][6][9][10]	increased risk for triple-negative breast cancer [8]
Lifetime risk of ovarian cancer	10-45% [12]	no increased risk [7]	as low as < 3 % [7]	≤ 5 % [7]	10-30% according to family history [8]
Gene	*BRCA1*, *BRCA2*	*CHEK2*	*ATM*	*PALB2*	*RAD51C*, *RAD51D*

Table 2: How to improve prognosis in the carriers of hereditary breast cancer gene mutation. [7][16].

The aim is to improve the early detection of cancer
Regular increased follow-up to enable early detection of cancer for early diagnosis
When the breast cancer risk is moderate or high according to pedigree or gene test result. [7][16]
Occurrence can be prevented by surgical procedures
The risk of ovarian and breast cancer can be greatly reduced by salpingo-oophorectomy, such as in PV of *BRCA1* and *BRCA2* [17] *or in PV of RAD51C or RAD51D* [7][8]
The risk of breast cancer can be greatly reduced by mastectomy in high risk, such as in PV of *BRCA1* and *BRCA2* [7][17]
Sometimes genetic information can guide the choice of medication or other treatment
• In the carriers of *TP53* mutation, radiation therapy and X-ray imaging will be avoided [7]

as hereditary variants and predispose to so-called hereditary cancer. However, today we are also increasingly interested in finding out the variants of moderate risk for breast cancer [23]. More information is being constantly gained on how PVs, for example of the *CHEK2* gene, affect the risk of breast cancer. In sporadic cases the inherited low-risk PVs can cause cancer even though any of the inherited PV´s alone only has a low-risk [24]. GWAS associated studies attempt to identify these low-risk variants. According to Vogelstein's research group, chance has a major impact in the development of cancer-causing mutations during DNA replication in normal, noncancerous stem cells [25].

Two different cases with PV in *CHEK2*

From the year 2017, genetic panels were used in 17% of diagnostic studies in Hereditary Breast and Ovarian Cancer (HBOC) families in the Department of Clinical Genetics in Turku University Hospital, in southwestern Finland. Other diagnostic tests analyzed *BRCA1* and *BRCA2* genes. In 2019, multigene next generation sequencing was used in all screening studies to obtain a family diagnosis. The diagnostic gene panel contains at least the following 18 high and moderate risk genes (*ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, FANCM, MLH1, MSH2, MSH6, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11* and *TP53).*

CASE 1

Three of four sisters have had treatment for breast cancer but no common genetic etiology was found (Figure 1). Two of sisters have had unilateral breast cancer and one have had bilateral. Figure1 shows the gene tests done to the siblings. Germinal CHEK2 c.1100del was observed in one sister with unilateral breast cancer, but the other sister with bilateral breast cancer and estrogen receptor status of positive did not have *CHEK2* c.1100del. Neither the third sister with unilateral breast cancer had *CHEK2* c.1100del. Germinal PV in *BRCA1* or *BRCA2* has not been found in this family. Additionally, no other known PV was found in the genes associated with breast cancer susceptibility (Figure 1). The sisters combined have three female children, none of whom have had breast cancer.

The four sisters have had combined 4 breast cancers. The pedigree indicates that the family has a high-risk for breast cancer with unknown PV(s) to current gene panels. According to pedigree and gene test results follow-up recommendation, mammography and breast ultrasound, was given to the cancer patients, their healthy sister and their daughters from the age of 37 years, 5 years earlier than the earliest cancer in family. If bilateral mastectomy is done no follow-up is required. The mastectomy is prophylactic treatment for those patients with high risk for breast cancer. Healthy sister lives abroad and has agreed with her treating doctor on risk-reducing bilateral mastectomy.

CASE 2

In the family one sister had triple-negative breast cancer at the age of range 40-50 years has both CHEK2 c.1100del and PALB2 c.1592del. The content of the panel is mentioned above. A genetic panel study was conducted to determine the cause of triple negativity. Based on the pedigree, there was no reason to suspect a high risk of breast cancer. The patients' sisters did not have breast cancer. No healthy sister had CHEK2 c.1100del, but PALB2 c.1592del was found. PALB2 c.1592del is associated with a breast cancer risk of approximately 40%. Therefore, carriership of PALB2 c.1592del leads to mammography and breast magnetic resonance imaging regularly from the age of 30 years. No woman in this family had ovarian cancer. Therefore, there was no indication for risk-reducing bilateral salpingo-oophorectomy.

STUDY AUTHORIZATION AND CONSENT

This study is a hospital quality research, which has been authorized and has valid ID. In the study analyzed data was from patients who had been treated at the hospital. As no new samples

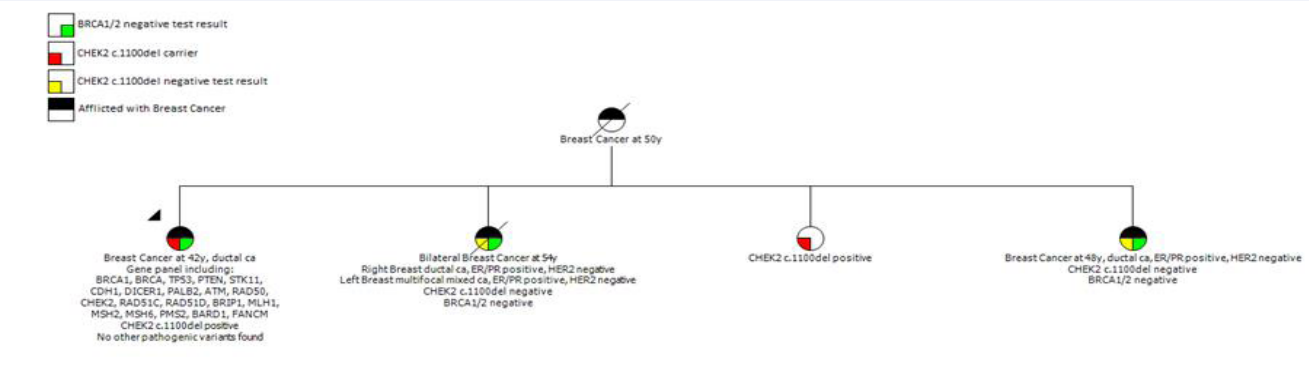

Figure 1 Pedigree for case 1.

were required a separated ethics board permit was not required. The Turku Clinical Research Center provides services in the field of health scientific research for researchers of the University of Turku and the Turku special responsibility area. Consent was received from the siblings to present their medical records in the pedigree in case number one. In case two pedigrees are not shown and clinical information is anonymized. The study complies with the 1964 Helsinki Declaration and the General Data Protection Regulation 2016 (EU) of the Data Protection Directive.

DISCUSSION

Crucial for the cancer risk of individual is the combined effect of all PVs, most of which currently cannot be identified by gene panels. The pedigree is important in the assessment of cancer risk. Variant-specific segregation analysis in the family provides information on the significance of the found moderate risk variant. Breast cancer risk varies from 20 to 60 % in PV of *CHEK2* in different families (Table 1). PVs in PALB2 gene associated with moderate risk for breast cancer in a recent population based study [5] although for some PVs in PALB2 highly increased lifetime risk for developing breast cancer has also been published *(*Table 1).

In our case examples, *CHEK2* PV did not associate with other breast cancer cases in the family. Bilaterality has been associated with *CHEK2* c.1100del [26,27]. In our case there was sister with bilateral breast cancer, but she did not have *CHEK2* c.1100del. In the second case, triple negativity was the reason for the genetic testing, which found both *CHEK2* c.1100del and *PALB2 c.1592del. PV* in *PALB2* is associated with triple-negative breast cancer. *PALB2* mutations may slightly increase ovarian cancer risk. Previously unknown or insufficient evidence has been found between *PALB2* and ovarian cancer risk [9]. Now, findings point to stronger association between *PALB2* and ovarian cancer risk, but still the risk is only approximately 5 % or less [7].

Both cases show that patient´s cancer specific differences in the same family are due to differences in the genetic etiology. Genetic panels enable to explore PVs in known high and moderate risk breast cancer genes. In some people, the risk of cancer can be highly associated with many low-risk variants that are not well known today. It is hoped that a further tool for identifying patients at high risk of cancer will be a polygenic risk score (PRS). Currently, scientific studies are examining the possibility to use polygenic risk scores to predict the risk of contralateral breast cancer of a breast cancer patient and also the cancer risk for 1st degree relatives [11]. PRS is not yet available for clinic work.

It is important that local variant profiles are investigated. It has been established that the presence of *the CHEK2* c.1100del variant varies in Finland and is clearly more common in Eastern Finland than in Western Finland [11]. The FinnGen study found that the risk of breast cancer was higher for western Finnish carriers of the *CHEK2* c.1100del variant because their PRS value was on average higher than that of eastern Finnish carriers [11].

Polygenic risk factors for breast cancer have been previously published for instance in *BRCA1* and *BRCA2* families. In low frequency double germ-line heterozygous mutations' carriership of moderate and high-risk genes, such as *CHEK2*, *ATM*, *PALB2*, *BRCA1* and *BRCA2*, have been observed with breast cancer risk [28,29], and in a Finnish study at least one moderate-risk gene PV was found in 12.5% of *BRCA1* families as well as in 17.0% of *BRCA2* families [30].

Today, the criterion for a referral to a clinical geneticist is defined as suspecting a high breast cancer risk in the family, i.e. a sufficient number of breast cancer cases. Therefore, those individuals in whom a *CHEK2* PV or other moderate risk PV is found typically belong to a high risk breast cancer pedigree. The clinical geneticist interprets the results of gene test variants and family cancer cases. Today, there are challenges in evaluating the risk of breast cancer in relatives in families with *CHEK2* PV. The Boadicea, the CanRisk web tool calculation algorithm may help with the relative's risk assessment in families. As this information about moderate risk genes is gathered at an increasing pace, counseling about the cancer risk becomes more specific not only screening due to breast and ovarian cancer risk but also other cancer risks. Currently, colonoscopy screening is not recommended in PV of *CHEK2* [31].

Currently, only part of the normal variation of the moderate risk genes is known. This leads to some of the genome variants found to be so-called variant of unknown significance (VUS) is a change whose significance is currently unknown, and which cannot be classified as harmless (benign) or pathogenic, that explains susceptibility to cancer. Genetic variants are

currently classified according to a five-level ACMG classification [32,33]. When additional information becomes available, VUS classification may changes.

CONCLUSION

Nowadays, we are increasingly interested in identifying moderate risk pathogenic variants from cancer patient. As population frequency of moderate risk alleles is higher than in high-risk alleles and sequencing technology is developing, it is expected that moderate risk families will be identified in growing numbers in the future. Gene associated cancer risks have been explored in large prospective studies. However, mutation profile in local geographical areas is still required for efficient care. Crucial for the cancer risk of individual is the combined effect of all PVs, most of which currently cannot be identified. The pedigree is important in the assessment of cancer risk. Variant-specific segregation analysis in the family may provide information on the significance of the variant. The Boadicea, the CanRisk calculation algorithm can help with the relative's risk assessment in families. As the information about moderate risk genes is gathered at an increasing pace, there is a need to update international follow-up recommendations frequently for genes.

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