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 behaviour under human-controlled 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 and wild populations spanning the Mediterranean, our analyses reveal divergence at key genes involved in pathways that translate oxygen and chemical cues into immune, endocrine and reproductive outcomes. Standout candidates include *ahrra* within the ancient AHR–ARNT/HIF signalling system, *kdm6al*, a chromatin regulator coordinating developmental and stress responses, and *pigm*, a GPI-anchor biosynthesis gene shaping cell-surface composition and host defence. These functions are shared widely across animals, from invertebrates to vertebrates, suggesting that domestication often proceeds by tuning long-standing sensory circuitry to human-altered conditions. This convergence points to a measure of predictability in the genomic response to captivity, links molecular pathways to ecological traits such as stress tolerance and reproduction and offers broad 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.

Keywords: artificial selection; genome-wide divergence; environmental sensing mechanisms; rapid adaptation; marine teleost

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 value of molecular ecology approaches, particularly genome-wide scans, in identifying genes mediating adaptive responses (Jia and Zhao 2014; Liu et al., 2017; Uffelmann et al., 2021; Tsare, Klapa, and Moschonas 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 et al., 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, is an excellent model for investigating early-stage domestication. Selective breeding began in the 1990s, and farmed populations have since experienced reduced effective population sizes over the past five generations, accompanied by marked genetic differentiation from their wild counterparts (Teletchea, 2021; Saura et al., 2021; Gkagkavouzis et al., 2021; Penaloza et al., 2021; Villanueva et al., 2022). 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., 2023; Moulistanos et al., 2025). However, a comprehensive genome-wide analysis of 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. Previously, we 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., 2023). This analysis revealed regions of marked differentiation between farmed and wild populations, underscoring the dataset’s potential to uncover selection targets associated with domestication (Moulistanos et al., 2023). Here, we extend the investigation genome-wide to identify genes and genomic regions associated with domestication-related traits, thereby providing novel insights into the molecular mechanisms of adaptation to human-controlled environments.

Materials and Methods

Studied populations

We analyzed pooled whole-genome sequencing data from 10 farmed and 10 wild gilthead seabream populations (Table 1; Figure 1), sampled across six Mediterranean countries (Peñaloza et al., 2021). To ensure analytical robustness, we excluded seven populations from the original dataset, which initially comprised 12 farmed and 15 wild 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).

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 & 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).

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 & 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.

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 & 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 & 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).

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.

Functional annotation and gene network analysis

For each "divergent" and "strongly divergent" SNP, we identified neighboring genes located within a 200-kilobase (Kbp) window centered on the SNP (±100 Kbp) (Barson et al. 2015; Star et al. 2016). 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 seabass_V1.0 assembly (GenBank ID: GCA_000689215.1) 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}.

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 & Haarmann-Stemmann, 2010; Haarmann-Stemmann & Abel, 2006; Vogel & Haarmann-Stemmann, 2017).

Results

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 (Figure 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) (Figure 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 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 (Figure 3a,b; Table S1). Among these, one SNP on chromosome 19 was uniquely identified as "strongly divergent" using the C_2 statistic ($C_2 = 34.732$, $P\mathit{adj} = 8.71 \times 10^{-5}$; Figure 3c), highlighting strong selective differentiation at this locus between farmed and wild populations.

Annotation of sequences within 200 Kbp window of each selected SNP identified 10 of the 13 SNPs, distributed across six chromosomes, encompassing 62 protein-coding genes corresponding to 58 unique zebrafish orthologs (chromosomes 3, 10, 11, 14, 19, and 23; Table S1). Notably, two genes—*pigm* and *ahrra*—were positioned near the "strongly divergent" SNP on chromosome 19, suggesting potential involvement in population-specific adaptations.

Network analysis using the STRING zebrafish interactome revealed 45 of the identified genes with potential regulatory and functional interactions (Figure 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 (Figure 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. Among these, *ahrra* and *pigm* showed the strongest divergence, while *kdm6al* emerged as a central hub in the inferred regulatory network. *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, Qiao, Duan, & Nevo, 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.

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 & Abel, 2006; Hahn, Allan, & Sherr, 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 & Haarmann-Stemmann, 2010; Haarmann-Stemmann & Abel, 2006; Vogel & 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, Clark, Reid, Hahn, & Nacci, 2017; Whitehead, Pilcher, Champlin, & Nacci, 2012), the HIF pathway plays a central role in oxygen homeostasis and hypoxia tolerance across vertebrates (Fang Li, Qiao, Duan, & Nevo, 2021; Mandic, Joyce, & Perry, 2021).

Evidence from a range of taxa, including hybrid sturgeon under experimental hypoxia (Ren, Tian, Cheng, Liu, & Yu, 2024), schizothoracine fish from the Tibetan Plateau (J. Chen et al., 2020; Guan, Chi, Xiao, Chen, & He, 2014), crucian carp hybrids differing in hypoxia tolerance (Luo et al., 2024), and paddy field carp adapted to shallow, low-oxygen rice paddies (Fangcheng 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, Le Luyer, Cook, Ritchie, & Bernatchez, 2019), 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 (Y. Shen et al., 2023), as shown in farmed strains such as paddy field carp

(Fangcheng 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 et al., 2015; Xiong et al., 2015), Tibet chicken embryos (Liu, Wang, Liu, Wang, & Bao, 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*) (Q. Q. Li et al., 2023), and high-temperature adaptation in carp (Cheng et al., 2024; W. He, Cao, & Fu, 2015), 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 (R. He et al., 2020; Segner et al., 2021), morphological divergence in Arctic charr and groupers (Ahi et al., 2015; R. He et al., 2020), 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, Fujita, & Maeda, 2008; Maeda et al., 2001). The GPI-anchor is found on many blood cells andanchors 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., 2022). Interestingly, infections by iridoviruses—particularly lymphocystis disease virus (LCDV), the most frequently reported viral pathology in gilthead seabream farms (Cordero, Cuesta, Meseguer, & Esteban, 2016)—remain a major and persistent challenge in Mediterranean aquaculture (Leiva-Rebollo, Labella, Borrego, & Castro, 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, Gao, Gaertig, Wang, & Cheng, 2001) and mucin-like glycoproteins of the freshwater-fish parasite *Trypanosoma carassii* (Borges, Link, Engstler, & Jones, 2021; Lischke et al., 2000), and GPI-anchor signals from *Cryptocaryon irritans* drive robust surface display in *Tetrahymena* (Watanabe, Asada, Inokuchi, Kotake, & Yoshinaga, 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 seabass formed an interconnected regulatory/functional interaction map-based knowledge-based zebrafish interactome. These candidates formed connected subnetworks (hubs) in which the ortholog *kdm6al* showed the highest degree, marking it as the principal hub (Figure 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 (X. Q. Chen et al., 2025; Hu, Li, Xu, & Chen, 2022; J. Wang et al., 2025; Q. Wang et al., 2025; 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 (Q. K. 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, Cádiz, Rondeau, Koop, & Yáñez, 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 & Shama, 2019); endocrine perturbation in Nile tilapia shows broad gonadal transcriptional shifts consistent with developmental plasticity (Teng, Zhao, Chen, Xue, & Ji, 2021); Atlantic killifish adapted to polluted, hypoxic estuaries exhibit coordinated gene-expression and DNA-methylation changes (Aluru, Venkataraman, Murray, & DePascuale, 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, Quinn, Seeb, Seeb, & McKinney, 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. In seabass, 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 seabass.

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, Lohse, & Brothers, 2019; L. M. Chen, Choi, Haddad, & Boron, 2007; Du et al., 2025; Hasvold et al., 2016; Jakubauskienė & Kanopka, 2021; Mellor et al., 2025; Povea-Cabello, Brischigliaro, & Fernández-Vizarra, 2024; Schwappacher et al., 2013; Schweizer et al., 2023; Seigneuric et al., 2007; Soto, Pinilla, Olguín, & Castañeda, 2025; Takahashi et al., 2017; Torosyan et al., 2021; M. qing Wang et al., 2025; You et al., 2025; Zang et al., 2025; Z. Bin 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, Whyte, & Mutch, 2021; L. Hu et al., 2017; Mahapatra, Naik, Swain, & Mohapatra, 2023; Mohammadi, Sorensen, & Pilecki, 2022; Peracchi et al., 2017; Segars & Trinkaus-Randall, 2023; Senda, Matsumine, Yanai, & Akiyama, 1999; Yamanaka et al., 2013); sensory–neural tuning (hydrodynamics/noise/light): *intu/cplane4*, *tubb2*, *ank3b*, *camkva*, *myoz2a*, *taar13c* (Choi, Duboue, Macurak, Chanchu, & Halpern, 2021; Gomez-Campo et al., 2024; Ippolito, Thapliyal, & Glauser, 2021; Martín-salazar & Valverde, 2022; Miettinen et al., 2023; S. Watanabe et al., 2022; Zhao et al., 2025); and pathogen/parasite pressure: *uba7*, *rnf25/ao7*, *gnai2b*, *pigt*, *mst1ra* (Grimholt, Sindre, & Sundaram, 2025; M. A. Hahn et al., 2022; Ham et al., 2024; Jing et al., 2022; S. F. Liu & Malik, 2006; Salisbury et al., 2024; H. Zhang et al., 2023). Together, these assignments suggest that domestication in seabass taps conserved environmental sensing and adaptive response genes. See Figure 5 for the gene–stressor mapping that underpins these conclusions.

Conclusion

This study provides a genome-wide overview of domestication-driven genetic divergence in gilthead seabream, identifying key genes and genomic regions associated with life-history traits and the molecular circuitry of environmental sensing, including stress response, immune function, and reproduction. By integrating Pool-Seq data from 20 populations across the Mediterranean in farm–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 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 husbandry 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, points to a broadly conserved regulatory hub under selection 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 human-altered environments, where fluctuating oxygen regimes and pathogen exposure are pervasive. Overall, this work connects microevolution under captivity to fundamental biology 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 across taxa. The candidate genes identified here are promising targets for functional assays and comparative analyses, and they provide markers to track domestication trajectories and interactions between cultured and wild populations.

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Author Contributions

A.Mo: data curation (equal), investigation (equal), methodology (equal), project administration (supporting), visualization (equal), writing – original draft (equal), writing – review and editing (equal). **A.Mi**: methodology (supporting), visualization (supporting). **K.G**: methodology (supporting), project administration (equal), visualization (supporting), writing – review and editing (supporting). **N.K**: methodology (supporting), project administration (supporting), writing – review and editing (supporting). **E.A**: investigation (supporting), methodology (supporting), supervision (supporting), writing – review and editing (supporting). **A.T**: conceptualization (supporting), funding acquisition (supporting), investigation (supporting), methodology (supporting), project administration (supporting), supervision (equal), writing – review and editing (supporting). **E.P.A:** conceptualization (supporting), investigation (equal), methodology (equal), visualization (supporting), writing – original draft (equal), writing – review and editing (lead). **S.P**: conceptualization (lead), data curation (lead), formal analysis (lead), funding acquisition (lead), investigation (equal), methodology (equal), project administration (equal), resources (lead), software (lead), supervision (equal), validation (lead), visualization (equal), writing – original draft (equal), writing – review and editing (lead).

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Competing financial interests

Authors declare no competing interests.

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.

Data availability

Raw sequence reads are available in NCBI's Sequence Read Archive (SRA) under accession number PRJEB40423. All the scripts developed for the data analysis are available on GitHub: https://github.com/spirospapakostas/PoolSeq_Sparus_aurata_Domestication.git.

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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).

Origin	Population ID	Country	Number of individuals per pool	Number 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 Penaloza et al. (2021)

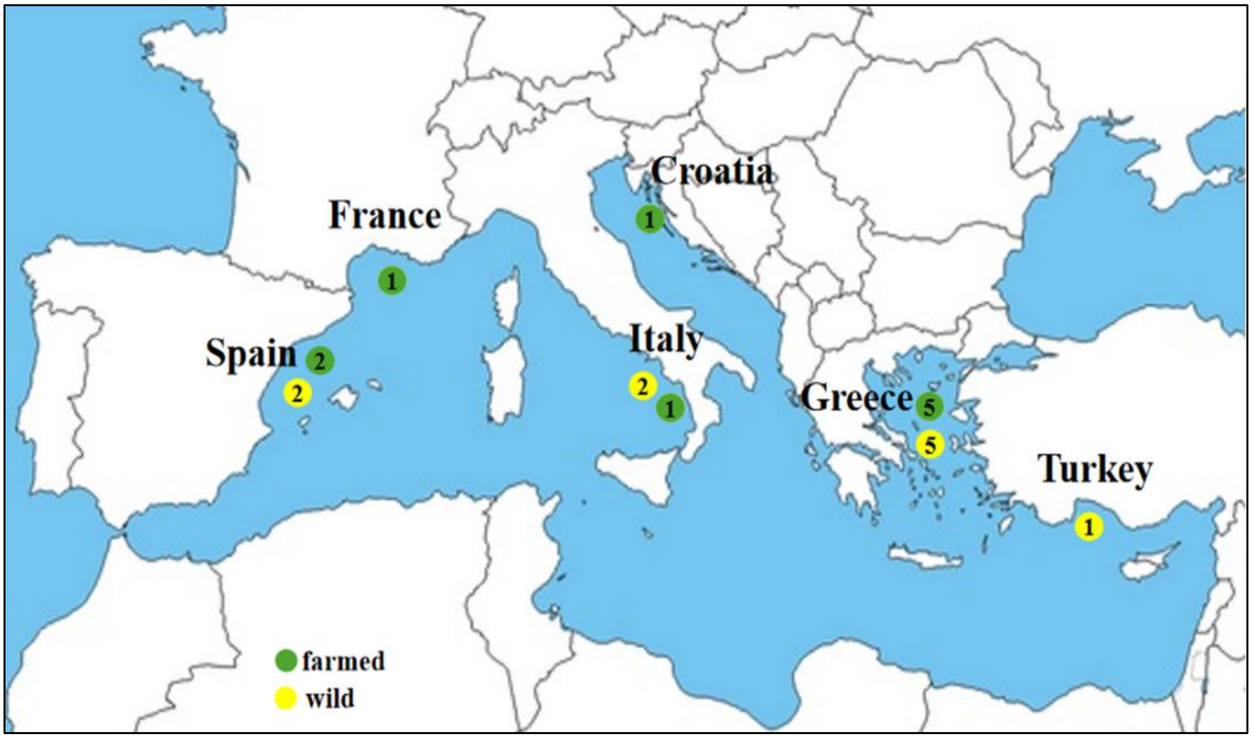

Figure 1. Geographic distribution of studied farmed and wild gilthead seabream populations in the Mediterranean region.

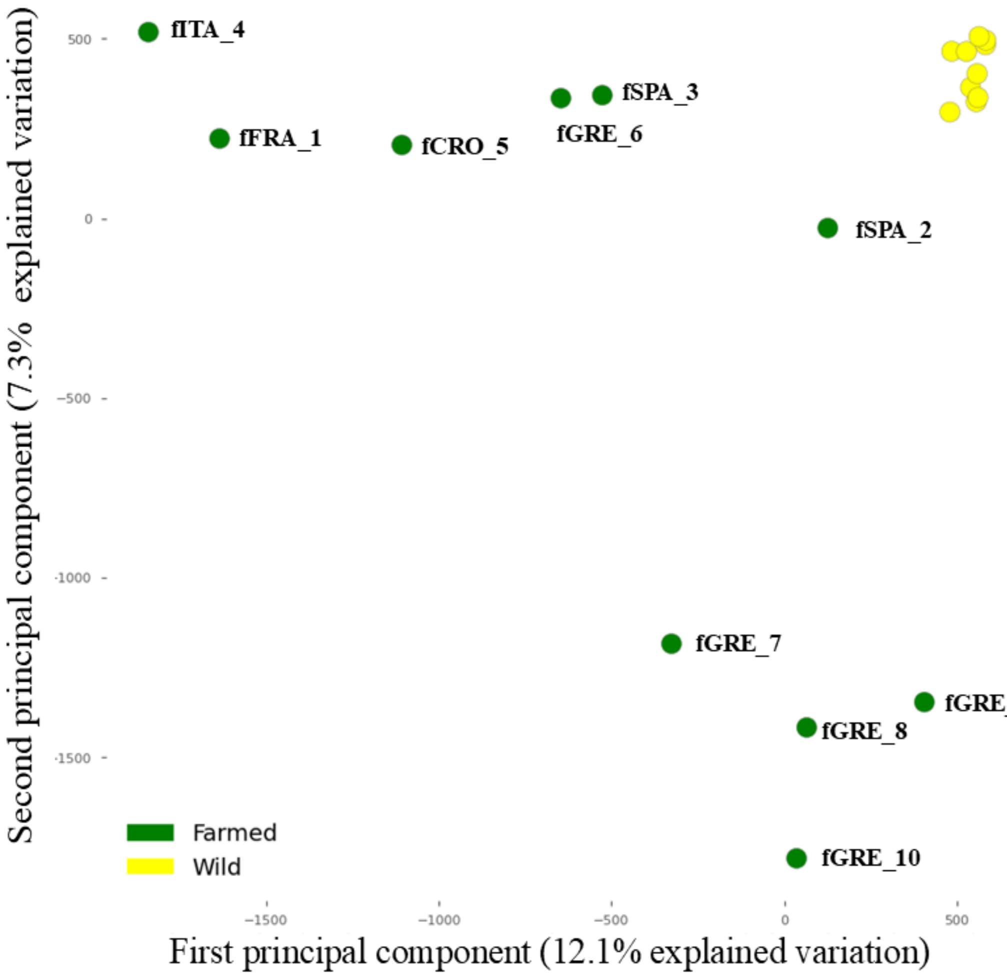

Figure 2. Population structure of studied gilthead seabream populations. Principal component analysis (PCA) was conducted on 5,282,885 SNPs for the farmed and wild populations of gilthead seabream across the Mediterranean region with information of each population ID based on Table 1.

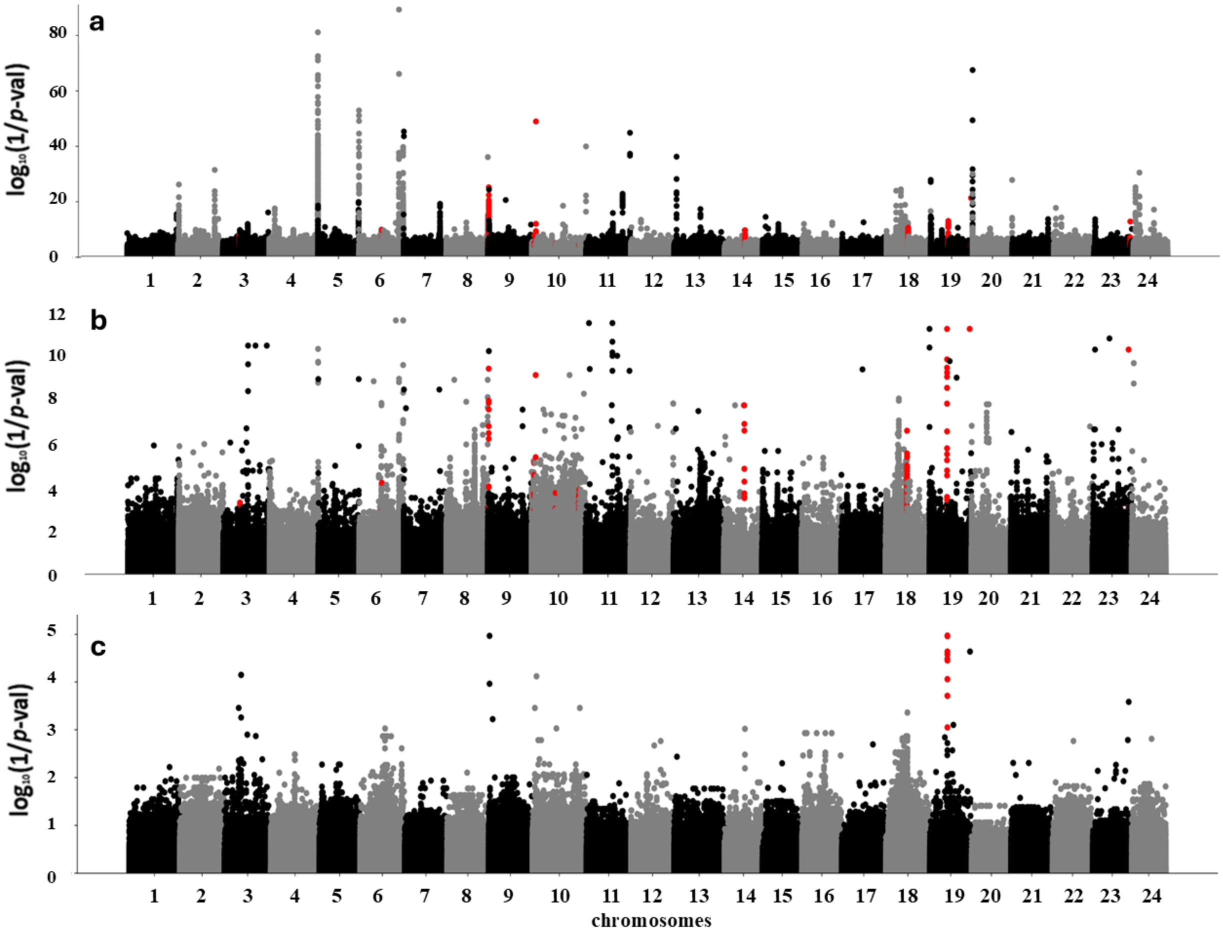

Figure 3. Manhattan plots depict the statistical significance of tests from the three genome scan methods across the gilthead seabream genome. Panel "a" shows the $\log_{10}(1/p\text{-val})$ of Fisher's exact test in F_{ST}-based method using PoPoolation2, while panel "b" and "c" displays the corresponding 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. Chromosomes' names are labeled on the *x*-axis.

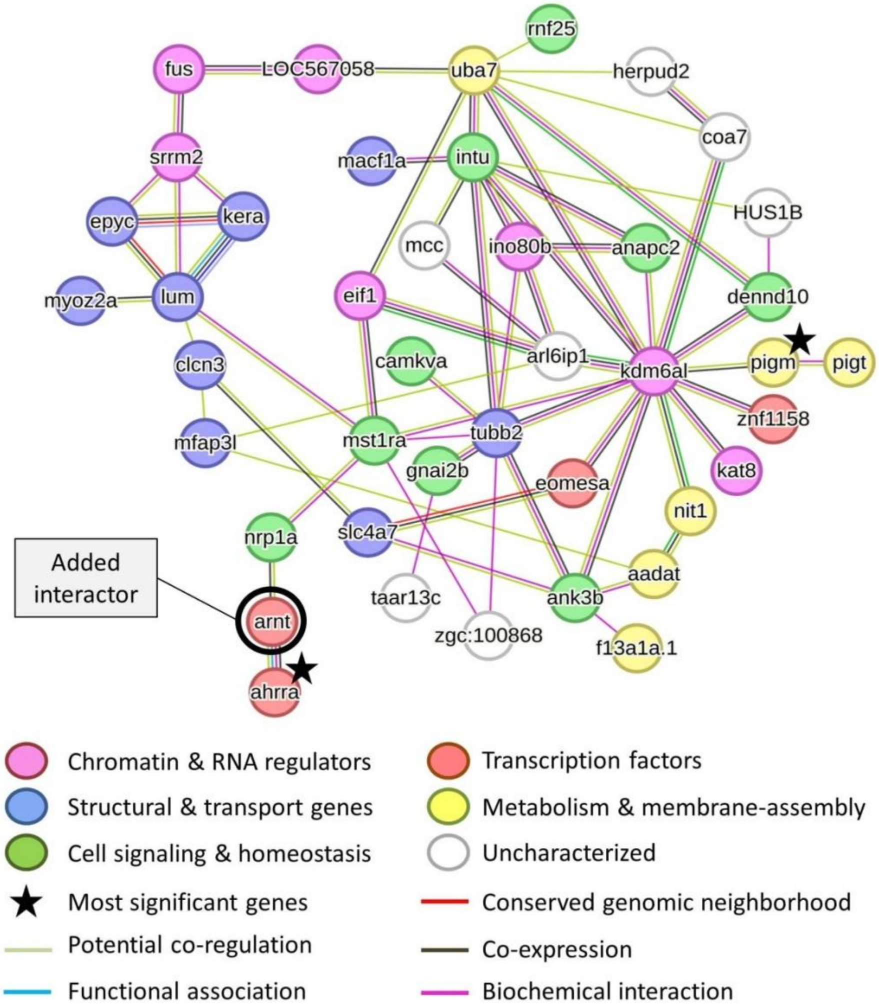

Figure 4. Predicted interactions between the identified genes in this study. Out of the 58 protein coding genes, 46 showed potential functional/regulatory interactions through knowledge-based zebrafish interactome database (string-db.org). The connecting lines between the genes represent knowledge-based 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.

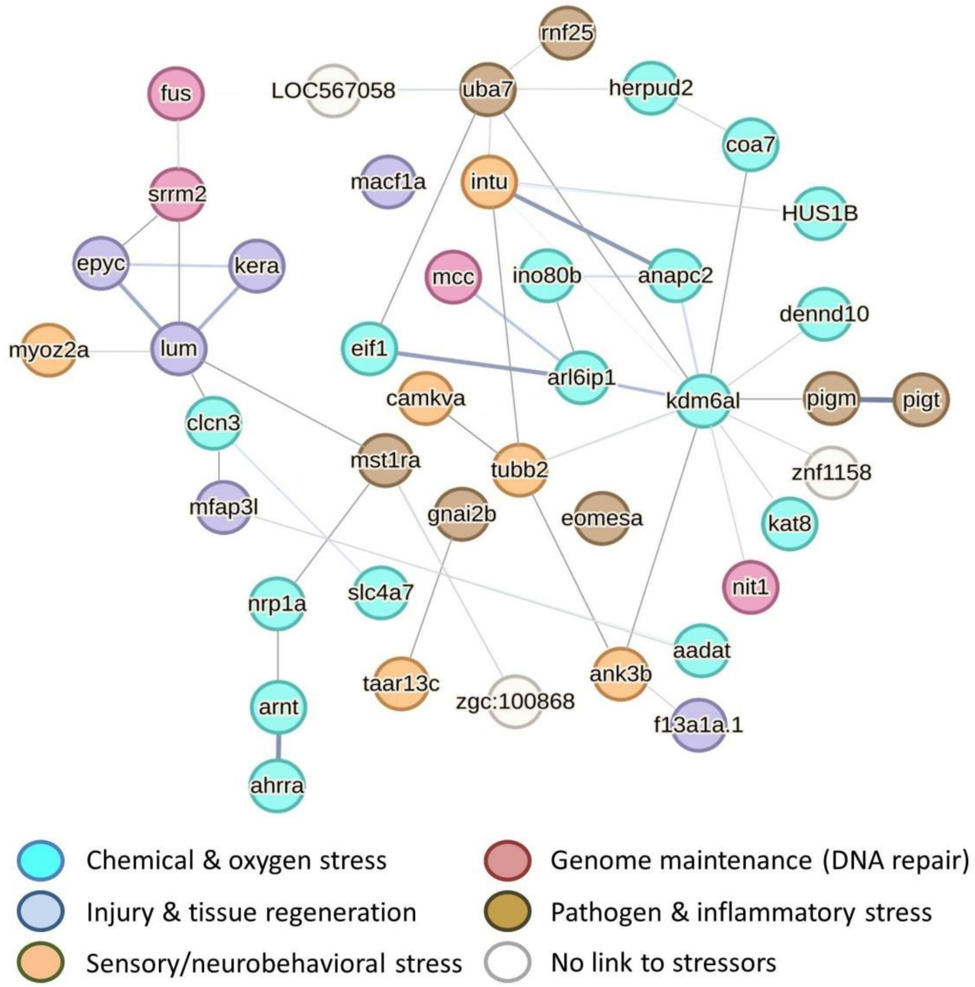

Figure 5. Predicted links between the network genes and various environmental stressors. Links to the stressors were inferred by integrating: (i) orthology-based annotations (Ensembl, UniProt, and ZFIN), (ii) Reactome and KEGG data, and (iii) peer-reviewed literature, prioritizing teleost evidence and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