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Highly conserved regulators of environmental sensing and adaptation drive domestication in gilthead seabream (*Sparus aurata*)

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ABSTRACT

Domestication in fish involves rapid and complex changes in life-history, physiology and behavior under human-controlled aquaculture conditions. In gilthead seabream (*Sparus aurata*), a species with a relatively recent domestication history, we used genome-wide population comparisons to show that domestication targets a core set of highly conserved regulators of environmental sensing mechanisms. Across farmed stocks and wild populations spanning the Mediterranean, our analyses reveal divergence at key genes involved in pathways that translate oxygen and chemical cues into stress, immune, endocrine and reproductive outcomes. Standout candidates include *ahrra* within the ancient AHR–ARNT/HIF signaling system, *kdm6al*, a chromatin regulator coordinating developmental and stress responses, and *pigm*, a GPI-anchor biosynthesis gene shaping cell-surface composition and host defense. These functions are shared widely across animals, from invertebrates to vertebrates, suggesting that domestication often proceeds by tuning long-standing sensory circuitry to aquaculture conditions. This convergence points to a measure of predictability in the genomic response to captivity, links molecular pathways to production-relevant traits such as stress tolerance and reproduction, and offers actionable hypotheses for rapid adaptation in species during domestication. By identifying these conserved regulators through empirical data, our results connect microevolution under domestication with fundamental biology and provide tractable gene sets for testing how ancient pathways are repurposed during contemporary evolution and for monitoring in aquaculture.

1. Introduction

Domestication provides a compelling case of evolution, wherein species are subjected to novel human-mediated selective pressures that drive coordinated changes in physiology, behavior, and life-history traits (Ahmad et al., 2020; Purugganan, 2019; Milla et al., 2021). Unlike terrestrial livestock, the domestication of fish is relatively recent (Teletchea, 2015), offering a unique opportunity to study the early stages of adaptation under controlled conditions. In fish, these evolutionary changes can emerge within only a few generations, affecting growth, stress tolerance, reproductive timing, and immune competence (Howe et al., 2024; Milla et al., 2021; Nguyen, 2016). As such, domestication acts as a natural experiment for examining how ecological pressures shape genomic architecture.

Adaptive traits under domestication are often polygenic, with individual loci exerting small effects that cumulatively influence physiology and life-history strategies (Mohamed et al., 2019; Sinclair-Waters et al., 2020; Moulistanos et al., 2024). This complexity has underscored the

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value of molecular ecology approaches, particularly genome-wide scans, in identifying genes mediating adaptive responses (Jia and Zhao, 2014; Liu et al., 2020; Uffelmann et al., 2021; Tsare et al., 2024). In fish domestication, selective breeding frequently targets traits such as growth, stress resilience, immune competence, and reproduction, which together determine the performance and sustainability of farmed populations (Chavanne et al., 2016; Janssen et al., 2017; Abdel-Tawwab et al., 2019; Tillotson et al., 2018). Genomic tools, especially whole-genome scans using high-density SNPs, have become invaluable for detecting loci under selection, uncovering mechanisms of local adaptation, and elucidating the molecular basis of key life-history traits (Sinclair-Waters et al., 2020; Yoshida and Yáñez, 2021; Moulistanos et al., 2024). However, the genetic underpinnings of domestication remain poorly understood in many species, highlighting the importance of genome-wide studies to inform both sustainable aquaculture practices and our understanding of evolutionary and molecular processes.

The gilthead seabream (*Sparus aurata*), a cornerstone species in Mediterranean aquaculture, represents an excellent model for investigating early-stage domestication. Selective breeding programs were initiated in the early to mid-1990s across several Mediterranean countries. Industry-wide summaries indicate that gilthead seabream breeding programs typically encompass approximately one to five generations of selection, depending on the breeding nucleus and country (Villanueva et al., 2022; Janssen et al., 2017). Analyses of established commercial nuclei in Greece and France further suggest that programs initiated in the 1990s have undergone approximately four to six generations of structured selection (Saura et al., 2021). This relatively recent domestication history is consistent with reduced effective population sizes in farmed stocks and measurable genetic differentiation from their wild counterparts (Teletchea, 2021; Saura et al., 2021; Gkagkavouzis et al., 2021; Peñaloza et al., 2021; Villanueva et al., 2022).

Growth rate has been the primary selection objective, given its strong impact on production efficiency and time to market (Chavanne et al., 2016; Janssen et al., 2017). Feed efficiency has likewise become increasingly important as breeding programs seek to reduce production costs and environmental impacts. Disease resistance, particularly against major bacterial pathogens and parasitic infections prevalent in Mediterranean aquaculture, represents another key breeding target (Abdel-Tawwab et al., 2019; Tillotson et al., 2018). Additional traits under selection include survival under intensive farming conditions, body conformation, fillet yield, and product quality characteristics. More recently, breeding objectives have expanded to incorporate robustness and tolerance to environmental stressors such as temperature variability and hypoxia, as well as aspects of reproductive control aimed at optimizing production cycles (Teletchea, 2021; Saura et al., 2021). This multi-trait selection framework provides important biological context for interpreting genomic regions exhibiting elevated differentiation between farmed and wild populations.

To date, only a limited number of genes and QTLs linked to domestication have been identified, primarily associated with morphometric traits, stress response, immunity, and reproduction (Boulton et al., 2011; Loukovitis et al., 2011; Loukovitis et al., 2012; Žužul et al., 2022; Gkagkavouzis et al., 2021; Moulistanos et al., 2024, 2025; Moulistanos et al., 2025). However, a comprehensive genome-wide analysis at the resolution of individual genes is still lacking. Filling this gap is crucial to understanding the genetic architecture of domestication-related traits in gilthead seabream.

To address this gap, we set out to characterize genome-wide signatures of domestication in gilthead seabream. We analyzed Illumina Pool-Seq data from 10 farmed and 10 wild populations distributed across the Mediterranean, originally generated by Peñaloza et al. (2021) for the development of SNP arrays in gilthead seabream and European seabass. In that dataset, farmed populations are defined as fish originating from commercial hatcheries or established breeding programs; however, the precise number of selected generations for each sampled population is not individually reported. We have previously used this dataset to investigate two chromosomes containing the candidate genes *six6* and *vgll3*, known to influence maturation in Atlantic salmon (Barson et al., 2015; Sinclair-Waters et al., 2020; Moulistanos et al., 2024). That hypothesis-driven analysis revealed localized regions of differentiation between farmed and wild populations, underscoring the dataset's potential to uncover selection targets associated with domestication (Moulistanos et al., 2025). Here, we move beyond locus-specific analyses to conduct a comprehensive genome-wide scan, integrating multiple differentiation statistics to identify divergence hotspots and positional candidate genes associated with domestication-related traits, thereby providing novel insights into the molecular mechanisms of adaptation to human-controlled environments.

2. Materials and methods

2.1. Studied populations

We analyzed pooled whole-genome sequencing data from 10 farmed and 10 wild gilthead seabream populations (Table 1; Fig. 1), sampled across six Mediterranean countries (Peñaloza et al., 2021). Table 1 reports the population IDs, country of origin, number of individuals included per pool, and number of pools prepared for each population as originally described by Peñaloza et al. (2021). The number of individuals per pool ranged from 13 to 25 in farmed populations and was 25 in all wild populations. Precise latitude and longitude coordinates for sampling locations were not reported in the original dataset publication (Peñaloza et al., 2021) and are therefore not available for inclusion here; population origin is reported at the country level as provided in the original resource. Likewise, farm-level environmental metadata (e.g., temperature regimes or local rearing conditions) were not available in the original dataset, and consequently we avoided attributing observed genomic differentiation patterns to specific environmental gradients in the absence of direct environmental information. Genome-wide population genetic parameters, including genetic diversity and differentiation among farmed and wild populations, were previously evaluated using the same dataset by Peñaloza et al. (2021) and were therefore not re-estimated here, as the present study focuses on identifying domestication-related divergence signals.

To ensure analytical robustness, we excluded seven populations from the original dataset, which initially comprised 12 farmed and 15 wild

Table 1
Classification of studied gilthead seabream populations. Farmed and wild populations sampled across Mediterranean countries are listed, with population IDs as reported in Peñaloza et al. (2021).[1]

Origin	Population ID	Country	Number of individuals per pool	Number of pools prepared
Farmed	fFRA_1	France	25	2
	fSPA_2	Spain	25	2
	fSPA_3	Spain	25	2
	fITA_4	Italy	25	1
	fCRO_5	Croatia	25	2
	fGRE_6	Greece	14	1
	fGRE_7	Greece	13	1
	fGRE_8	Greece	25	2
	fGRE_9	Greece	25	2
	fGRE_10	Greece	25	2
Wild	wSPA_4	Spain	25	2
	wSPA_5	Spain	25	2
	wITA_7	Italy	25	2
	wITA_8	Italy	25	2
	wGRE_9	Greece	25	2
	wGRE_10	Greece	25	2
	wGRE_11	Greece	25	2
	wGRE_12	Greece	25	2
	wGRE_13	Greece	25	2
	wTUR_14	Turkey	25	2

[1] Labelling was done according to Peñaloza et al. (2021).

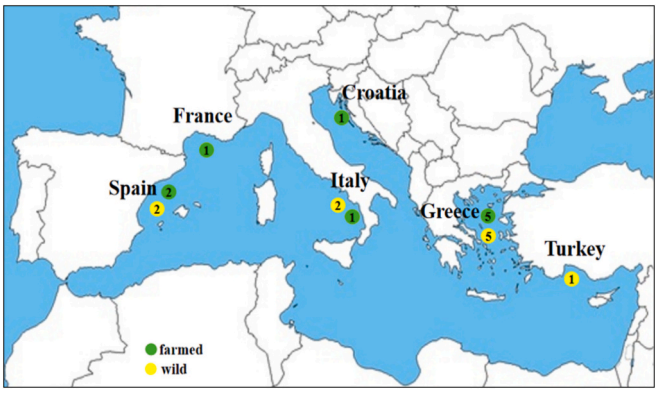

Fig. 1. Geographic distribution of studied farmed and wild gilthead seabream populations in the Mediterranean region.

populations. This filtering was informed by previous population structure analyses (Peñaloza et al., 2021; Villanueva et al., 2022). Three populations of the Atlantic Ocean origin were removed to maintain a Mediterranean focus (Peñaloza et al., 2021). Two wild populations were also removed: one due to a very low effective population size ($N_e < 70$) relative to other wild populations (Villanueva et al., 2022), while another was removed because of its unusually high F_{ST}, suggesting substantial genetic divergence (Peñaloza et al., 2021). Two farmed populations, one from Egypt and one from Israel, were also excluded: the Egyptian population exhibited admixture proportions similar to wild populations, while the Israeli population showed high F_{ST} compared to other farmed groups (Peñaloza et al., 2021).

2.2. DNA extraction and pooling

The Pool-Seq data analyzed in this study were originally generated by Peñaloza et al. (2021). For each population, genomic DNA was extracted individually from multiple fish using the standardized protocols described in the original publication. Equal quantities of high-quality genomic DNA from each individual were combined to construct a biological pool per population, ensuring balanced representation of allele frequencies.

Each population therefore represents a biological pool composed of individuals sampled from the same hatchery (farmed populations) or geographic location (wild populations). In cases where two pools were prepared for a given population (Table 1), these represent technical sequencing replicates derived from the same set of individuals rather than independent biological replicates. To avoid pseudoreplication, technical replicates were merged prior to read mapping and allele frequency estimation, resulting in a single pooled dataset per population. All downstream allele frequency estimation and genome scan analyses were therefore conducted at the population level.

2.3. Read mapping

Pool-Seq data for each population were obtained from the NCBI Sequence Read Archive under the accession ID PRJEB40423. To ensure data quality, the sequences were filtered using Trimmomatic (Bolger et al., 2014) with the following parameters in paired-end mode: ILLUMINACLIP: TruSeq3-PE.fa:2:30:10; LEADING:5; TRAILING:5; SLIDINGWINDOW:3:15; MINLEN:100. Subsequently, the filtered reads were mapped to the reference assembly (GCA_900880675.2) using the bwa mem algorithm (Li and Durbin, 2009). Finally, only properly paired reads were extracted with a mapping quality of at least 15 (corresponding to a maximum 3% misalignment probability) using samtools (Li et al., 2009).

2.4. SNP genotyping

To ensure accurate genotype frequency estimation, properly paired reads from each population in Table 1 were sorted and merged across technical replicates using samtools. Read counts for each genomic position with mapped reads were obtained with bam-readcount v.1.0 (Khanna et al., 2022). Genomic positions were then filtered using an AWK script, with a minimum read depth of 55 counts required. Allele frequencies below 1% were excluded to minimize potential sequencing errors and incorrect mappings, following common practice in population genomic analyses (Linck and Battey, 2019). Finally, biallelic SNPs and their corresponding genotypes were identified using an in-house Python function. The Python scripts employed for the simulations and SNP typing are available at the GitHub link provided in the Data Availability section.

2.5. PCA and genome scan analyses

To assess and characterize differentiation between the studied farmed and wild populations, a Principal Component Analysis (PCA) was performed using the Python package 'sklearn'. Allele frequencies were compared between farmed and wild populations using two programs: PoPoolation2 (Kofler et al., 2011) and BayPass v. 2.1 (Gautier, 2015), both of which accommodate Pool-Seq data. Custom Python scripts were developed to generate the required input files for these analyses. The *p*-values produced by both programs were adjusted for multiple testing using the Benjamini–Hochberg method (Benjamini and Hochberg, 1995), as implemented in the 'stats' package in Python.

PoPoolation2 was used to calculate pairwise F_{ST}, estimating the genetic differentiation between farmed and wild populations by averaging F_{ST} across SNPs. Statistical significance for each SNP was assessed with Fisher's exact test. BayPass was run in Pool-Seq mode with an extended burn-in of 10,000 iterations (twice the default), followed by 10,000 recorded samples with a thinning interval of 25, resulting in a post–burn-in MCMC chain of 250,000 iterations. Default settings were otherwise applied. BayPass provided the XtX and C_2 differentiation statistics. The XtX statistic, analogous to F_{ST} but adjusted for covariance among allele frequencies, reduces sensitivity to outlier populations (Günther and Coop, 2013). The C_2 statistic evaluates differentiation across multiple SNPs simultaneously, incorporating shrinkage toward population means to provide a more robust, genome-wide measure of differentiation (Olazcuaga et al., 2020).

2.6. Identification of divergence signals

SNPs were initially classified based on their statistical differentiation between farmed and wild gilthead seabream populations. Loci with adjusted *p*-values below 10^{-3} in both PoPoolation2 (F_{ST}) and BayPass (XtX) analyses were considered "divergent", representing the most strongly divergent SNPs. Among these, we further applied the C_2 approach to highlight loci showing exceptionally pronounced allele frequency differences. SNPs with C_2 *p-values* below 10^{-3} were designated as "strongly divergent" only when at least one additional SNP with a *p-value* below 10^{-3} was present within a 100 kbp window on either side. These clusters of significant SNPs represent the strongest candidates for farmed–wild divergence.

As a complementary framework, we additionally implemented a Composite Selection Signal (CSS) approach (Verity et al., 2017) to formally integrate evidence across the three independent statistics (F_{ST}, XtX, and C_2). For each SNP, values from the three tests were converted into genome-wide ranks to standardize the scale of the statistics and avoid distributional assumptions. A composite score was then calculated as the mean rank across methods, thereby prioritizing loci that consistently exhibit extreme values across multiple selection metrics. By integrating differentiation-based (F_{ST}), covariance-based (XtX), and contrast-based (C_2) statistics, the CSS framework reduces reliance on

any single test and increases robustness to method-specific biases or demographic confounding effects. SNPs with the lowest composite ranks were considered the strongest candidates, as they represent loci jointly supported by multiple independent signals of divergence.

2.7. Functional annotation and gene network analysis

To further explore the potential functional relevance of differentiated regions, we annotated SNPs located within ±100 kbp of "divergent" and "strongly divergent" loci. This window size was selected based on previous teleost studies demonstrating that genomic intervals of similar scale capture linkage blocks surrounding selected loci (Barson et al., 2015; Star et al., 2016), indicating that windows of this magnitude are appropriate for identifying positional candidate genes linked to selected variants in fish genomes. Genome annotations from BioMart (Sparus_aurata.fSpaAur1.1.113.gff3) were employed to perform this mapping (Smedley et al., 2009). Sequences of the identified genes were downloaded from the Ensembl fSpaAur1.1 assembly (GenBank ID: GCF_900880675.2) and employed to identify better-annotated zebrafish (*Danio rerio* Hamilton 1822) orthologs via local BLASTx using zebrafish UniProtKB/Swiss-Prot identifiers (https://www.uniprot.org/blast). In each case, the top BLASTx hit was selected, with a maximum *E*-value threshold of 10^{-3}. The resulting annotations are reported in Supplementary Table S1.

To evaluate whether candidate genes located within differentiated genomic regions were non-randomly associated with specific functional properties, we performed Gene Ontology (GO) enrichment analyses using g:Profiler (Raudvere et al., 2019). Zebrafish orthologs corresponding to the identified positional candidate genes (Supplementary Table S1) were used as input, with *Danio rerio* specified as the reference background. Enrichment was tested across the GO Biological Process, Molecular Function, and Cellular Component categories, and statistical significance was determined using Benjamini–Hochberg false discovery rate (FDR) correction.

This set of gene orthologs was submitted to STRING v12.0 to construct a knowledge-based interaction network (Szklarczyk et al., 2023). STRING infers putative links from multiple evidence streams, including regulatory relationships, subcellular co-localization, documented biochemical/physical interactions, and patterns of co-expression/co-regulation, to assign confidence scores to gene-gene connections. To allow the detection of broader interaction patterns among candidate genes, the minimum interaction score was set to 0.15. To better capture key regulatory pathways, we included the *arnt* (HIF-1β) gene as a direct interactor of *ahrra*, enabling the network to reflect potential functional and regulatory relationships with other candidate genes (Abel and Haarmann-Stemmann, 2010; Haarmann-Stemmann and Abel, 2006; Vogel and Haarmann-Stemmann, 2017).

3. Results

3.1. Population differentiation and principal component analysis

Allele frequencies of 5,282,885 biallelic SNPs across the gilthead seabream genome were examined. Principal component analysis (PCA) demonstrated clear differentiation between farmed and wild populations (Fig. 2). The first principal component accounted for 12.1% of the total variation, and the second principal component explained 7.3% of the variation. Within the farmed populations, two distinct subgroups were observed: one composed exclusively of Greek farmed populations, and another representing farmed populations from across the Mediterranean (Croatia, France, Greece, Italy, and Spain) (Fig. 2).

3.2. Identification of differentiated genomic regions and candidate genes

To identify genomic regions showing differentiation between farmed and wild populations, we applied two complementary genome scan

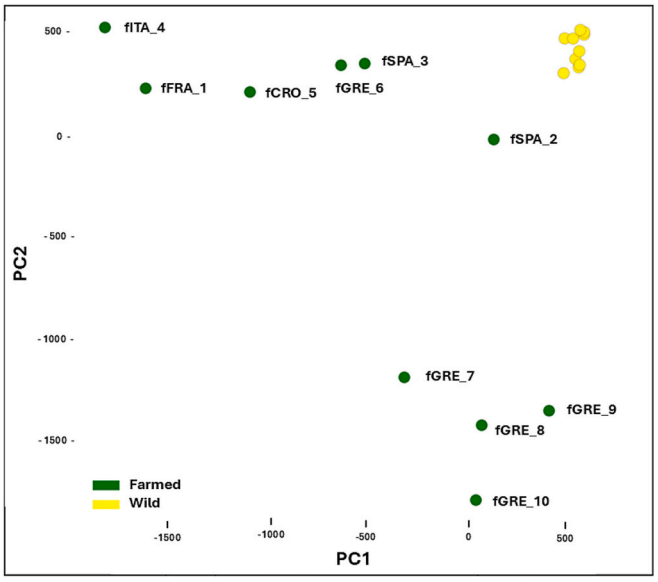

Fig. 2. Population structure of the studied gilthead seabream populations. Principal component analysis (PCA) was conducted on 5,282,885 SNPs for the farmed and wild populations of gilthead seabream across the Mediterranean region with information of each population ID based on Table 1.

approaches: PoPoolation2 (F_{ST}) and BayPass (XtX). These analyses detected 13 "divergent" SNPs across eight chromosomes (3, 6, 9, 10, 14, 18, 19, and 23, Fig. 3a, b, Table S1). Among these, one SNP on chromosome 19 was uniquely identified as "strongly divergent" using the C_2 statistic ($C_2 = 34.732$, $Padj = 8.71 \times 10^{-5}$; Fig. 3c), indicating marked selective differentiation at this locus between farmed and wild populations.

To formally integrate evidence across all three outlier statistics, we implemented a Composite Selection Signal (CSS) framework (Verity et al., 2017), combining genome-wide rankings of F_{ST}, XtX, and C_2 into a unified composite score. This integrative analysis reinforced the non-random concentration of divergence signals on chromosome 19. Notably, seven of the 10 highest-ranking CSS SNPs clustered within a narrow genomic interval between positions 10,647,485 and 10,650,957 bp, corresponding precisely to the region identified as "strongly divergent" by the C_2 statistic. An additional top-ranked CSS SNP was also located on chromosome 19, whereas the remaining two top-ranked CSS SNPs were located on chromosomes 23 and 10. Notably, these three SNPs were also classified as "divergent" in the original F_{ST}, XtX, and C_2 genome scans. The concordance among these results highlights a consistent hotspot of farmed–wild differentiation on chromosome 19, supporting this region as a prominent candidate target of domestication-related divergence in gilthead seabream.

Annotation within ±100 kbp of each divergent or strongly divergent SNP revealed that 10 of the 13 SNPs were located in proximity to annotated genes. Across these intervals, 62 protein-coding genes were identified, corresponding to 58 unique zebrafish orthologs (Supplementary Table S1). These genes constitute the complete set of positional candidate genes identified in this study. Classification of outlier SNPs according to genomic annotation (Supplementary Table S1) showed that differentiated variants occur predominantly in intergenic or non-coding regions, with fewer located within intronic or coding sequences, indicating no apparent enrichment of coding variants among detected divergence signals. We emphasize that these genes represent candidates within differentiated genomic regions and should not be interpreted as causal targets of selection. Regional Manhattan-style plots (±100 kb) illustrating F_{ST}, XtX, and C_2 statistics across each candidate interval are provided in Supplementary Figs. S1 – S12. Notably, two genes, *pigm* and *ahrra*, were located near the "strongly divergent" SNP on chromosome

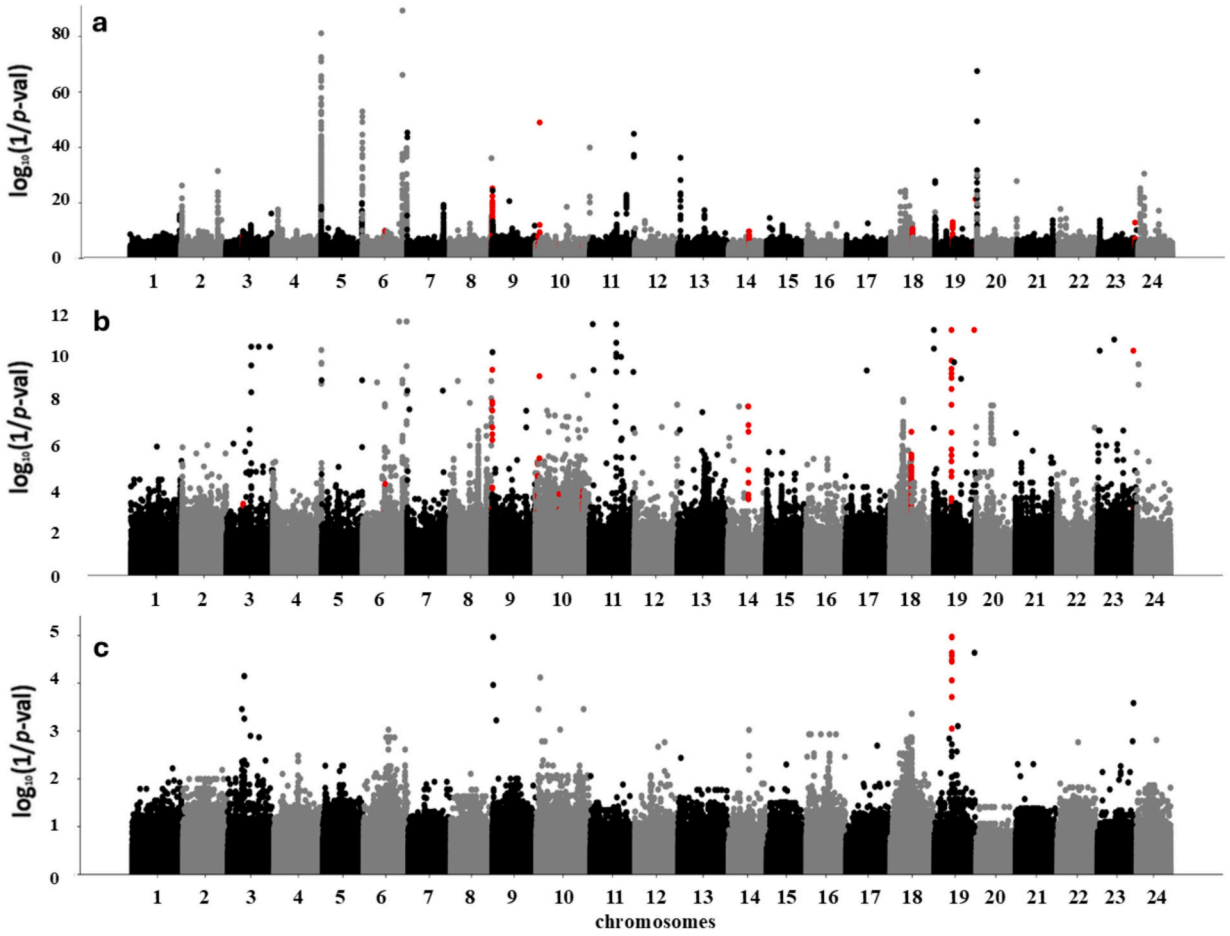

Fig. 3. Manhattan plots depict the statistical significance of tests from the three genome scan methods across the gilthead seabream genome. Panel "a" shows the $\log_{10}(1/p\text{-val})$ of Fisher's exact test in F_{ST}-based method using PoPoolation2, while panel "b" and "c" display the corresponding values from the Chi-squared distribution in XtX-based method and $C_{2,}$ respectively, using BayPass. *p*-values were adjusted for multiple testing using the Benjamini–Hochberg method. Red dots indicate genomic regions of SNPs with statistical significance at $\log_{10}(1/p\text{-val})$, corresponding to $P_{adj} = 10^{-3}$. These SNPs include those identified as "divergent" by meeting significance thresholds in both PoPoolation2 (F_{ST}) and BayPass (XtX), as well as those flagged by C_2 as "strongly divergent" between farmed and wild gilthead seabream populations. Chromosome names are labeled on the *x*-axis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

19 (Fig. S10).

Gene ontology enrichment analysis did not identify any GO categories significantly enriched after multiple-testing correction (FDR < 0.05). Network analysis using the STRING zebrafish interactome revealed 45 of the identified genes with potential regulatory and functional interactions (Fig. 4). Among these, *kdm6al* emerged as a central hub with numerous interaction partners, while *uba7*, *intu*, and *arl6ip1* also exhibited high connectivity. Importantly, *pigm* and *ahrra*, the two genes next to the "strongly divergent" SNP, were also network members, showing interactions with other candidate genes. This analysis identified multiple forms of connectivity among candidate genes, including co-regulation, functional associations, conserved genomic neighborhoods, co-expression, and biochemical interactions (Fig. 4).

4. Discussion

Domestication involves exposure to novel environmental, demographic and sensory conditions, and here we used a Pool-Seq dataset of gilthead seabream populations across the Mediterranean to investigate its genomic architecture. From nearly 5.3 million SNPs, we identified 58 protein-coding genes that were consistently differentiated between farmed and wild fish, highlighting them as candidate domestication loci. These genes were defined based on SNPs surpassing our differentiation thresholds across multiple statistics (F_{ST}, XtX and C_2) and located within or in close proximity (±100 kbp) to annotated protein-coding regions (Table S1). We emphasize that these represent positional candidate genes within differentiated genomic regions rather than confirmed causative targets of selection. Among these, *ahrra* and *pigm* showed the strongest divergence, while *kdm6al* emerged as a central hub in the inferred regulatory network.

Importantly, these genomic signals must be interpreted within the demographic and breeding context of Mediterranean seabream domestication. The separation of Greek farmed populations from Western Mediterranean stocks in PCA space (Fig. 2) supports heterogeneous breeding histories among farmed lineages. Previous SNP-based analyses have likewise shown that farmed gilthead seabream populations can exhibit measurable genetic differentiation from one another, whereas wild Mediterranean populations display comparatively weaker large-scale genetic structure (Gkagkavouzis et al., 2021). Because breeding programs were initiated independently across countries, typically using locally sourced broodstock, the farmed populations analyzed here likely represent multiple semi-independent domestication trajectories (Teletchea, 2021; Saura et al., 2021). Shared genomic signals, such as the chromosome 19 hotspot, may therefore reflect convergent responses to common aquaculture-related selective pressures, whereas other differentiated regions may represent lineage-specific divergence shaped by demographic history, and distinct breeding practices. Consistent with this interpretation, the Composite Selection Signal (CSS) analysis

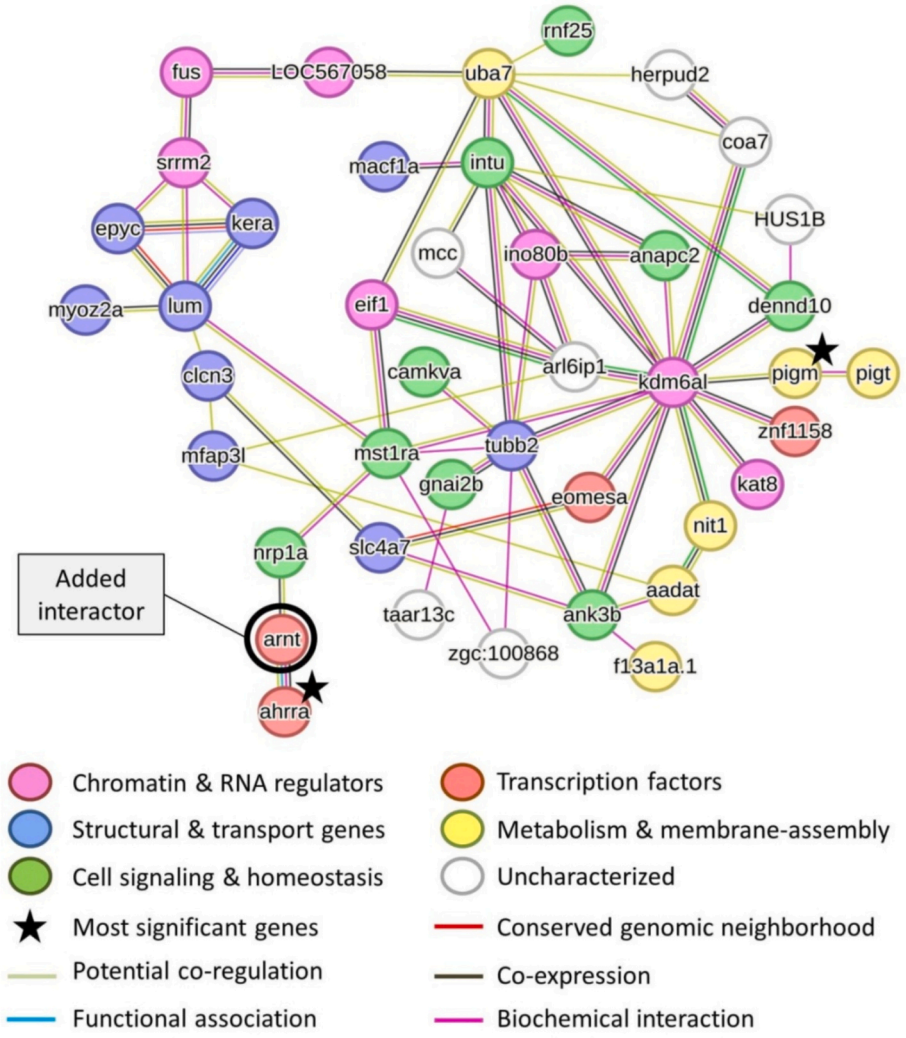

Fig. 4. Predicted interactions between the identified genes in this study. Out of the 58 protein coding genes, 46 showed potential functional/regulatory interactions through knowledge-based zebrafish interactome database (string-db.org). The connecting lines between the genes represent knowledge-based interactions in zebrafish such as protein binding, co-regulation, intracellular co-localization and biochemical interaction. *Arnt* was added as a known dimerization partner of *ahrra* to represent the AHR signaling pathway and reveal potential regulatory interactions with other candidate genes in the network.

reinforced the prominence of this region by identifying concordant differentiation signals across multiple statistical approaches, further supporting chromosome 19 as a robust candidate target of domestication-related divergence.

Within this framework of partially independent domestication pathways, the functional identity of the highlighted genes provides insight into the types of selection pressures operating under farming conditions. *Ahrra* encodes the aryl hydrocarbon receptor repressor A, a transcriptional modulator interacting with the ARNT/HIF axis and linking xenobiotic and oxygen-sensing pathways (Haarmann-Stemmann & Abel, 2006; Fang Li et al., 2021). *Pigm*, a GPI-anchor biosynthesis gene, may affect immune function, pathogen recognition and reproductive processes through the organization of cell-surface proteins (Almeida et al., 2006). *Kdm6al*, an H3K27 demethylase, forms a dominant hub that connects oxygen and stress responses to chromatin regulation (Chakraborty et al., 2019; Minikes et al., 2025). Comprehensive network interrogation revealed genes associated with environmental sensing and stress responses, including oxidative/xenobiotic stress, oxygen homeostasis, density-related injury, sensory-neural tuning, and pathogen/parasite defense.

Collectively, these findings indicate that domestication in gilthead seabream engages conserved regulators of environmental sensing and adaptation, linking genomic divergence to physiological and life-history traits relevant under farming conditions. Modern seabream breeding programs explicitly prioritize growth rate, feed efficiency, disease resistance, survival under intensive conditions, and product quality traits. However, domestication also imposes implicit selection pressures, including tolerance to high stocking densities, fluctuating oxygen regimes, handling stress, and altered sensory environments. The prominence of genes associated with oxygen sensing, stress integration, and chromatin regulation in our results suggests that adaptation to these implicit environmental pressures may leave clearer genomic signatures than highly polygenic traits such as growth or feed efficiency (Pritchard et al., 2010; Barghi et al., 2020), which may involve numerous small-effect loci that are more difficult to detect in pooled sequencing analyses (Schlötterer et al., 2014).

Given the relatively recent history of gilthead seabream domestication and the reduced effective population sizes of farmed stocks, it is plausible that some of these differentiated loci reflect linkage to nearby causative variants (genetic hitchhiking) rather than direct functional targets (Maynard Smith and Haigh, 1974; Nielsen et al., 2005; Höllinger et al., 2019). Accordingly, the genomic regions highlighted here may contain both adaptive mutations and linked neutral polymorphisms shaped by selection. The absence of significant GO enrichment further

suggests that domestication-related divergence in gilthead seabream is not concentrated within a single overrepresented functional pathway, but instead reflects distributed effects across multiple regulatory and physiological systems, consistent with a polygenic model of adaptation (Höllinger et al., 2019; Barghi et al., 2020). Arguably, many primary breeding targets in aquaculture, such as growth rate and feed efficiency, are highly polygenic traits influenced by numerous loci of small effect. Such architectures are less likely to produce strong, localized differentiation signals detectable through genome-wide outlier approaches, particularly under a pooled sequencing framework. In contrast, genes functioning as regulatory hubs or mediators of environmental sensing and stress integration may generate more pronounced divergence signals, especially under the combined influence of deliberate selection and intensive farming conditions. In addition to SNP-based divergence, structural variants, such as chromosomal inversions and copy number variation, may also contribute to domestication-related differentiation, as such variants are increasingly recognized as important drivers of adaptation and population divergence (Wellenreuther and Bernatchez, 2018; Mérot et al., 2020). However, their robust detection and characterization is limited under a pooled short-read sequencing framework and will require future studies incorporating individual-level resequencing and long-read genomic technologies.

The *ahrra* gene encodes the aryl hydrocarbon receptor repressor A, a nuclear protein that enables DNA-binding activity and functions as a transcriptional repressor in the cellular response to xenobiotic (foreign) compounds (Haarmann-Stemmann and Abel, 2006; Hahn et al., 2009). It acts upstream of the aryl hydrocarbon receptor (AHR) pathway through its principal interactor, ARNT (also known as HIF-1β), the aryl hydrocarbon receptor nuclear translocator, which serves as a shared dimerization partner for both AHR and components of the hypoxia-inducible factor (HIF) pathway (Abel and Haarmann-Stemmann, 2010; Haarmann-Stemmann and Abel, 2006; Vogel and Haarmann-Stemmann, 2017). While the AHR pathway is best known for mediating cellular responses to environmental pollutants and xenobiotics, with documented adaptive changes in wild fish populations inhabiting contaminated environments (Hamilton et al., 2016; Reid et al., 2016; Whitehead et al., 2017; Whitehead et al., 2012), the HIF pathway plays a central role in oxygen homeostasis and hypoxia tolerance across vertebrates (Li et al., 2021; Mandic et al., 2021).

Evidence from a range of taxa, including hybrid sturgeon under experimental hypoxia (Ren et al., 2024), schizothoracine fish from the Tibetan Plateau (Chen et al., 2020), crucian carp hybrids differing in hypoxia tolerance (Luo et al., 2024), and paddy field carp adapted to shallow, low-oxygen rice paddies (Li et al., 2025), demonstrates the centrality of HIF-axis genes, including ARNT, in coping with hypoxic conditions. Similar adaptive signals have been detected in farmed common carp (Cheng et al., 2024; Suo et al., 2022) and Australasian snapper exposed to aquaculture stressors such as high temperature and crowding (Wellenreuther and Bernatchez, 2018), which often co-occur with fluctuating oxygen availability. In aquaculture contexts, variation in HIF signaling has been implicated in adaptation to farming environments with variable or low oxygen availability (Shen et al., 2023), as shown in farmed strains such as paddy field carp (Li et al., 2025), where the HIF-1 pathway appears to contribute to enhanced hypoxia resilience. Beyond fish, convergent selection on HIF-pathway genes has been reported in multiple high-altitude and hypoxia-tolerant species, including Tibetan sheep (Song et al., 2024), yaks (Wu, 2016; Xiong et al., 2015), Tibet chicken embryos (Liu et al., 2020), plateau-adapted dogs (Gou et al., 2014), and reindeer (Pokharel et al., 2023), as well as in goats acclimatized to high elevation (Tang et al., 2025), emphasizing the pathway's broad evolutionary importance. Even in non-hypoxia stress contexts, such as acute heat exposure in golden pompano (*Trachinotus ovatus*) (Li et al., 2023), and high-temperature adaptation in carp (Cheng et al., 2024), HIF signaling can be part of the integrated stress response.

Although direct evidence for AHR pathway involvement in domestication is currently limited, its interaction with ARNT links it functionally to the HIF system, suggesting that selection on genes such as *ahrra* could influence both xenobiotic sensitivity and oxygen-related physiological traits relevant to adaptation in farming conditions. Repeated cases of strong selection on the AHR axis in pollution-tolerant killifish (Miller et al., 2024; Reitzel et al., 2014) demonstrate how environmental stressors can shape this pathway. Variation in AHR-related genes has also been linked to adaptive traits, including immune responses (Segner et al., 2021), morphological divergence in Arctic charr and groupers (Ahi et al., 2015), and molecular adaptations in deep-sea fishes (Lemaire et al., 2018). Together, these examples highlight how toxins, hypoxia and developmental pressures can all drive divergence through ARNT-centered signaling.

The *pigm* gene encodes a transmembrane protein with mannosyltransferase activity that is located in the endoplasmic reticulum and is involved in glycosylphosphatidylinositol (GPI)-anchor biosynthesis (Almeida et al., 2006). In mammals and other eukaryotes, PIG-M (GPI mannosyltransferase I) catalyzes the first mannose addition to the GPI precursor within the ER lumen, a committed step in assembling mature GPI anchors (Kinoshita et al., 2008; Maeda et al., 2001). The GPI-anchor is found on many blood cells and anchors proteins to the cell surface; thus, *pigm* function is required to maintain homeostasis of blood coagulation and neurological function (Almeida et al., 2006). Although direct studies on *pigm* in fish are scarce, metabolic genes are often implicated in adaptive responses to domestication and farming environments, where shifts in diet, growth rate, and immune function exert selection pressures. Consistent with a role in stress and disease resistance, a vertebrate PIG-M ortholog enhances antiviral defense in the Chinese giant salamander (*Andrias davidianus*) during iridovirus challenge, implicating GPI-anchor biosynthesis in host protection under pathogen pressure (Zhang et al., 2019). Interestingly, infections by iridoviruses—particularly lymphocystis disease virus (LCDV), the most frequently reported viral pathology in gilthead seabream farms (Cordero et al., 2016)—remain a major and persistent challenge in Mediterranean aquaculture (Leiva-Rebollo et al., 2020; López-Bueno et al., 2016; Mhalhel et al., 2023). While megalocytiviruses such as RSIV are important in marine finfish, recent risk assessments suggest that nearby wild fish are not a significant source of RSIV outbreaks (Kawato et al., 2024). These findings suggest that the observed SNP differentiation in *pigm* may reflect differences in resistance to related viral infections between farmed and wild gilthead seabream populations in this study. Moreover, multiple fish pathogens rely on GPI-anchored surface antigens, e.g., the I-antigens of *Ichthyophthirius multifiliis* (Clark et al., 2001) and mucin-like glycoproteins of the freshwater-fish parasite *Trypanosoma carassii* (Borges et al., 2021; Lischke et al., 2000), and GPI-anchor signals from *Cryptocaryon irritans* drive robust surface display in *Tetrahymena* (Watanabe et al., 2024), underscoring the host–parasite interface where variation in GPI-AP biogenesis (potentially via *pigm* function) could alter susceptibility and immune recognition.

Beyond immunity, GPI-anchored proteins also shape reproductive interactions; in guppy (*Poecilia reticulata*), the Ly6/uPAR protein Bouncer, a GPI-AP, regulates sperm binding to oocytes, suggesting that shifts in GPI-anchor biosynthesis may influence fertilization traits that often diverge between farmed and wild stocks (Yoshida et al., 2024). These organismal and mechanistic observations align with broader evidence that GPI anchors act as evolutionary “linchpins” organizing surface repertoires across eukaryotes, making the biogenesis pathway, including PIG-M, a plausible target of selection under domestication (Borges et al., 2021). Thus, variation in *pigm* may affect glycosylation-dependent processes, including nutrient utilization efficiency, structural cell integrity, and possibly pathogen defense, traits that are critical under aquaculture conditions. This functional relevance, combined with its identification among divergent genes in farmed gilthead seabream, positions *pigm* as a credible candidate influencing metabolic adaptation during fish domestication and breeding. Taken together, the links to pathogen defense and fertilization provide concrete routes by which pigm-mediated tuning of the GPI-anchored proteome could contribute

to phenotypic divergence between farmed and wild fish populations.

Except for the two most significant genes already discussed, 46 SNPs located near protein-coding genes that differentiate farmed from wild gilthead seabream formed an interconnected regulatory/functional interaction map-based knowledge-based zebrafish interactome. These positional associations were inferred based on physical proximity and functional annotation; consequently, they should be interpreted as candidate signals pending higher-resolution validation. These candidates formed connected subnetworks (hubs) in which the ortholog *kdm6al* showed the highest degree, marking it as the principal hub (Fig. 4). KDM6A is an H3K27 demethylase that links oxygen status to chromatin regulation (Chakraborty et al., 2019) and can also mediate HIF-independent oxygen sensing relevant to ferroptosis (Minikes et al., 2025), providing a direct route from environmental oxygen to gene-expression programs. Interestingly, ferroptosis-related mechanisms are emerging as adaptive responses of fish to hypoxic conditions (Chen et al., 2025; Hu et al., 2022; Wang et al., 2025a, 2025b; Zhang et al., 2025). Across vertebrates, *KDM6A* repeatedly appears among leading candidates in adaptation and domestication. Signals including *KDM6A* are reported for helmeted guinea fowl domestication (Shen et al., 2021), altitudinal selection in dairy sheep (Ben Jemaa et al., 2025), and horse domestication (Gu et al., 2023). In goats, a *KDM6A* indel associates with litter size, genome-wide scans implicate *KDM6A* in selection for this trait (Cui et al., 2018; Lai et al., 2016), and studies of heat-stress tolerance in subtropical herds also highlight this locus (Aboul-Naga et al., 2025). In aquaculture, dense genome-wide analyses in farmed coho salmon detect selection signatures that include *kdm6a* (López et al., 2021). Complementary fish studies reinforce a chromatin-regulatory role in environmental responses: a survey of chromatin-modifying enzymes in stickleback emphasizes *Kdm6a* within an adaptation-relevant toolkit (Fellous and Shama, 2019); endocrine perturbation in Nile tilapia shows broad gonadal transcriptional shifts consistent with developmental plasticity (Teng et al., 2021); Atlantic killifish adapted to polluted, hypoxic estuaries exhibit coordinated gene-expression and DNA-methylation changes (Aluru et al., 2025); hilsa shad diverge morpho-genetically across heterogeneous migratory habitats (Asaduzzaman et al., 2020); and a retained chromosomal inversion underlies alternative freshwater ecotypes in rainbow trout (Arostegui et al., 2019). Together, the network topology (*kdm6al* as the dominant hub) and the convergent literature across domestication, altitude, heat stress, reproduction, hypoxia/pollutants, and aquaculture selection support a *KDM6A*-centered regulatory axis as a credible mediator of environment-to-phenotype change. However, whether *kdm6al* itself represents the primary selective target or is embedded within a broader linked haplotype remains to be resolved. Disentangling these possibilities will require finer-scale analyses of haplotype structure, allele-specific expression, and functional perturbation. In gilthead seabream, this is consistent with contrasts between farmed and wild conditions (e.g., oxygen regimes, temperature profiles, density, diet). In future, focused validation, allele-specific and seasonal expression assays, H3K27 mark profiling, and genotype-by-environment tests, should clarify how *kdm6al*-linked networks contribute to domestication-related traits in gilthead seabream.

Finally, the functional search for the rest of the genes within the identified network in the context of their potential involvement in sensing and responding to relevant environmental stressors in farming conditions revealed that an oxygen/xenobiotic–oxidative stress axis includes: *coa7*, *nrp1a*, *herpud2*, *arl6ip1*, *kat8*, *ino80b*, *hus1b*, *anapc2*, *eif1*, *fus*, *srrm2*, *aadat*, *slc4a7* and *clcn3* (Blondeau-Bidet et al., 2023; Chee et al., 2019; Chen et al., 2007; Du et al., 2025; Hasvold et al., 2016; Jakubauskienė and Kanopka, 2021; Mellor et al., 2025; Povea-Cabello et al., 2024; Schwappacher et al., 2013; Schweizer et al., 2023; Seigneuric et al., 2007; Soto et al., 2025; Takahashi et al., 2017; Torosyan et al., 2021; Wang et al., 2025a, 2025b; You et al., 2025; Zang et al., 2025; Zhang et al., 2019); density related physical injury (barrier repair, tissue regeneration and wound healing): *f13a1a.1*, *lum*, *kera*, *epyc*, *mfap3l*, *macf1a*, *mcc*, *nit1* (Alshehri et al., 2021; Hu et al., 2017; Mahapatra et al., 2023; Mohammadi et al., 2022; Peracchi et al., 2017; Segars and Trinkaus-Randall, 2023; Senda et al., 1999; Yamanaka et al., 2013); sensory–neural tuning (hydrodynamics/noise/light): *intu/cplane4*, *tubb2*, *ank3b*, *camkva*, *myoz2a*, *taar13c* (Choi et al., 2021; Gomez-Campo et al., 2024; Ippolito et al., 2021; Martín-salazar and Valverde, 2022; Miettinen et al., 2023; Watanabe et al., 2024; Zhao et al., 2025); and pathogen/parasite pressure: *uba7*, *rnf25/ao7*, *gnai2b*, *pigt*, *mst1ra* (Grimholt et al., 2025; Hahn et al., 2022; Ham et al., 2024; Jing et al., 2022; Liu and Malik, 2006; Salisbury et al., 2024; Zhang et al., 2023). Together, these assignments suggest that domestication in gilthead seabream taps conserved environmental sensing and adaptive response genes. See Fig. 5 for the gene–stressor mapping that underpins these conclusions. These findings therefore provide a region-level framework for understanding domestication-associated divergence in gilthead seabream and establish a foundation for future fine-mapping and experimental validation.

The repeated involvement of hypoxia- and stress-related pathways is also particularly relevant in the context of projected climate change in the Mediterranean, where rising sea surface temperatures and variable dissolved oxygen levels are expected to increase environmental stress in aquaculture systems (Bindoff et al., 2019). These trends are anticipated to intensify thermal and hypoxic stress in coastal farming environments (Saraiva et al., 2019). Although our study does not directly assess climate adaptation, loci associated with oxygen sensing and stress integration may contribute to physiological resilience under warming and hypoxic conditions. Incorporating genomic information from these candidate regions into selective breeding programs could therefore, in principle, support the development of more climate-resilient farmed stocks. However, functional validation and genotype–environment interaction studies will be required to determine the extent to which these loci confer advantages under future climatic scenarios.

5. Conclusion

This study provides a genome-wide overview of domestication-driven genetic divergence in gilthead seabream, identifying genomic regions and candidate genes associated with life-history traits and the molecular circuitry of environmental sensing, including stress response, immune function, disease resistance, and reproduction. By integrating Pool-Seq data from 20 populations across the Mediterranean in farmed–wild comparisons with robust genome scan and network analyses, we uncovered 58 candidate genes near highly differentiated SNPs, with a particularly strong signal on chromosome 19. Among these, *ahrra*, *pigm*, and *kdm6al* emerged as strong candidates based on their genomic differentiation and known regulatory roles. These candidate genes are linked to pathways such as ARNT/HIF signaling, GPI-anchor biosynthesis, and epigenetic regulation via chromatin remodeling; core mechanisms by which organisms translate oxygen availability and chemical cues into coordinated immune, endocrine, metabolic, and reproductive outcomes beyond any single aquaculture context. While the specific genomic targets differ among populations, the implicated functions are strikingly consistent and are shared broadly across animals, hinting at constrained evolutionary routes and a degree of predictability in responses to captivity. Our results indicate that domestication acts on a conserved set of interconnected regulators that control sensory and hypoxia/chemical signaling and its downstream physiological integration. The recurrent involvement of *kdm6al* across vertebrate studies, alongside our signal here, suggests that this locus or its surrounding regulatory landscape may represent a conserved hub frequently involved in adaptive divergence that aligns developmental programs with stress and immune responses. Likewise, the roles of *ahrra* and *pigm* in oxygen sensing and host defense suggest a general mechanism for rapid adjustment to aquaculture environments, where fluctuating oxygen regimes and pathogen exposure are pervasive. Overall, this work connects microevolution under captivity to fundamental biology

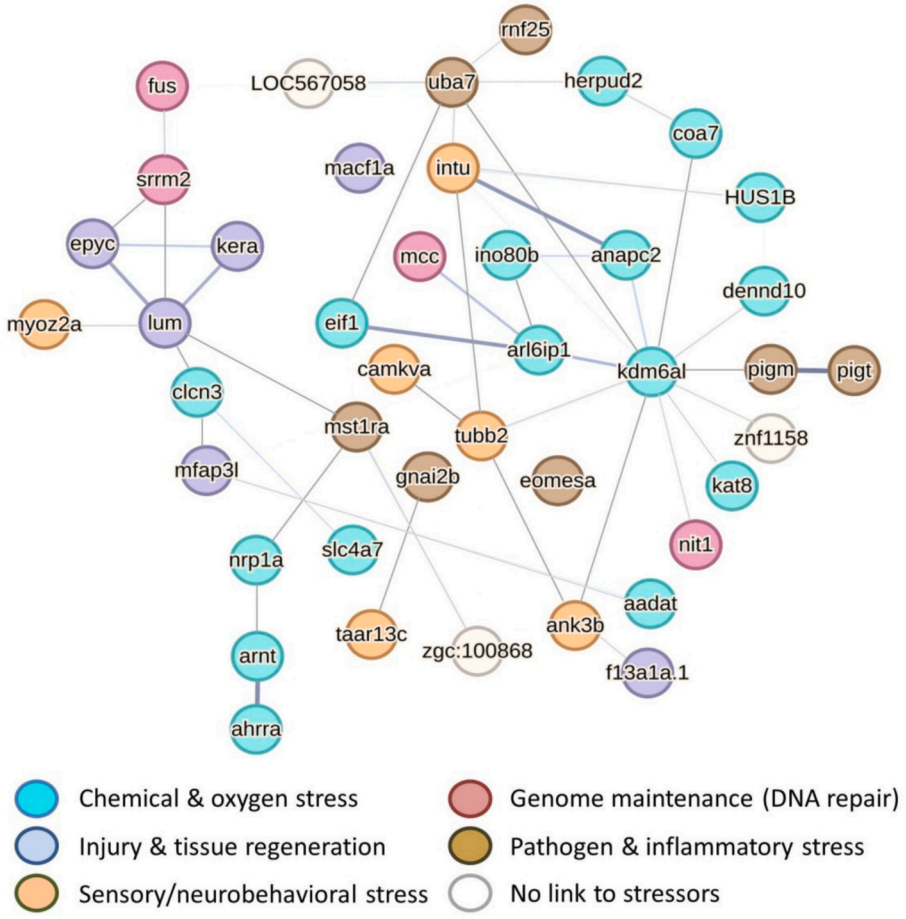

Fig. 5. Predicted links between the network genes and various environmental stressors. Links to the stressors were inferred by integrating: (i) orthology-based annotations (Ensembl, UniProt, and ZFIN), (ii) Reactome and KEGG data, and (iii) peer-reviewed literature, prioritizing teleost evidence and the most relevant farm stressor (hypoxia; nitrogenous wastes/chemicals/oxidants; density related physical injury; hydrodynamics, noise and light; pathogen pressure).

by showing how long-standing sensory and regulatory circuits are retuned during domestication, and it offers a comparative framework and tractable gene sets for testing general principles of rapid adaptation relevant to aquaculture. The candidate genes identified here are promising targets for functional assays and comparative analyses, and they provide markers to guide broodstock selection, track domestication trajectories and interactions between cultured and wild populations.

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Ethical approval

No ethical approval was required for this study, as it used previously published datasets and did not involve any new animal experimentation. All data used were obtained from publicly available sources that complied with relevant ethical and legal standards at the time of their collection.

CRediT authorship contribution statement

Aristotelis Moulistanos: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Alexandros Mitsis:** Visualization, Methodology. **Konstantinos Gkagkavouzis:** Writing – review & editing, Visualization, Project administration, Methodology. **Nikoleta Karaiskou:** Writing – review & editing, Project administration, Methodology. **Efthimia Antonopoulou:** Writing – review & editing, Supervision, Methodology, Investigation. **Alexandros Triantafyllidis:** Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Ehsan Pashay Ahi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Spiros Papakostas:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

Authors declare no competing interests.

Data availability

We have shared the data publically and in the attached files

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