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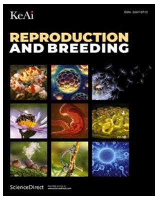

Progress on stress resistance breeding in fish

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ABSTRACT

With the continuing development of the aquaculture industry, the stress associated with many environmental factors has severely restricted the growth of fish, reduced fish resistance to disease, and had a large negative impact on fishery production. Therefore, it is of great importance for the sustainable development of aquaculture to cultivate new fish varieties with strong stress resistance. Traditional hybridization and gynogenesis, selective breeding, modern breeding techniques such as molecular marker-assisted breeding and whole genome selection breeding can be used to develop efficient and accurate fish breeding strategies, and to cultivate new fish varieties with high stress resistance. This paper reviews the status of research on fish breeding for disease resistance, cold resistance, high temperature tolerance, hypoxia tolerance, salt tolerance, saline-alkali tolerance as well as non-specific stress resistance traits, analyzes trends in research on fish breeding for stress tolerance, and explores future development directions. Furthermore, this paper proposes new ideas for fish seed industry innovation to promote its continuous and sustainable development.

1. Introduction

China's fishery development has been remarkable, and its total aquaculture production has ranked first in the world for more than 30 consecutive years, making China a global leader in fishery production [1]. However, with the continuous development of aquaculture activities, the disorderly expansion of aquaculture and the blind pursuit of high density and high yield have created problems such as poor water quality, environmental pollution, and animal diseases [1–3]. The stress of many environmental factors severely limits the growth of fish and reduces fish resistance, which has a substantial impact on fishery production. Therefore, to overcome these difficulties, it is necessary to breed new genetically improved fish varieties that have higher resistance to disease, low temperature, high temperature, and low oxygen than current varieties [1].

The resistance of fish to various stress factors is called stress resistance, which is the ability of fish to adapt to environmental stressors such as disease resistance, cold resistance, high temperature resistance, low oxygen tolerance, and salt tolerance [4]. For a long time, people have cultivated fish with high stress resistance, such as crucian carp (*Carassius auratus*) [5], tilapia (*Oreochromis niloticus*) [6], large yellow croaker (*Larimichthys crocea*) [7], and salmon (*Salmo salar*) [8], using traditional hybridization and selective techniques based on the phenotypic selection [9]. Gynogenesis, in combination with selective breeding, is also considered to be an efficient way to rapidly establish pure line with desirable characteristics. Farmed grass carp (*Ctenopharyngodon idella*) are readily susceptible to various kinds of diseases that cause high percentages of morbidity and mortality, leading to greatly reduced yields. While our previous studies confirmed that gynogenetic grass carp has excellent characteristics of fast growth and strong disease resistance [10,11].

Nowadays, breeding techniques such as family selection, along with molecular marker-assisted selection (MAS) and whole-genome selective breeding or genomic selection, are laying solid foundation for the development of fish stress-resistant breeding [12]. Family breeding is a process of improving the homozygosity of target genes, establishing families with good characteristics, and obtaining stable new varieties with good characteristics. Molecular marker technology is an auxiliary means of traditional selective breeding techniques, which can accurately identify the molecular markers or candidate genes associated with certain traits. Of which, quantitative trait locus (QTL) refers to the location of genes controlling quantitative traits in the genome. QTL mapping is a statistical analysis to locate chromosomal regions associated with a target trait, based on the genetic linkage of genotype (SSR or

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Table 1
Breeding for disease resistance.

Species	Stress resistance trait	Breeding technique	Description
"Xiangyun" Crucian Carp 2	disease resistance	hybridization	stronger resistance to SVCV GCRV [18]
allogyogenetics silver crucian carp "Zhongke No.5" (*Carassius auratus gibelio*)	disease resistance	gynogenesis, group selection and MAS	increased resistance to crucian carp herpesvirus and increased antibody against myxosporidiosis [24]
grass carp (*Ctenopharyngodon Idella*)	disease resistance	gynogenesis	biochemical parameters obviously superior to those of common grass carp [10]
genetically improved farmed tilapia (GIFT, *Oreochromis niloticus*)	resistance to *Streptococcus agalactis*	family selection	improved resistance to *Streptococcus agalactis* and rapid growth [6]
rainbow trout (*Oncorhynchus mykiss*)	anti BCWD	family selection	improved resistance against *Flavobacterium psychrophilum* BCWD [25]
	anti IPNV	QTL mapping	9 genetic QTLs associated with susceptibility to IPNV were identified [27]
Atlantic salmon (*Salmo salar*)	anti IPNV	QTLs and disease-causing genes identification	QTLs and disease-causing genes for IPNV resistance were identified [28]
	anti ISA	GWAS and SNP arrays	the first GWAS analysis of ISA resistance [8]
red sea bream (*Pagrus major*)	anti RSIVD	family selection and marker-assisted selection	QTL *Pma4_014* was used for the cultivation of RSIVD-resistant bream varieties [28]
large yellow croaker (*Larimichthys crocea*)	resistance to *Pseudomonas plecoglossicida*	GWAS based on the whole-genome resequencing	3 candidate regions associated with disease resistance were found [30]
	anti VWND	genomic selection	progeny with high resistance to VWND [7]
yellow drum (*Nibea albiflora*)	resistance to *Vibrio harveyi*	GWAS	8 candidate genes related to *V. harveyi* resistance were found [31]
Zebrafish (*Danio rerio*)	Resistance to virus	transgenesis	zebrafish lacking sirt5 with enhanced ability to resist RNA virus infection; sirt3-knockout zebrafish with reduced resistance to GCRV and SVCV in vivo [34–37]

SNP markers) to the phenotype (trait). Genome-wide association study (GWAS) detects the genetic variation diversity of multiple individuals on a genome-wide scale, obtains the genotype (SNPs or CNVs) of each individual in the population, performs statistical association analysis with the traits (often referred to as phenotype), and then mines candidate loci and genes based on the linkage disequilibrium [12]. GWAS is also a MAS tool that uses all molecular markers distributed throughout the genome to establish associations with target phenotypes [13].

Genomic selection (GS) uses genome-wide linkage disequilibrium of DNA markers (e.g., SNPs) to capture the effects of these variables and to estimate the effect values of these markers in large reference or training populations. Genomic estimated breeding values (GEBV) are calculated by genotyping candidate breeding strains, and strains with the highest ranked GEBV are selected for the purpose of rapidly producing superior progeny [1,2,12]. These breeding techniques can accurately and quickly identify genome-level relationships between individuals, thus substantially shortening the breeding cycle. Meanwhile, these techniques can also significantly reduce the genetic bias in parent selection and balance among multiple different traits, to better achieve the purpose of multi-objective genetic improvement [14].

China has abundant fishery resources, and fish species breed in diverse environments. Fish represent an ideal model for anti-stress breeding of complex traits because of their high fertility and selectivity [7]. Generally, anti-stress breeding objectives include disease resistance, temperature resistance, hypoxia tolerance, and non-specific resistance traits [15]. This review summarized the research status of fish anti-stress breeding in recent years, analyzed the research trend of fish stress breeding, and discussed future development directions. This work lays a foundation for breeding fish varieties with high stress resistance, provides new ideas for fish seed industry innovation, and can revitalize the development of the fish seed industry [1].

2. Status of stress resistance breeding

2.1. Breeding for disease resistance

Diseases have seriously affected the sustainable development of fish aquaculture. There is currently no systematic regimen to reduce the incidence of disease, which makes antibiotics and chemotherapy the common options and induces potential hazards to the ecological environment and human health [16]. Vaccines seem to be an effective approach to eliminate fish disease. However, there are not many varieties of vaccines with production approvals, which cannot fully cover the main diseases of major aquaculture species and are not sufficient to support a complete integrated disease immunization prevention and control system [2]. Therefore, improving the disease resistance of cultured fish species is a very desirable strategy to reduce aquaculture diseases. The cultivation of disease-resistant fish varieties has become an important effort and is one of the most intensively studied topics in the cultivation of improved fish varieties in the world [9].

Obtaining genetic variants associated with disease resistance in fish species is the primary condition for breeding research on disease resistance. Under specific selection pressure, genetic modification has been used to produce genetic variants of fish species, which not only improves the genetic traits of fish, but also increases the yield, genetic stability, and environmental protection (Table 1) [17]. Triploid "Xiangyun Crucian Carp 2", derived from the hybridization of the improved allotetraploid and improved diploid crucian carp, possesses the advantages of sterility, rapid growth, improved disease and stress resistance [18–20]. "Xiangyun Crucian Carp 2" had stronger resistance to spring viremia of carp virus (SVCV) and grass carp reovirus (GCRV) than its parents [20], indicating that natural immune mechanism of "Xiangyun Crucian Carp 2" was changed after hybridization. It was hypothesized that a high proportion of chimeric genes or other potential mechanisms result in genotypic alteration of hybrid fish [21,22]. Allogyogenetics silver crucian carp "Zhongke No.5", was derived from utilizing gynogenesis, group selection and molecular marker-assisted selection [23]. According to the variety profile, its resistance to crucian carp herpesvirus increased by 12.6 % and the antibody against myxosporidiosis increased by 21.0 % compared with "Zhongke No.3" [24]. In addition, the experimental data confirmed the anti-disease superiority in gynogenetic grass carp, which is beneficial to the aquaculture. The immune biochemical parameters of gynogenetic grass carp were obviously superior to those of common grass carp [10]. Hefang grass carp (HFGC) is produced using gynogenetic grass carp as the female parent and common grass carp (GC) as the male parent. HFGC had improved non-specific immunity. Furthermore, HFGC had better intestinal barrier function than GC, and had potential advantage in resisting the intrusion of external pathogens [11].

Family selection for disease resistance has been highly successful for several species and diseases (Table 1). Shen et al. [6] evaluated the disease resistance and growth performance of 42 families of genetically improved farmed tilapia (GIFT, *Oreochromis niloticus*) from the F_5 generation by injecting *Streptococcus agalactiae* into the abdomen for infection. Seven families with strong resistance to disease and rapid growth were selected to produce the F_6 generation. Their disease resistance and growth were greatly improved. Bacterial cold water disease (BCWD) is a frequent cause of mortality in freshwater rainbow trout (*Oncorhynchus mykiss*). Family-based selective breeding was used to develop three lines of rainbow trout (resistant, control, and susceptible lines) that differ in their resistance to *Flavobacterium psychrophilum* under controlled laboratory conditions. Three generations of selective breeding improved rainbow trout disease resistance against natural challenge with *Flavobacterium psychrophilum* during early life-stage rearing [25]. Selective breeding for disease resistance offers new opportunities for improving fish welfare and reducing the use of orally delivered therapeutics.

Mapping of QTL has been a major goal for aquaculture genetics and breeding research and has yielded some successful practical results (Table 1) [26]. Ozaki et al. [27] constructed a regional linkage map of rainbow trout and identified nine genetic QTL associated with susceptibility to infectious pancreatic necrosis virus (IPNV) by single-point and interval mappings. Houston et al. [28] also identified QTLs and disease-causing genes for IPNV resistance of Atlantic salmon as part of determining the genetic variation and genome region related to the disease resistance of the species. The above genetic information is now widely used in aquaculture to control IPNV.

Marker-assisted selection (MAS) can be built on the principle of detecting quantitative trait loci (QTL) affecting the trait of interest and selecting animals based on whether they carry favorable alleles at the QTL (Table 1). Sawayama et al. [29] reported the use of family selection and marker-assisted selection (MAS) to cultivate red sea bream (*Pagrus major*) strains resistant to red sea bream iridovirus disease (RSIVD). Marker-assisted selection using a QTL linked to the RSIVD-resistant trait (*Pma4_014*) was conducted, and individuals inheriting the resistant allele of *Pma4_014* (+) were selected. RSIVD-resistant individuals were selected as G_0 and G_1 population was constructed through breeding. The QTL *Pma4_014* associated with RSIVD resistance was used for auxiliary screening to obtain G_2 individuals with the *Pma4_014* resistance allele. It was found that G_2 had a higher survival rate and could be used as the base population for further cultivation of RSIVD-resistant bream varieties.

Genomic studies can obtain abundant polymorphic molecular markers associated with disease resistance in farmed fish species (Table 1). Holborn et al. [8] conducted the first GWAS analysis of infectious salmon anemia (ISA) resistance in Atlantic salmon populations using high-density SNP arrays. The results will be helpful for breeders to develop a set of gene improvement programs to improve ISA resistance. Wan et al. [30] performed a GWAS on the trait of resistance to *Pseudomonas plecoglossicida* infection in 222 extreme-phenotype samples of a large yellow croaker population using the whole-genome resequencing technology. Three candidate regions associated with disease resistance were found on chromosomes 3, 5 and 20 on the basis of 254,110 detected SNPs. Luo [31] conducted a GWAS on resistance to *Vibrio harveyi* infection in 345 individuals of yellow drum (*Nibea albiflora*). 54 SNPs related to *V. harveyi* resistance of yellow drum were mined from a total of 4,340,537 SNPs for GWAS and located on chromosome 14. After scanning the genes surrounding each significant SNP, 8 candidate genes were found to be related to *V. harveyi* resistance (especially the SPHK1 gene).

Genomic selection (GS) has been proved to be a useful method for selective breeding (Table 1). Bai et al. [7] bred large yellow croaker for resistance to visceral white node disease (VWND) by GS technique. The results showed that the progeny had high disease resistance. This study was the first time VWND was predicted using trait data of offspring and provides a good foundation for additional genetic analysis and molecular-level research.

Table 2
Breeding for low temperature resistance.

Species	Breeding technique	Description
“Xiangyun” and “Xiangyun No. 2” Crucian Carp	hybridization	sustaining growth when the water temperature is below 10 °C [5,42]
“Xiangyun” Carp	hybridization	feeding and growing normally when the water temperature is below 10 °C [42]
hybrid snakehead (*Channa argus* × *Channa maculata*)	hybridization	overwintering naturally in northern China [43]
mrigal carp (*Cirrhinus mrigala*)	gynogenesis	surviving the natural winter for more than 50 days with a temperature below 10 °C [44]
Takifugu "Zhongyang 1" (*Takifugu obscurus*)	population selection	The cold-tolerant ability reaches more than 6 °C and the overwintering rate increased by 11.8 % [45]
tiger puffer (*Takifugu rubripes*)	QTL mapping	8 QTLs associated with cold resistance traits of tiger puffer were identified in 6 LGs [46]
Takifugu fasciatus	QTL localization	3 candidate genes related to the cold tolerance were screen out [47]
	proteomic profiles using iTRAQ	3 significantly up-regulated proteins and 2 significantly down-regulated proteins were validated [48]
blue tilapia (*Oreochromis aureus*)	population selection	Mother effect has an important influence on the inheritance of cold resistance in tilapia [50]
Taiwan tilapia (*Oreochromis* spp.)	SNP markers and cDNA libraries	cold resistance–related genes were identified [51]
Nile tilapia (*Oreochromis niloticus*)	microsatellite labeling technology	The UNH879 and UNH916 labeled alleles are relatively common among cold-tolerant animals [52]
genetically improved farmed tilapia (GIFT, *Oreochromis niloticus*)	QTL mapping along with candidate genes and SSR markers screening	9 candidate genes in a QTL interval on chrLG18 and 6 microsatellite markers were found significantly associated to cold-tolerance trait [49]
common carp (*Cyprinus carpio*)	hybridization and QTL mapping	A locus associated with the cold tolerance trait of common carp was mapped on linkage group 5 [53]
large yellow croaker (*Larimichthys crocea*)	GWAS and transcriptome analysis	8 significant SNPs loci on 6 chromosomes were identified [54]
Pearl gentian grouper (*Epinephelus fuscoguttatus* ♀ × *Epinephelus lanceolatus* ♂)	transcriptome analysis by RNA-seq and SMRT-Seq	Key genes and biological pathways related to cold stress were screened out [56]

Infectious diseases are the main obstacle to the development of aquaculture. They are also an important subject in the fields of gene editing, transgenesis and biological breeding (Table 1). Zhao et al. [32] targeted two basic target genes necessary for the early transcription of cyprinid herpesvirus-3 (CyHV-3) and found CyHV-3 replication was inhibited with CRISPR/Cas9. Integrating vector-engineered antimicrobial peptide genes (AMGs) by CRISPR/Cas9-mediated genome editing and transgenesis are effective to modulate the fish' s innate immune system. Wang et al. [33] recruited 544 data entries from a pool of empirical studies, which included 23 studies spanning 12 diseases. Their findings revealed that the efficiency of transgenic AMGs against pathogens was fish-, pathogen- and AMG-specific. Transgenic AMGs were more inhibitory to bacteria compared to viruses and parasites. A team from Wuhan found that SIRT5 inhibited the expression of antiviral genes such as interferon by catalyzing the desuccinylation of lysine at position 7 of the adaptor protein MAVS, and there were no significant differences in growth, development, and reproduction between zebrafish lacking sirt5 and wild-type zebrafish, but their ability to resist RNA virus infection was significantly enhanced [34,35]. SIRT3, another member of the Sirtuin protein family, could induce the expression of antiviral genes such as interferon by deacetylating the same site of the MAVS protein, and zebrafish with sirt3 knockout have significantly reduced resistance to grass carp reovirus (GCRV) and carp spring viremia virus (SVCV) infections in vivo experiments [36,37]. Since disease resistance is almost universally heritable, gene editing plays a key role in identifying disease-causing mutations, and provides important molecular markers for the cultivation of disease-resistant fish species [38].

2.2. Breeding for low temperature resistance

Fish are aquatic poikilothermic vertebrates. Water temperature has a significant impact on their physiology and behavior [39]. Bartolini et al. [39] found that temperature affected fish social behavior and energy consumption, and that lower temperature led to more cohesive shoals and reduced fish activity. Portner and Peck [40] showed that many physiological functions of aquatic species, such as growth, metabolism, reproduction, food consumption, and body stability, were affected by water temperature fluctuations. Antiglycoproteins, molecular chaperones, metabolic enzymes, and membrane channel proteins all participate in the stress response of fish to low temperature [41]. The vast territory of China encompasses a wide range of climates with extreme temperature fluctuations. Severely cold weather occurs frequently in winter, posing a threat to fishery production from shock, disease, and even death. Understanding the low-temperature adaptation mechanism of fish is of great significance for the cultivation of cold-tolerant fish strains [9]. In addition, because of the increasing number of tropical fish species introduced into China, research on the low-temperature adaptability of tropical fish is increasingly a focus.

Crossbreeding, artificial gynogenesis, population selection, and cell engineering techniques can be used to breed fish with stronger cold resistance (Table 2). “Xiangyun” carp and “Xiangyun” crucian carp originated from hybridization can normally feed and grow when the water temperature is below 10 °C [42]. “Xiangyun” crucian carp No. 2 can sustain growth in spring and winter when the water temperature is even lower [5]. The snakehead hybrids, which were obtained by the crossbreeding of *Channa argus* and *Channa maculate*, can overwinter naturally in northern China [43]. Gynogenetic mrigal carp (GMC, *Cirrhinus mrigala*) was obtained after the matured eggs activated by UV-irradiated common carp sperm. The GMC population survived the natural winter for more than 50 days with a temperature below 10 °C, while all the normal MC individuals perished. The cold tolerance of gynogenetic mrigal carp was significantly improved. The results indicated that the artificial gynogenesis method improved the cold tolerance of mrigal carp [44].

Takifugu “Zhongyang 1” (*Takifugu obscurus*) was derived from the population selection technology with low temperature tolerance as the main selection and breeding trait (Table 2). The cold-tolerant ability of “Zhongyang No.1” reaches more than 6 °C, and the overwintering rate increased by 11.8 %. Its cold-tolerant gene plays an important role in production, which not only improves the growth rate, prolongs the effective growth period and improves the quality of puffer fish, but also effectively solves the overwintering problems caused by the lowering of the temperature, greatly reduces the breeding cost and expands the breeding area of puffer fish in the country [45]. In addition, Liu et al. [46] constructed a high-density genetic linkage map of the tiger puffer (*Takifugu rubripes*), which was consisted of 4416 bin markers distributed over 22 linkage groups (LGs). QTL mapping results revealed eight QTLs associated with cold resistance traits of tiger puffer were identified in six LGs for the first time, which explained 13.6–16.3 % of the phenotypic variation. Zhang et al. [47] constructed a high-density genetic linkage map of *Takifugu fasciatus*, which was consisted of 4891 bin markers distributed across 22 LGs. Three candidate genes (HSP90, HSP70, and HMGB1) related to the cold tolerance of *T. fasciatus* were screen out by QTL localization analysis. To shed further light on the molecular mechanisms of low temperature adaptation in fish, Wen et al. [48] compared the proteomic profiles on the *T. fasciatus* liver at 12 °C and 26 °C using iTRAQ. A total of 160 differentially abundant proteins (DAPs) were identified. Three significantly up-regulated proteins (CIRB, HSP90 and GST) and two significantly down-regulated proteins (FLNB and A2ML1) were validated with parallel reaction monitoring (PRM) assays. Furthermore, the changes in abundance of proteins that are involved in oxidative stress, mitochondrial enzymes and signal transduction were validated at the transcriptional level with qPCR.These results provide a theoretical basis for the selection and breeding of cold-tolerant *Takifugu*.

Tilapia is an important economic fish worldwide. The high mortality of tilapia caused by low water temperature has become a major problem in overwinter aquaculture [49]. Nitzan et al. [50] proposed that the optimum living temperature of most tropical tilapia varieties is 25–28 °C. They adopted a three-generation selective breeding program to cultivate blue tilapia (*Oreochromis aureus*) to improve its cold resistance (Table 2). The results showed that the mother effect has an important influence on the inheritance of cold resistance in tilapia. Chu et al. [51] screened and verified the cold tolerance population of Taiwan tilapia (*Oreochromis* spp.) using SNP gene marker technology, constructed cDNA libraries of brain, gill, liver, and muscle tissues of cold-tolerant (CT) and cold-sensitive (CS) strains, and identified cold resistance–related genes (Table 2). This study can be used to identify genetic polymorphisms and cold tolerance traits of Taiwan tilapia, and also to further explore the physiological and biochemical molecular regulatory pathways of fish tolerance to environmental temperature stress. Silva et al. [52] analyzed the genetic characteristics of tilapia using microsatellite labeling technology, evaluated cold tolerance and performance of different Nile tilapia populations, and concluded that the UNH879 and UNH916 labeled alleles are relatively common among cold-tolerant animals (Table 2). This information will help to guide selective breeding to obtain tilapia that is more adaptable to low temperatures. Ai et al. [49] identified a genome-wide significantly mapped QTL interval on chrLG18 associated with cold tolerance in GIFT tilapia by ddRAD-seq technology (Table 2). Nine candidate genes in this QTL were found differentially expressed exposed to cold stress. Six microsatellite markers were significantly associated to cold-tolerance trait. This research was beneficial to assisted screening and functional analysis of molecular markers for cold tolerance of tilapia.

Sun and Liang [53] reported the first marker linked to cold tolerance in carp (*Cyprinus carpio* L.) (Table 2). A genetic linkage map was created using a hybrid system with two carps, one of which is cold tolerant and the other cold sensitive. A locus associated with the cold tolerance trait of common carp was mapped on linkage group 5. Suo et al. [54] conducted an integrative analysis of GWAS and transcriptome analysis to reveal the molecular mechanism of cold-stress response in large yellow croaker (Table 2). A total of 8 significant SNPs loci on 6 chromosomes were identified in the GWAS analysis. This study provided insights into the cold tolerance of large yellow croaker and contributed to genome selection for low-temperature-resistant large yellow croaker.

Blödorn et al. [55] reported that miRNAs play a major regulatory role in the cold adaptation of teleost fish, among which at least 71 miRNAs were reported to be differentially expressed in fish at low temperatures (Table 2). These miRNAs regulate shifts in the energy metabolism, lipid and amino acids biosynthesis, cell differentiation and signaling pathways. These findings highlight miRNAs as potential targets for the development of new predictive tools for cold tolerance in teleost fish. With more research, new miRNA-based technologies will also be applied to aquaculture fish. Miao et al. [56] used RNA-seq and SMRT-Seq technologies to investigate the liver transcriptomic response

Table 3
Breeding for high temperature resistance.

Species	Breeding technique	Description
turbot "Duobao No. 2" (*Scophthalmus maximus*)	population selection and family selection	The ability to tolerate high temperature was increased by more than 2 °C [61–63]
rainbow trout (*Oncorhynchus mykiss*)	traditional selective breeding	LT50 for embryos of the selected strain was significantly higher than those of the normal strains [64,65]
	selective breeding and transcriptome analysis	miR-301b-5p and its target gene *nfatc2ip* associated with temperature-tolerant were screened out [68]
large yellow croaker (*Larimichthys crocea*)	microsatellite markers with BSA technology	4 fragments amplified by microsatellite markers were related to thermal tolerance [66]
Atlantic salmon (*Salmo salar*)	stress stimuli and transcriptome analysis	The transcriptome mechanisms that contribute to short-term heat tolerance were elucidated [67]

to low-temperature stress in Pearl gentian grouper (*Epinephelus fuscoguttatus* ♀ × *Epinephelus lanceolatus* ♂), a fish species of high commercial value in the aquaculture industry in Asia (Table 2). Key genes and biological pathways related to cold stress were screened out, which were significantly enriched in carbohydrate metabolism, lipid metabolism, signal transduction, and endocrine system pathways. The results will expedite the understanding of different adaptive mechanisms to profound environmental temperature changes and provide insights into the molecular breeding of cold-tolerant pearl gentian grouper varieties [56].

2.3. Breeding for high temperature resistance

With global warming, rising air and water temperatures have had an impact on the stability of water bodies and changed aquatic ecosystems, thereby affecting the sustainable development of fisheries. Sudden changes in water temperature or sustained high temperatures can disrupt cellular homeostasis, which in turn affects fish metabolism, protein degradation, immune defenses, growth and development, population size, and leads to an increased risk of disease in fish [57,58], and may also result in delay or interruption of reproductive processes, and lead to an imbalance in offspring, food supply, and predators [59]. Temperature tolerance is an important trait from both an economic and ecological perspective in fish. In-depth research should be conducted on the survival conditions of fish under global warming, and fish germplasm resources with high temperature tolerance could be selected and bred to ensure the sustainable development of the fish culture industry.

Turbot (*Scophthalmus maximus* L.) is a cold-water marine fish with high economic value in Europe and Asia [60]. Ma et al. [61] produced high temperature tolerance strains and sensitive strains through a series of selection experiments which used survival data and upper thermal tolerances (UTT) obtained from a thermal challenge (Table 3). After one generation of population selection and three generations of successive line selection, a new variety of turbot, “Duobao No. 2”, was selected and bred for its high temperature tolerance and its growth performance has also been significantly improved. The ability of turbot “Duobao No. 2” to tolerate high temperature was increased by more than 2 °C [61–63]. As a typical cold-water fish culture species, rainbow trout, and the problems of high temperature in summer and global warming have also had a great impact on the rainbow trout industry, and the cultivation of new varieties of rainbow trout that are resistant to high temperatures is an effective way to solve the constraints of this industry. Ineno et al. [64] established a rainbow trout strain by selecting successively for many generations at high temperatures (Table 3), and the hatching rate, fry mortality and the upper 50 % lethal temperatures (LT50) for embryos of the selected strain were significantly higher than those of the normal strains. They also conducted high-temperature stress treatment on the F_1 and F_2 generations of this new heat-resistant rainbow trout variety [65]. Both generations showed heat-resistant characteristics, indicating that the heat-resistant trait could be stably inherited by the next generation. Thermal tolerance to high temperature was also evaluated in the large yellow croaker. Chen et al. [66] conducted a preliminary study on three heat-resistant microsatellite markers using bulked segregation analysis (BSA) technology (Table 3). These markers have six amplified fragments in which four were related to thermal tolerance. The results provide useful molecular markers for thermal-tolerance breeding of large yellow croaker.

Table 4
Breeding for hypoxia tolerance.

Species	Breeding technique	Description
blunt snout bream (*Megalobrama amblycephala*)	gynogenesis and transcritome analysis	Gynogenetic BSB showed a higher tolerance to hypoxia than wildtype BSB and many DEGs related to hypoxia response were revealed [72–74]
	selective breeding combined with transcriptome analysis and SNP markers screening	The hypoxia tolerance of F_5 population was improved, the *Egln2* type II and *hif2αb* diplotype II had a significant correlation with hypoxia-tolerant traits [75–77,86]
hybrid catfish (*Ictalurus punctatus* ♀ × *Ictalurus furcatus* ♂)	hybridization and QTLs detection	4 linkage groups associated with tolerance to low dissolved oxygen and genes involved in PI3K/Akt/mTOR were identified [79]
golden pompano (*Trachinotus ovatus*)	genome-wide resequencing combined with SNPs and candidate genes detection	4 SNPs and 16 potential candidate genes associated with the hypoxia tolerance trait were identified [80]
Pelteobagrus vachelli	genome-wide QTL detection by ddRAD-seq	Sema7a was induced after hypoxia exposure and reoxygenation [81]
common carp (*Cyprinus carpio*)	hypoxia stress stimuli and genotyping by SNP array	4 SNPs and 23 genes for hypoxia adaptation associated traits were identified [82]
Nile tilapia (*Oreochromis niloticus*)	QTLs and candidate genes with SNPs identification	4 genome-wide significant QTLs and SNPs in exons of both GPR132 and ABCG4 genes associated hypoxia tolerance were identified [70]

Transcriptome analysis of many fish species under high-temperature stress will help us better understand the mechanisms of fish response to external environmental stimuli. For example, transcriptome analysis was used to explore the characteristics of differentially expressed genes (DEGs) in the liver of Atlantic salmon after high-temperature stress (Table 3), and the results elucidate the transcriptome mechanisms that contribute to short-term heat tolerance in the liver of Atlantic salmon, providing a theoretical basis for the breeding of high-temperature tolerant fish [67]. To understand the immune response mechanism of rainbow trout under high-temperature stress, rainbow trout individuals from high-temperature tolerant, sensitive and control groups were screened through high-temperature stress experiments, and transcriptome sequencing analysis of mRNA and miRNA in liver tissues of the three groups were performed (Table 3). miR-301b-5p and its target gene *nfatc2ip*, which were expressed in the tolerant and sensitive groups, were screened out. To screen and validate high-temperature-tolerant components is the basis for assisting the selection and breeding of high-temperature-tolerant fish varieties [68].

2.4. Breeding for hypoxia tolerance

Hypoxia is one of the most critical aquatic environmental factors. High-density aquaculture has recently experienced serious economic losses caused by changes in the oxygen content of water and the lack of nutrients. Exposure to hypoxia induces both acute and chronic stress responses, which interferes with the growth, reproduction, immunity, metabolism, and other life activities of cultured organisms, altering cell morphology and structure as well as swimming and eating habits [69–71]. Developing hypoxia-tolerant strains or varieties is one of the sustainable and economical solutions to this aquaculture problem.

Artificial gynogenesis is an efficient method to improve the hypoxia tolerance (Table 4). Blunt snout bream (*Megalobrama amblycephala*, BSB) is an important economic freshwater fish species in China, and it is hypoxia-sensitive. Gynogenetic BSB (GBSB, $2n = 48$) was obtained from BSB eggs activated by UV-irradiated sperm of the koi carp (*Cyprinus carpio haematopterus*). GBSB showed a higher tolerance to hypoxia than BSB [72]. To explore the molecular mechanisms underlying the enhanced hypoxia tolerance of GBSB, comparative analyses of the liver transcriptomes of GBSB and BSB exposed to hypoxia conditions were conducted. A total of 7295 DEGs in the livers of GBSB and BSB were identified, and pathway analyses revealed that many DEGs were associated with hypoxia response [73]. In another study, gynogenesis BSB (GBSB-R) is generated by artificial gynogenesis with UV-inactivated sperms of red crucian carp (RCC), which is regarded as one kind of freshwater fish with the strongest hypoxia-tolerance. In view of hypoxia stress tests, physiological indexes and gene expression, the experimental data confirm that the GBSB-R is a new strain with improved hypoxia tolerance, especially compared with the wildtype BSB [74].

Selective breeding of new hypoxia-tolerant strains is also important for aquaculture (Table 4). Since 2007, Li et al. [75,76] performed selective breeding under hypoxic stress in a wild-caught blunt snout bream population from Poyang Lake, China. In 2017, the selectively bred F_5 population was obtained, and the tolerance of this population to hypoxia stress was significantly improved [77]. Two completed linked SNP sites at 397 and 715 within exons of the *Egln2* gene were identified after examination of transcriptome data from blunt snout bream of the hypoxia-tolerant strain, which can form two haplotypes, namely, haplotype 1 ($C^{397}G^{715}$) and 2 ($T^{397}T^{715}$). Haplotype 1 occurred mainly in hypoxia sensitive control blunt snout bream, whereas haplotype 2 was predominantly found in blunt snout bream of the hypoxia-tolerant strain. The study indicated that blunt snout bream with the *Egln2* type II genotype had a significant correlation with hypoxia-tolerant traits. Thus, the haplotype 2 can be used as a marker for future practical programs aimed at selective breeding of hypoxia-tolerant blunt snout bream [77]. In addition, hypoxia-inducible factor (HIF) is the most critical factor in the HIF pathway, which strictly regulates the hypoxia stress process of fish. Zhao et al. found two linkage-disequilibrium SNP sites at exon 203 and 752 of the *hif2αb* gene in blunt snout bream. Haplotype II ($A^{203}A^{752}$) and its homozygous diplotype II ($A^{203}A^{203}A^{752}A^{752}$) appeared frequently in a selected strain of blunt snout bream with hypoxia tolerance. The results indicated that the hypoxia-tolerant-related diplotype II of *hif2αb* has the potential to be used as a molecular marker in future genetic breeding of hypoxia-tolerant strain [76,78].

The QTLs detection and GWAS of the hypoxia adaptation traits of several fish species were conducted (Table 4). Zhong et al. [79] identified four linkage groups (LG2, LG4, LG23, and LG29) associated with tolerance to low dissolved oxygen in the channel catfish × blue catfish interspecific system. Multiple significant SNPs were found to be physically linked in genomic regions containing significant QTL for low oxygen tolerance on LG2 and LG23. Analysis of genes within the associated genomic regions suggested that many of these genes were involved in PI3K/Akt/mTOR and other pathways. San et al. [80] selected 100 individuals of golden pompano (*Trachinotus ovatus*) to explore the SNPs and related candidate genes affecting hypoxia tolerance trait based on genome-wide resequencing technology. Four SNPs were identified to be suggestively significantly associated with the hypoxia tolerance trait. 16 potential candidate genes affecting hypoxia tolerance trait were detected surrounding the suggestive SNPs. These SNPs can be used as molecular markers to screen for hypoxic tolerance and for further applications in the genetic breeding of pompanos. Zhang et al. [81] constructed a high-resolution genetic linkage map by making use of 5059 ddRAD markers in *Pelteobagrus vachelli*. One significant genome-wide QTL for hypoxia tolerance was detected, and one candidate gene, Sema7a, was induced after hypoxia exposure and reoxygenation. Moreover, a hypoxia stress experiment was carried out in the breeding population of common carp, and hypoxia-sensitive and hypoxia-tolerant individuals with extreme traits were selected as the screening samples. The Carp 250 K single nucleotide polymorphism (SNP) array was used for genotyping. Four associated SNPs for hypoxia adaptation traits (carp229220, carp195901, carp001519, and carp063890) were identified, and 23 genes were found in the neighboring regions of the four SNPs, including TNF receptor-associated factor 4 (*traf4*). Putative genomic regions related to hypoxia adaptation for domesticated common carp were obtained in this study, which shed new light on the underlying mechanisms of hypoxia adaptation [82].

The application of advanced genome technology can quickly screen and identify genes related to hypoxia traits, providing potential genetic markers for molecular assisted breeding (Table 4) [70]. Li et al. [70] identified four genome-wide significant QTLs and many suggestive QTLs for hypoxia tolerance in Nile tilapia, and further analysis revealed that SNPs in exons of both GPR132 and ABCG4 genes located in genome-wide QTL intervals were significantly associated with hypoxia-tolerant traits. This study not only enhances the understanding of the molecular basis involved in hypoxia tolerance of fish, but also provides a scientific basis for cultivating excellent fish strains that can tolerate low oxygen stress through molecular assisted selection.

To reveal the genetic mechanism underlying hypoxia adaptation, it is important to identify candidate genes associated with hypoxia adaptation traits, besides the molecular markers. Fish can adapt to hypoxic physiological responses, including blood vessel and red blood cell generation, glucose metabolism, cell growth, vasodilation and contraction, through the regulation of target genes [83–85]. For instance, the transcriptional levels of hypoxia inducible factors alpha (HIF-α) and their inhibiting factor (FIH-1) were found to be regulated temporally and spatially after low oxygen challenge in channel catfish (*Ictalurus punctatus*), a species highly hypoxia tolerant [83]. *HIF-1a* and vascular endothelial growth factor (*VEGF*) have an important role in enhancing hypoxia tolerance in Oscar (Astronotus ocellatus), an extreme tolerant species to low oxygen condition [85]. *Hif-1α* knockout zebrafish had a significantly higher mortality rate during hypoxia [84]. Transcriptome data related to growth and hypoxia response are available for blunt snout bream. Li et al. performed de novo transcriptome sequencing for the liver and gills of the fast-growth family and slow-growth family derived from "Pujiang No.1" F_{10} blunt snout bream that were under hypoxic stress and normoxia, respectively (Table 4). The results suggest that growth performance of the fast-growth family should be due to complex gene regulatory mechanisms of these putative differential expression (DE) genes between growth and hypoxia [86].

2.5. Breeding for salt tolerance

Salinity is an important environmental factor affecting the survival of fish. Salinity stress affects fish metabolism, survival, reproduction, development, growth, and physiological functions [87,88]. Fish breathe through their gills, which are covered with capillaries. Changes in salinity can cause damage to the gills such as vascular congestion, lamellar fusion, hyperplasia of mucosal cells and gill epithelium, loss of structural integrity of columnar cells, and increase in chlorine cells, which then affect the functionality of gills and the morphology of the

Table 5
Breeding for salt tolerance.

Species	Breeding technique	Description
Malaysia red tilapia strain (*Oreochromis* spp.)	family selection and QTL mapping	A long QTL cluster across chrLG18 for the salt-tolerant trait was revealed [92]
genetically improved farmed tilapia (GIFT, *Oreochromis niloticus*)	population selection and GWAS	A long QTL cluster across chrLG18 for the salt-tolerant trait was revealed [92]
	QTL mapping with microsatellite and SNPs markers	Two significant QTL intervals (chrLG4 and chrLG18) on salinity-tolerant traits were identified [93]
	candidate genes with SNPs genotyping	5 SNPs in the EPC1 gene and 7 SNPs in POLD3 associated with the salt tolerance trait were identified [95,96]
red tilapia (*Oreochromis mossambica*)	transcriptome analysis with DEGs and SNPs detection	3 DEGs (*nmrk2, ptprf* and *arhgef18a*) and 3 SNPs in *ptprf* gene correlated with salinity tolerance were identified [97]
cobia (*Rachycentron canadum*)	transcriptome analysis with candidate genes identification	8805 DEGs adapted to hypo-salinity and 11,866 DEGs adapted to hyper-salinity were identified [87]
greater amberjack (*Seriola dumerili*)	transcriptome analysis with candidate genes identification	18 DEGs in the 40 vs. 30 ppt salinity group and 417 DEGs in the 20 vs. 30 ppt salinity group were identified [98]
half-smooth tongue sole (*Cynoglossus semilaevis*)	transcriptome analysis with DEGs and candidate genes identification	2137 DEGs and 218 DEGs were identified in low and high salinity, respectively [99]

Table 6
Breeding for saline-alkali tolerance.

Species	Breeding technique	Description
genetically improved farmed tilapia (GIFT, *Oreochromis niloticus*)	GWAS and QTL interval localization	A QTL interval on chrLG1 associated with ammonia-nitrogen tolerance and 4 DEGs within the QTL were identified [106]
orange-spotted grouper (*Epinephelus coioides*)	GWAS with SNPs and candidate genes identification	25 amine-tolerant SNPs and 7 candidate genes were identified, of which Sgk3 was involved in ammonia excretion and played a key role in reducing ammonia toxicity [107]
Nile tilapia (*Oreochromis niloticus*)	acute carbonate alkalinity stimuli and gene expression	Ammonia metabolism-related genes were upregulated to various degrees in different tissues after gradient alkalinity stresses at 12–24 h [108].
hybrid tilapia (*Oreochromis mossambicus* ♀ × *O. urolepis hornorum* ♂)	hybridization and transcriptome analysis along with DEGs and candidate genes validation	1958, 1472 and 1315 upregulated and 1824, 1940 and 1735 downregulated genes were identified in the salt stress, alkali stress and saline-alkali stress groups [110]

fish body [89–91].

Mapping QTLs and identifying the markers linked to salinity-tolerant traits could improve the tolerance of fish species through marker-assisted selection (Table 5). Tilapia is an important agricultural and economic resource worldwide [92]. The production of tilapia adapting to brackish water can become economically feasible by breeding new varieties with salt tolerance and rapid growth [93]. Gu et al. [93] identified two significant QTL intervals (chrLG4 and chrLG18) on salinity-tolerant traits by using the QTL-seq and linkage-based analysis. Expression analysis indicated that at least 10 genes near or within the QTL interval were significantly differentially expressed in intestines, brains, or gills under 10, 15, or 20 ppt challenges. Jiang et al. [92] carried out the first GWAS analysis on salt tolerance in tilapia. The QTLs associated with salt tolerance were investigated in a mass cross population from the GIFT line of Nile tilapia using a ddRAD-seq-based GWAS and in a full-sib family from the Malaysia red tilapia strain (*Oreochromis* spp.) using QTL-seq. The study confirmed the major QTL interval that is located at nearly 23.0 Mb of chrLG18 in Nile tilapia and revealed a long QTL cluster across chrLG18 controlling for the salt-tolerant trait in both red tilapia and Nile tilapia.

Identifying candidate genes involved in osmoregulation provides a basis for the breeding of saline tilapia by MAS technology (Table 5). Osmotic regulation strategies include sensing changes in environmental salinity and regulating signaling networks encoding information about the direction and magnitude of salinity change [94]. The *Enhancer of Polycomb Homolog 1* (*EPC1*) gene in Nile tilapia was characterized [95]. 5 SNPs in the *EPC1* gene were significantly associated with the salt tolerance trait by genotyping 192 extreme individuals from a full-sib tilapia family. The individuals with heterozygous SNP genotypes in the population were significantly less tolerant than the other individuals with the homozygote genotypes. It is suggested that the *EPC1* gene may be a candidate gene related to osmoregulation process in tilapia. 7 SNPs in a subunit of DNA polymerase delta, POLD3, were identified, and these SNPs were significantly associated with saline tolerance traits in the same full-sib family of Nile tilapia (N = 192). The expression of the POLD3 gene was also dramatically regulated at brain, gill and intestine in response to the acute salinity challenges [96]. These data indicate genes close-linked with osmoregulation played important roles in saline tolerance of tilapia and could contribute to developing molecular markers for breeding of salt-tolerant tilapia in future.

Transcriptome analysis makes DEG datasets available for further identifying functional genes of salinity tolerance (Table 5). The skin transcriptomic responses of the Nile tilapia GIFT line were investigated after three and a half months of salinity challenge with a concentration of 0, 17 and 27 ppt, respectively. Three DEGs, *nmrk2*, *ptprf* and *arhgef18a*, were detected and located within the identified major QTL at chrLG18. Three SNPs in the differentially expressed gene *ptprf* were found significantly correlated with salinity tolerance in a red tilapia family [97]. Genes and biological processes in response to different salinity levels were analyzed by RNA-seq in cobia (*Rachycentron canadum*) [87], Greater Amberjack (*Seriola dumerili*) [98], and half-smooth tongue sole (*Cynoglossus semilaevis*) [99]. A large number of DEGs related to salinity adaptability were revealed. These DEGs were highly represented in steroid biosynthesis, lipid metabolism, energy metabolism, osmoregulation, and immune response. The candidate genes provide valuable information for studying the molecular mechanism of salinity adaptation in marine fish.

Salinity is recognized to be a major environment factor that influences cellular hemostasis and functions in fish. Precise QTL localization, MAS technology and transcriptomic data all act as useful resource for research on fish biology and the breeding of salt-tolerant fish.

2.6. Breeding for saline-alkali tolerance

With the development of high-density intensive aquaculture, saline-alkali, and ammonia-nitrogen stress have become important factors limiting the development of aquaculture [1]. Studies have found that alkaline salts ($NaHCO_3$ and Na_2CO_3) are more destructive to organisms than neutral salts ($NaCl$ and Na_2SO_4) [100]. Saline-alkali water has high carbonate alkalinity, high pH, complex ionic composition, and other physicochemical characteristics that cause changes in NH_3 and NH_4^+ balance [101]. Ammonia poisoning is an important manifestation of alkali stress [102]. Under normal conditions, most freshwater and marine bony fish species discharge nitrogen waste in the form of ammonia mainly through their gills. Under conditions of high alkali and high pH, ammonia will accumulate in large quantities in plasma and tissues, inducing respiratory and metabolic alkalosis [102,103]. Ammonia is the main metabolic end product of proteins or amino acids that cannot be digested and absorbed in the body. It is toxic to all vertebrates, seriously affects the growth, survival, and reproduction of fish, and can lead to death [104,105].

Zhu et al. [106] identified a QTL interval on chrLG1 associated with ammonia-nitrogen resistance in the GIFT strain of Nile tilapia by *ddRAD-seq*-based GWAS (Table 6). This study provides valuable genomic resources for the screening of molecular markers and functional analysis of the ammonia-nitrogen tolerance of tilapia. Xu et al. [107] conducted a GWAS on ammonia tolerance in orange-spotted grouper (*Epinephelus coioides*) by genome resequencing (Table 6). A total of 25 amine-tolerant SNPs and 7 candidate genes were identified, of which Sgk3 was involved in ammonia excretion and played a key role in reducing ammonia toxicity. These results could promote the advancement of MAS to improve the alkaline tolerance of grouper and other fish.

Fish can cope with ammonia poisoning caused by high alkaline stress by regulating the expression of ammonia metabolism-related genes, increasing the conversion of ammonia to urea and glutamine, or reducing the production of ammonia in their metabolism [108,109]. Wu et al. [108] investigated the ammonia metabolism pathway of *Oreochromis niloticus* after acute carbonate alkalinity gradient stresses, and revealed that ammonia metabolism-related genes, glutamine synthetase (GS), carbonic anhydrase 5A(CA-5A), glutaminase 2(GLS2), carbamoyl phosphate synthetase 1 (CPS1) and ammonium transporter Rh type C-2 like (Rhcgl2), were upregulated to various degrees in different tissues after different alkalinity stresses at 12–24 h. Su et al. [110] sequenced the transcriptomes of gills in hybrid tilapia under saline-alkali stress and DEGs involved in osmoregulation were identified (Table 6). The study is helpful to elucidate the osmoregulation mechanism of aquatic animals adapting to saline-alkali challenge.

2.7. Breeding for non-specific stress resistance

The stress theory was proposed by the Canadian physiologist Hans Selye in 1936, which refers to a series of systemic non-specific responses without specific pathological damage produced by biological organisms after being stimulated by external adverse factors, also known as stress response [111]. When fish are subjected to one or more external environmental stresses, such as disease, low temperature, fasting, crowding, fishing, transport, etc., their neuroendocrine, metabolic, immune changes and behavioral consequences will occur, which will further affect disease resistance, the growth, reproduction, and other production performance of fish [112–115]. Stress resistance can be divided into specific stress resistance and non-specific stress resistance. Specific stress resistance includes resistance to certain disease, cold, high temperature, low oxygen, and so on. Non-specific stress resistance mainly refers to a comprehensive adaptive ability that enables individuals to resist or endure multiple and various environmental stress [3], such as non-specific immune responses, adaptation to high-density aquaculture, transportation resistance, etc. There was evidence that the hypothalamic-pituitary-interrenal (HPI) axis, which is activated in response to most forms of stress in fish, plays a dominant role in the neuroendocrine regulation under environmental stress [116,117]. Cortisol, the end product of HPI activation in most fishes, may be involved in the regulation of non-specific stress resistance.

Table 7
Breeding for non-specific stress resistance.

Species	Breeding technique	Description
carp (*Cyprinus carpio*)	androgenesis combined with selective breeding	A high heritability estimate of 0.60 (0.37–0.90) was found in the carp population used [102, 118]
rainbow trout (*Oncorhynchus mykiss*)	selective breeding for stress response	Two different strains of rainbow trout with high and low stress responsiveness were bred on the basis of their plasma cortisol response [119]
Atlantic salmon (*Salmo salar*)	selective breeding for stress response	The variations in hormone content and the hematological indices are of high application value for detecting the response to stress [117]
	polyploid breeding for stress response	Triploid salmon exhibited greater sensitivity to stress than diploid salmon [120]
gilthead sea bream (*Sparus aurata*)	selective breeding for stress tolerance using cDNA microarray	4 major temporal gene expression profiles were identified, revealing the complex nature of adaptive stress response [121]
European seabass (*Dicentrarchus labrax*)	stress tolerance trial and transcript expression analysis	Processing of BDNF is a central mechanism in adaptation to stress [122]

Studies on non-specific stress resistance have been carried out in carp [118], rainbow trout [119], Atlantic salmon [120], gilthead seabream (*Sparus aurata* L.) [121], European seabass (*Dicentrarchus labrax*) [122], etc. Pottinger and coworkers bred two different strains of rainbow trout with high and low stress responsiveness on the basis of their plasma cortisol response to a defined stressor through selective breeding for about 10 years (Table 7), and under a standardized confinement stress, the high-responding group (HR fish) had significantly higher plasma cortisol concentrations than the low-responding group (LR fish) [119, 123]. Furthermore, individuals of the LR fish recovered food intake more readily after transferring to a new environment, and the HR fish displayed greater locomotor ability in the presence of foreign invaders [124]. Specifically, LR fish quickly surpassed the HR fish in acquiring the social dominance of the group [125]. The two strains differed significantly in terms of food utilization rates, and the LR fish also showed higher feed efficiency (growth per unit feed consumed) [126]. In addition, the study by Ruiz-Gomez et al. showed that the behavioral strategies of rainbow trout to cope with stress responses are plastic [115]. These results suggest that there are several potential benefits of selection for low stress responsiveness in aquaculture.

There are differences in the intensity of stress response among different species and populations of fish, and the differences are heritable [113,118,119]. In the study of Cyprinidae and Salmonidae fish under stress, it was found that the heritability of cortisol level, an indicator of the primary stress response, was variable between species. For example, it was in 0.6 in carp [118], 0.27–0.50 in rainbow trout [113, 119,127], and only 0.03–0.05 in Atlantic salmon [113]. Non-specific stress resistant breeding of fish is conducive to selecting varieties that adapt to various aquaculture environment and can quickly recover from stress. Through analyzing cellular and molecular biological bases that cause such genetic differences in stress response capacity among species or populations, it is feasible to cultivate new varieties or strains of non-specific stress resistant fish by cross-breeding, family selection, modern cellular engineering and genetic engineering.

3. Conclusion and perspectives

Based on the above research about fish stress resistance breeding, it is found that traditional hybridization, gynogenesis and selective breeding has proved to be effective in cultivating new varieties or strains

Table 8
New varieties of stress resistance breeding fish.

Species	Registration no.	Stress Resistance Trait	Breeding technique	Breeding institution
"Xiangyun" Carp	GS-02-001-2001	low temperature resistance	hybridization	College of Life Sciences, Hunan Normal University [42]
"Xiangyun" Crucian Carp	GS-02-002-2001	low temperature resistance	hybridization	College of Life Sciences, Hunan Normal University [42]
"Xiangyun" Crucian Carp 2	GS-02-001-2008	Disease resistance, low temperature resistance and hypoxia tolerance	hybridization	College of Life Sciences, Hunan Normal University [5]
hybrid snakehead (*Channa argus* × *Channa maculata*)	GS-02-002-2014	low temperature resistance	hybridization	Chinese Academy of Fishery Sciences [43]
allogyogenetics silver crucian carp "Zhongke No.5" (*Carassius auratus gibelio*)	GS-01-001-2017	disease resistance	gynogenesis, group selection and MAS	Chinese Academy of Fishery Sciences [24]
Takifugu "Zhongyang 1" (*Takifugu obscurus*)	GS-01-003-2018	low temperature resistance	population selection	Jiangsu Zhongyang Group Yangtze River Rare Fish Development and Protection Engineering Technology Research Center [45]
turbot "Duobao No. 2" (*Scophthalmus maximus*)	GS-02-004-2022	high temperature resistance	family selection and QTL identification	Yellow Sea Fisheries Research Institute, Chinese Academy of Fishery Sciences [61,63]

of carp [42], tilapia [6] and rainbow trout [64]. With the development of high-throughput sequencing technology and the completion of genome sequencing of a variety of economic fish, fish breeding techniques are undergoing profound transformation. QTL mapping was widely used to accurately locate favorable genetic information of target traits and improve the accuracy of breeding programs [128]. The identification of genome-wide molecular markers for different traits are dramatically increasing in various fish species. GWAS can assist in the identification of whole genome loci for disease-resistant, cold-resistant, hypoxia-resistant, and saline-resistant in fish [129]. Fish breeding databases containing vast amount of molecular information will further facilitate the identification of molecular modules or markers strongly correlated with specific traits at the genome-wide level, thus to achieve large-scale screening of candidate parents with a small number of markers, and greatly shorten the breeding cycle and accelerate the breeding process of economic fish. Consequently, modern breeding techniques such as molecular marker-assisted selection and whole genome selection breeding were increasingly frequently applied in the breeding of fish for disease resistance, cold resistance, hypoxia tolerance, salt tolerance, and saline-alkali tolerance. New fish varieties cultivated with stress resistance were listed in Table 8.

For future research on stress resistance breeding of fish, a combination of conventional breeding techniques and genome-wide marker-assisted selection can be used. Firstly, conventional breeding methods are used to select phenotypes of excellent stress resistance traits, and then all the marker loci related to stress resistance traits are obtained through whole genome assisted breeding methods. Finally, the optimal combinations are found through the software, which can rapidly breed new aquatic varieties with strong stress resistance.

Meanwhile, modern molecular biology techniques will be integrated into the process of fish germplasm production. Liquid-phase microarray technology and multiplex PCR technology, combined with high-throughput sequencing, are being gradually applied to molecular marker-assisted breeding [130]. The first domestic largemouth bass 100K cGPS "Zhehu 1" was developed using cGPS (Genotyping by Pinpoint Sequencing of captured targets) technology independently developed by Huazhi Biotechnology. Based on the previous research, the chip enriches 561 loci related to growth, immunity, gender and high temperature resistance of largemouth bass, etc., which is beneficial for the identification and utilization of functional genes for high yield, disease resistance and high temperature resistance, etc., and the cultivation of new varieties. In addition, TILLING techniques [131] can be used to search for SNP markers in natural populations, thus integrating genetic maps and conducting molecular-assisted breeding. The CRISPR/cas9-mediated gene editing technology can rapidly improve target traits [132] and shorten the breeding time, which is of great significance for breeding new varieties with eminent resistance traits [133]. Innovative transgenesis based on CRISPR/Cas9 can site-directedly knock in exogenous genes at multiple loci, which may enhance favorable cross-resistance production traits.

In addition, through interdisciplinary research in functional genomics, molecular evolution, molecular toxicology and other disciplines, the molecular genetic mechanism of fish resistance to cold, salinity, hypoxia and disease will be revealed. These fundamental and theoretical studies on the aquatic sciences are conducive to solving the major critical technical problems that arise in the selection and production of germ plasm, promoting the breeding of more new fish varieties that are resistant to adverse environment. With the continuous innovation in efficient and accurate breeding technology, research on stress resistance breeding in aquatic animals can make significant breakthroughs in the near future.

CRediT authorship contribution statement

Jie Hu: Writing – review & editing, Project administration, Investigation. **Jie Yang:** Writing – original draft, Methodology, Formal analysis. **Huan Liao:** Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] H.H. Guo, Z. Hu, J.G. Zhang, G.W. Zou, H.W. Liang, Advances in environmental tolerance and resistance breeding in fish, J. Fish. China 47 (2023) 70–95.
[2] Q.Y. Wang, Fish vaccine technology development and application in China, J. Dalian Ocean Univ. 37 (2022) 1–9.
[3] W.Q. Lv, J.F. Gui, Stress coping strategy and its application in stress resistance breeding in fish, J. Fish. China 44 (2020) 505–513.

[4] Y.C. Shang, General Ecology, Peking University Press, 2002.

[5] S.J. Liu, A New Crucian Carp Variety-Xiangyun Crucian Carp 2, Rural Baishantong, 2018, p. 27.

[6] X.S. Shen, Q.Z. Ao, X. Gan, Y. Tan, Y.J. Luo, J.N. Liang, J.J. Zhu, Estimation of disease resistance and growth in F_5 generation families of GIFT Tilapia, South China Fisheries Science 14 (2018) 83–90.

[7] Y.L. Bai, J.Y. Wang, J. Zhao, Q.Z. Ke, A. Qu, Y.C. Deng, J.J. Zeng, J. Gong, J. Chen, Y. Pan, et al., Genomic selection for visceral white-nodules diseases resistance in large yellow croaker, Aquaculture 559 (2022) 738421.

[8] M.K. Holborn, K.P. Ang, J.A.K. Elliott, F. Powell, E.G. Boulding, Genome wide analysis of infectious salmon anemia resistance in commercial Saint John River Atlantic *salmon*, Aquaculture (2020) 514.

[9] G.L. Guo, A.J. Ma, L. Yue, Y.Q. Yue, G.Y. Wang, Progress of breeding for stress resistance in fish, Mar. Sci. 37 (2013) 148–156.

[10] K. Liu, J.X. Chen, S.F. Chen, P. Wu, L. Ding, K.K. Luo, J.S. Mao, G.Q. Wang, A comparison of immune related indicators between gynogenetic and common groups of grass carps, *Ctenopharyngodon idellus*, Life Sci. Res. 19 (2015) 213–217.

[11] G.G. Zhang, Preliminary Study on the Intestinal Disease Resistance of Hefang Grass Carp, Hunan Normal University, 2021.

[12] X. Zhou, F.Y. Gao, M.X. Lu, Progress on breeding of disease-resistance fishes, J. Dalian Ocean Univ. 36 (2021) 510–523.

[13] G.H. Yue, Recent advances of genome mapping and marker-assisted selection in aquaculture, Fish Fish. 15 (2014) 376–396.

[14] H.D. Daetwyler, R. Pong-Wong, B. Villanueva, J.A. Woolliams, The impact of genetic architecture on genome-wide evaluation methods, Genetics 185 (2010) 1021–1031.

[15] J.P. Lhorente, M. Araneda, R. Neira, J.M. Yanez, Advances in genetic improvement for salmon and trout aquaculture: the Chilean situation and prospects, Rev. Aquacult. 11 (2019) 340–353.

[16] K.D. Mahapatra, B. Gjerde, P.K. Sahoo, J.N. Saha, A. Barat, M. Sahoo, B. R. Mohanty, J. Ødegård, M. Rye, R. Salte, Genetic variations in survival of rohu carp (*Labeo rohita*, Hamilton) after *Aeromonas hydrophila* infection in challenge tests, Aquaculture 279 (2008) 29–34.

[17] L.F. Brito, H.R. Oliveira, B.R. McConn, A.P. Schinckel, A. Arrazola, J.N. Marchant-Forde, J.S. Johnson, Large-scale phenotyping of livestock welfare in commercial production systems: a new frontier in animal breeding, Front. Genet. 11 (2020) 793.

[18] S. Chen, J. Wang, S.J. Liu, Q.B. Qin, J. Xiao, W. Duan, K.K. Luo, J.H. Liu, Y. Liu, Biological characteristics of an improved triploid crucian carp, Sci. China C, Life Sci. 39 (2009) 479–484.

[19] S. Chen, Formation and Biological Characterizationof an Improved Triploid Crucian Crap, Hunan Normal University, 2009.

[20] H. Wu, L.F. Hou, J.Y. Huang, H. feng, Molecular cloning and preliminary functional study of *IFNa3* in No.2 of Xiangyun crucian carp, J. Fish. China 45 (2021) 1478–1490.

[21] S.J. Liu, Distant hybridization leads to different ploidy fishes, Science China, Life Sci. 53 (2010) 416–425.

[22] S.J. Liu, J. Luo, J. Chai, L. Ren, Y. Zhou, F. Huang, X.C. Liu, Y.B. Chen, C. Zhang, M. Tao, et al., Genomic incompatibilities in the diploid and tetraploid offspring of the goldfish × common carp cross, Proceedings of the National Academy of Sciences of the United States of America 113 (2016).

[23] J.X. Chen, P. Wu, L. Ding, C.S. Lv, K.K. Luo, G.Q. Wang, J.S. Mao, Preliminary research on the disease resistance of xiangyun crucian carp 2, Current Fisheries 40 (2015) 78–79.

[24] Y.Z. Zhou, Identification, Expression Profiles and Antiviral Activities of a Type I IFN from Gibel Carp Carassius auratus Gibelio, Huazhong Agric. Univ., 2019.

[25] G.D. Wiens, Y. Palti, T.D. Leeds, Three generations of selective breeding improved rainbow trout (*Oncorhynchus mykiss*) disease resistance against natural challenge with *Flavobacterium psychrophilum* during early life-stage rearing, Aquaculture 497 (2018) 414–421.

[26] R.D. Houston, Future directions in breeding for disease resistance in aquaculture species, Rev Bras Zootecn 46 (2017) 545–551.

[27] A. Ozaki, S.K. Khoo, Y. Yoshiura, M. Ototake, T. Sakamoto, J.M. Dijkstra, N. Okamoto, Identification of additional quantitative trait loci (QTL) responsible for susceptibility to infectious pancreatic necrosis virus in rainbow trout, Fish Pathol. 42 (2007) 131–140.

[28] R.D. Houston, C.S. Haley, A. Hamilton, D.R. Guy, J.C. Mota-Velasco, A.A. Gheyas, A.E. Tinch, J.B. Taggart, J.E. Bron, W.G. Starkey, et al., The susceptibility of Atlantic salmon fry to freshwater infectious pancreatic necrosis is largely explained by a major QTL, Heredity 105 (2010) 318–327.

[29] E. Sawayama, S.I. Kitamura, K. Nakayama, K. Ohta, H. Okamoto, A. Ozaki, M. Takagi, Development of a novel RSIVD-resistant strain of red sea bream (Pagrus major) by marker-assisted selection combined with DNA-based family selection, Aquaculture 506 (2019) 188–192.

[30] L. Wan, W.J. Wang, G.J. Liu, L.S. Dong, W.B. Li, Z.F. Han, K. Ye, Z.Y. Wang, A genome-wide association study of resistance to Pseudomonas plecoglossicida infection in the large yellow croaker (*Larimichthys crocea*), Aquacult. Int. 27 (2019) 1195–1208.

[31] S. Luo, A Genome-wide Association Study of Resistance to *Vibrio Harveyi* Infection in Yellow Drum (*Nibea Albiflora*) and the Study on the Function of Related Immune Gene, Jimei Univ., 2021.

[32] Y.C. Zhao, T.D. Wang, Z. Yu, H.M. Wang, B. Liu, C.Y. Wu, C.B. Teng, Inhibiting cyprinid herpesvirus-3 replication with CRISPR/Cas9, Biotechnol. Lett. 38 (2016) 573–578.

[33] J.H. Wang, Y. Cheng, Enhancing aquaculture disease resistance: antimicrobial peptides and gene editing, Review in aquaculture 16 (2023) 433–451.

[34] X.Y. Chen, S.J. Fan, C.C. Zhu, Q. Liao, J.H. Tang, G.Q. Yu, X.L. Cai, G. Ouyang, W. H. Xiao, X. Liu, Zebrafish sirt5 negatively regulates antiviral innate immunity by attenuating phosphorylation and ubiquitination of mavs, J. Immunol. 209 (2022) 1165–1172.

[35] X. Liu, C.C. Zhu, H.Y. Zha, J.H. Tang, F.J. Rong, X.Y. Chen, S.J. Fan, C.X. Xu, J. Du, J.J. Zhu, et al., *SIRT5* impairs aggregation and activation of the signaling adaptor MAVS through catalyzing lysine desuccinylation, The EMBO journal 39 (2020) e103285.

[36] X. Liu, C.C. Zhu, S.K. Jia, H.Y. Deng, J.H. Tang, X.Y. Sun, X.L. Zeng, X.Y. Chen, Z. X. Wang, W. Liu, et al., Dual modifying of MAVS at lysine 7 by SIRT3-catalyzed deacetylation and SIRT5-catalyzed desuccinylation orchestrates antiviral innate immunity, Proc. Natl. Acad. Sci. U S A 121 (2024) e2314201121.

[37] C.C. Zhu, W. Liu, S.K. Jia, X.Y. Sun, Z.X. Wang, H.Y. Deng, Y. Bai, W.H. Xiao, X. Liu, Grass carp (*Ctenopharyngodon idella*) SIRT3 enhances MAVS-mediated antiviral innate immunity in response to GCRV infection, Aquaculture 587 (2024) 740871.

[38] R.L. Gratacap, A. Wargelius, R.B. Edvardsen, R.D. Houston, Potential of genome editing to improve aquaculture breeding and production, Trends Genet. 35 (2019) 672–684.

[39] T. Bartolini, S. Butail, M. Porfiri, Temperature influences sociality and activity of freshwater fish, Environ. Biol. Fish. 98 (2015) 825–832.

[40] H.O. Portner, M.A. Peck, Climate change effects on fishes and fisheries: towards a cause-and-effect understanding, J. Fish. Biol. 77 (2010) 1745–1779.

[41] L.L. Liu, H. Zhu, Y.C. Yan, X.W. Wang, R. Zhang, J.Y. Zhu, Research progress of clod tolerance mechanism and functional genes in fish, Biotechnol. Bull. 34 (2018) 50–57.

[42] G.J. Zhou, Triploid New Fish-Xiangyun Crucian carp,Xiangyun Carp, Rural Practical Technology and Information, 2006, p. 60.

[43] B.X. Chen, J.X. Yi, K.C. Chen, M. Ou, H.Y. Liu, Q. Luo, X.W. Jiang, J. Zhao, Comparison of cold tolerance ability of three hybrid snakeheads, Journal of Aquaculture 41 (2020) 21–24.

[44] W.H. Li, Z.X. Zhou, X.L. Tian, H.Q. Li, J.S. Su, Q.L. Liu, P. Wu, S. Wang, J. Hu, Z. Y. Shen, et al., Gynogenetic *Cirrhinus mrigala* produced using irradiated sperm of *Cyprinus carpio* exhibit better cold tolerance, Reproduction and Breeding 3 (2023) 8–16.

[45] B.B. Yan, Y.P. Chen, Y.P. Lu, Z.L. Guo, Breeding technique of puffer fish new variety 'zhongyang No 1', Scientific Fish Farming (2019) 5–6.

[46] Z.F. Liu, X.N. Wang, A.J. Ma, L.G. Zhu, H.W. Chang, Z.B. Sun, Construction of a high-density genetic linkage map and QTL mapping of growth and cold tolerance traits in tiger puffer *Takifugu rubripes*, Aquaculture 561 (2022) 738613.

[47] Y. Zhang, J. Li, P. Chu, R.H. Shang, S.W. Yin, T. Wang, Construction of a high-density genetic linkage map and QTL mapping of growth and cold tolerance traits in *Takifugu fasciatus*, BMC Genom. 24 (2023) 645.

[48] X. Wen, X.Y. Zhang, Y.D. Hu, J.J. Xu, T. Wang, S.W. Yin, iTRAQ-based quantitative proteomic analysis of *Takifugu fasciatus* liver in response to low-temperature stress, J. Proteomics 201 (2019) 27–36.

[49] C.H. Ai, B.J. Li, J.H. Xia, Mapping QTL for cold-tolerance trait in a GIFT-derived tilapia line by ddRAD-seq, Aquaculture 556 (2022).

[50] T. Nitzan, T. Slosman, D. Gutkovich, J.I. Weller, G. Hulata, T. Zak, A. Benet, A. Cnaani, Maternal effects in the inheritance of cold tolerance in blue tilapia (*Oreochromis aureus*), Environ. Biol. Fish. 99 (2016) 975–981.

[51] P.Y. Chu, J.X. Li, T.H. Hsu, H.Y. Gong, C.Y. Lin, J.H. Wang, C.W. Huang, Identification of genes related to cold tolerance and novel genetic markers for molecular breeding in Taiwan Tilapia (*Oreochromis* spp.) via transcriptome analysis, Animals (Basel) 11 (2021) 3538.

[52] B.C.D. Silva, A. Pereira, N.D.C. Marchiori, K.H. Mariguele, H. Massago, G.H. F. Klabunde, Cold tolerance and performance of selected Nile tilapia for suboptimal temperatures, Aquacult. Res. 52 (2020).

[53] X.W. Sun, L.Q. Liang, A genetic linkage map of common carp (*Cyprinus carpio* L.) and mapping of a locus associated with cold tolerance, Aquaculture 238 (2004) 165–172.

[54] N. Suo, Y.D. Wu, Z.X. Zhou, Q. He, H.Q. Bai, H.N. Lin, Q.Z. Ke, P. Xu, Genome-wide association and expression analysis revealed the candidate variants and molecular Underpinnings of cold-stress response in large yellow croaker, Mar. Biotechnol. 24 (2022) 927–941.

[55] E.B. Blödorn, W.B. Domingues, L.S. Nunes, E.R. Komninou, D. Pinhal, V. F. Campos, MicroRNA roles and their potential use as selection tool to cold tolerance of domesticated teleostean species: a systematic review, Aquaculture 540 (2021) 736747.

[56] B.B. Miao, S.F. Niu, R.X. Wu, Z.B. Liang, B.G. Tang, Y. Zhai, X.Q. Xu, Gene expression profile and Co-expression network of pearl gentian grouper under cold stress by integrating illumina and PacBio sequences, Animals 11 (2021) 1745.

[57] W. Kraitavin, K. Yoshitake, Y. Igarashi, S. Mitsuyama, S. Kinoshita, D. Kambayashi, S. Watabe, S. Asakawa, Transcriptome analysis of Yamame (*Oncorhynchus masou*) in normal conditions after heat stress, Biology 8 (2019) 21.

[58] T. Zhou, Z. Yuan, S. Tan, Y. Jin, Y. Yang, H. Shi, W. Wang, D. Niu, L. Gao, W. Jiang, et al., A review of molecular responses of catfish to bacterial diseases and abiotic stresses, Front. Physiol. 9 (2018) 1113.

[59] A.F. Lopes, A.M. Faria, S. Dupont, Elevated temperature, but not decreased pH, impairs reproduction in a temperate fish, Sci. Rep. 10 (2020) 20805.

[60] J. Zhang, L. Sun, Transcriptome analysis reveals temperature-regulated antiviral response in turbot *Scophthalmus maximus*, Fish Shellfish Immunol. 68 (2017) 359–367.

[61] A.J. Ma, Z.H. Huang, X.A. Wang, L. Guo, J.L. Lei, Z. Yang, J.B. Qu, The selective breeding of thermal tolerance family and appraisal of performance in turbot *scophthalmus maximus*, Agricultural and Food Sciences 43 (2012) 797–804.

[62] A.J. Ma, Z.H. Huang, X.A. Wang, Y.H. Xu, X.L. Guo, Identification of quantitative trait loci associated with upper temperature tolerance in turbot, *Scophthalmus maximus*, Sci. Rep. 11 (2021) 21920.

[63] X.A. Wang, A.J. Ma, Z.H. Huang, Z.B. Sun, W.X. Cui, J.B. Qu, H. Yu, Estimation of genetic parameters for upper thermal tolerances and growth-related traits in turbot *Scophthalmus maximus*, J. Oceanol. Limnol. 37 (2019) 1736–1745.

[64] T. Ineno, S. Tsuchida, M. Kanda, S. Watabe, Thermal tolerance of a rainbow trout *Oncorhynchus mykiss* strain selected by high-temperature breeding, Fisheries Sci 71 (2005) 767–775.

[65] T. Ineno, K. Tamaki, K. Yamada, R. Kodama, S. Tsuchida, E. Tan, S. Kinoshita, K. Muto, T. Yada, S. Kitamura, et al., Thermal tolerance of a thermally selected strain of rainbow trout *Oncorhynchus mykiss* and the pedigrees of its F$_1$ and F$_2$ generations indicated by their critical thermal maxima, Fisheries Sci 84 (2018) 671–679.

[66] X.M. Chen, J.K. Li, Z.Y. Wang, M.Y. Cai, X.D. Liu, Thermal tolerance evaluation and related microsatellite marker screening and identification in the large yellow croaker *Larimichthys crocea*, Chin. J. Oceanol. Limnol. 35 (2017) 566–571.

[67] K.P. Shi, S.L. Dong, Y.G. Zhou, Y. Li, Q.F. Gao, D.J. Sun, RNA-seq reveals temporal differences in the transcriptome response to acute heat stress in the Atlantic salmon (*Salmo salar*), Comp. Biochem. Physiol. D Genomics Proteomics 30 (2019) 169–178.

[68] T.Q. Huang, W. Gu, E.H. Liu, B.Q. Wang, G.H. Wang, F.L. Dong, F.Y. Guo, W. L. Jiao, Y.C. Sun, X.C. Wang, et al., miR-301b-5p and its target gene *nfatc2ip* regulate inflammatory responses in the liver of rainbow trout (*Oncorhynchus mykiss*) under high temperature stress, Ecotoxicol. Environ. Saf. 242 (2022).

[69] K. Bianchini, P.A.K. Wright, Hypoxia delays hematopoiesis: retention of embryonic hemoglobin and erythrocytes in larval rainbow trout, *Oncorhynchus mykiss*, during chronic hypoxia exposure, J. Exp. Biol. 216 (2013) 4415–4425.

[70] H.L. Li, X.H. Gu, B.J. Li, C.H. Chen, H.R. Lin, J.H. Xia, Genome-wide QTL analysis identified significant associations between hypoxia tolerance and mutations in the GPR132 and ABCG4 genes in nile Tilapia, Mar. Biotechnol. 19 (2017) 441–453.

[71] H. Xu, X.M. Chen, G.Q. Wang, L.M. Cong, W. Chen, Research progress on hypoxia stress in aquaculture, Feed Industry 37 (2016) 33–37.

[72] D.B. Gong, L.H. Xu, C. Wu, S. Wang, Q.F. Liu, L. Cao, Z.W. Mao, Y.D. Wang, F. Z. Hu, R. Zhou, et al., Two types of gynogenetic blunt snout bream derived from different sperm, Aquaculture 511 (2019) 734250.

[73] D.B. Gong, L.H. Xu, W.H. Li, R.J. Shang, J.X. Chen, F.Z. Hu, S. Wang, Q.F. Liu, C. Wu, R. Zhou, et al., Comparative analysis of liver transcriptomes associated with hypoxia tolerance in the gynogenetic blunt snout bream, Aquaculture 523 (2020).

[74] W. Fu, X.B. Chu, W.Q. Xiao, T.Y. Shen, L.Y. Peng, Y.D. Wang, W.B. Liu, L. J.H, K. K. Luo, B. Chen, et al., Identification of gynogenetic *Megalobrama amblycephala* induced by red crucian carp sperm and establishment of a new hypoxia tolerance strain, Aquaculture 548 (2022) 737608.

[75] F.G. Li, G.D. Zheng, C.B. Wu, J. Chen, X.Y. Jiang, S.M. Zou, Establishment of hypoxia-tolerant F$_3$ generation of *Megalobrama amblycephala* and their growth performance under long-term hypoxia, J. Fish. China 42 (2018) 236–254.

[76] C.B. Wu, G.D. Zheng, X.Y. Zhao, S. Zhou, S.M. Zou, Hypoxia tolerance in a selectively bred F$_4$ population of blunt snout bream (*Megalobrama amblycephala*) under hypoxic stress, Aquaculture 518 (2019) 734484.

[77] D.D. Wang, X.N. Xu, C.B. Wu, J. Chen, S.M. Zou, Screening of hypoxia-tolerance related SNP in a selectively bred F$_5$ strain of blunt snout bream (*Megalobrama amblycephala*), Aquaculture 519 (2019) 734840.

[78] S.S. Zhao, X.L. Su, H.Q. Yang, G.D. Zheng, S.M. Zou, Functional exploration of SNP mutations in *HIF2αb* gene correlated with hypoxia tolerance in blunt snout bream (*Megalobrama amblycephala*), Fish Physiol. Biochem. 49 (2023).

[79] X.X. Zhong, X.Z. Wang, T. Zhou, Y.L. Jin, S.X. Tan, C. Jiang, X. Geng, N. Li, H. T. Shi, Q.F. Zeng, et al., Genome-wide association study reveals multiple novel QTL associated with low oxygen tolerance in hybrid catfish, Mar. Biotechnol. 19 (2017) 379–390.

[80] L.Z. San, B.S. Liu, B. Liu, K.C. Zhu, L. Guo, H.Y. Guo, N. Zhang, S.G. Jiang, D. C. Zhang, Genome-wide association study reveals multiple novel SNPs and putative candidate genes associated with low oxygen tolerance in golden pompano Trachinotus ovatus (Linnaeus 1758), Aquaculture 544 (2021) 737098.

[81] G.S. Zhang, J. Li, J.J. Zhang, X. Liang, T. Wang, S.W. Yin, A high-density SNP-based genetic map and several economic traits-related loci in *Pelteobagrus vachelli*, BMC Genom. 21 (2020) 700.

[82] B.Y. Wu, J. Xu, D.C. Cao, P. Xu, H.Y. Zhang, Y.X. Zhu, Y.L. Jiang, Z.X. Zhao, Genome-wide association analysis of hypoxia adaptation traits in common carp (*Cyprinus carpio*), Progress in Fishery Sciences 43 (2022) 98–106.

[83] X. Geng, J.B. Feng, S.K. Liu, Y.P. Wang, C. Arias, Z.J. Liu, Transcriptional regulation of hypoxia inducible factors alpha (HIF-α) and their inhibiting factor (FIH-1) of channel catfish (*Ictalurus punctatus*) under hypoxia, Comp. Biochem. Physiol. B Biochem. Mol. Biol. 169 (2014) 38–50.

[84] R.N. Jia, F. Lin, Q.H. Xu, Differential expression analysis of the ribosomal protein gene family in zebrafish gills under hypoxia stress, J. Shanghai Ocean Univ. 31 (2022) 318–327.

[85] R.B. Baptista, N. Souza-Castro, V.M. Almeida-Val, Acute hypoxia up-regulates HIF-1α and VEGF mRNA levels in Amazon hypoxia-tolerant Oscar (Astronotus ocellatus), Fish Physiol. Biochem. 42 (2016) 1307–1318.

[86] F.G. Li, J. Chen, X.Y. Jiang, S.M. Zou, Transcriptome analysis of blunt snout bream (*Megalobrama amblycephala*) reveals putative differential expression genes related to growth and hypoxia, PLoS One 10 (2015) e0142801.

[87] D.Y. Cao, J.F. Li, B.S. Huang, J.D. Zhang, C.H. Pan, J.S. Huang, H. Zhou, Q. Ma, G. Chen, Z.L. Wang, RNA-seq analysis reveals divergent adaptive response to hyper- and hypo-salinity in cobia, Rachycentron canadum, Fish Physiol. Biochem. 46 (2020) 1713–1727.

[88] X.Y. Zhang, H.S. Wen, H.L. Wang, Y.Y. Ren, J. Zhao, L. Yun, RNA-Seq analysis of salinity stress–responsive transcriptome in the liver of spotted sea bass (*Lateolabrax maculatus*), PLoS One 12 (2017) e0173238.

[89] F. Farzadfar, B. Doustshenas, A. Rezaie, S.M. Mousavi, Salinity induced alterations in ionic concentration of haemolymph and its effects on histopathology of gills and digestive gland in razor clam (*Solen dactylus*;von Cosel, 1989; Bivalvia, Solenidae), Molluscan Res. 41 (2021) 92–102.

[90] R. Takata, C.C. Mattioli, N. Bazzoli, J.D.C. Júnior, R.K. Luz, The effects of salinity on growth, gill tissue and muscle cellularity in *Lophiosilurus alexandri* juvenile, a Neotropical freshwater catfish, Aquacult. Res. 52 (2021) 4064–4075.

[91] T.T. Guo, Y. Yang, F. Meng, S.D. Wang, S.L. Xia, Y.X. Qian, M. Li, R.X. Wang, Effects of low salinity on gill and liver glycogen metabolism of great blue-spotted mudskippers (*Boleophthalmus pectinirostris*), Comp. Biochem. Physiol. C Toxicol. Pharmacol. 230 (2020) 108709.

[92] D.L. Jiang, X.H. Gu, B.J. Li, Z.X. Zhu, H. Qin, Z.N. Meng, H.R. Lin, J.H. Xia, Identifying a long QTL cluster across chrLG18 associated with salt tolerance in Tilapia using GWAS and QTL-seq, Mar. Biotechnol. 21 (2019) 250–261.

[93] X.H. Gu, D.L. Jiang, Y. Huang, B.J. Li, C.H. Chen, H.R. Lin, J.H. Xia, Identifying a major QTL associated with salinity tolerance in nile Tilapia using QTL-seq, Mar. Biotechnol. 20 (2018) 98–107.

[94] D. Kultz, Physiological mechanisms used by fish to cope with salinity stress, J. Exp. Biol. 218 (2015) 1907–1914.

[95] X.H. Gu, H.R. Lin, J.H. Xia, Significant association of SNP polymorphism in the tilapia enhancer of polycomb homolog 1 gene with salt tolerance, Aquacult. Res. 49 (2018) 1690–1698.

[96] X.H. Gu, B.J. Li, H.R. Lin, J.H. Xia, Unraveling the associations of the tilapia DNA polymerase delta subunit 3 (POLD3) gene with saline tolerance traits, Aquaculture 485 (2018) 53–58.

[97] H. Qin, Z.X. Zhu, H.R. Lin, J.H. Xia, Y.X. Jia, Exploring candidate genes in a major QTL region associated with salinity tolerance in the skin of Nile tilapia based on transcriptomic analysis, Aquaculture 526 (2020) 735380.

[98] Y.H. Peng, H.J. Shi, Y.Q. Liu, Y. Huang, R.C. Zheng, D.N. Jiang, M.Y. Jiang, C. H. Zhu, G.L. Li, RNA sequencing analysis reveals divergent adaptive response to hypo- and hyper-salinity in greater Amberjack (*Seriola dumerili*) Juveniles, Animals 12 (2022) 327.

[99] H.Y. Zhao, Q.K. Wang, H.H. Zhao, C.X. Chen, Transcriptome profiles revealed high- and low-salinity water altered gill homeostasis in half-smooth tongue sole (*Cynoglossus semilaevis*), Comp. Biochem. Physiol. Genom. Proteonomics 42 (2022) 100989.

[100] D.C. Shi, L.J. Yin, Difference between salt (NaCl) and alkaling (Na_2CO_3) stress on *Puccinellia tenuiflora* (Griseb.) J. Integr, Plant. Biol. 35 (1993) 144–149.

[101] Y.J. Zhou, Effects of Saline-Alkali Stress on Growth, Reproduction and Immune Function of *Fenneropenaeus chinensis*, Dalian Ocean University, 2023.

[102] M.P. Wilkie, P.A. Wright, G.K. Iwama, C.M. Wood, The physiological adaptations of the lahontan cutthroat trout (*Oncorhynchus clarki henshawi*) following transfer from well water to the highly alkaline waters of pyramid lake, Nevada (pH 9.4), Physiol. Zool. 67 (1994) 355–380.

[103] J. Sashaw, M. Nawata, S. Thompson, C.M. Wood, P.A. Wright, Rhesus glycoprotein and urea transporter genes in rainbow trout embryos are upregulated in response to alkaline water (pH 9.7) but not elevated water ammonia, Aquat. Toxicol. 96 (2010) 308–313.

[104] Y.K. Ip, S.F. Chew, Ammonia production, excretion, toxicity, and defense in fish, Front. Physiol. 1 (2010) 134.

[105] M.P. Wilkie, C.M. Wood, The adaptations of fish to extremely alkaline environments, Comp. Biochem. Phys. B Biochemistry and Molecular Biology 113 (1996) 665–673.

[106] Z.X. Zhu, Y.L. Lin, H. Qin, Y.Y. Xiong, D.L. Jiang, H.R. Lin, Z.L. Yu, J.H. Xia, Identifying a genome-wide QTL interval controlling for ammonia-nitrogen tolerance on chrLG1 of Nile tilapia, Aquaculture 543 (2021) 736946.

[107] T.F. Xu, X.H. Zhang, Z.Q. Ruan, H. Yu, J.M. Chen, S.J. Jiang, C. Bian, B. Wu, Q. Shi, X.X. You, Genome resequencing of the orange-spotted grouper (*Epinephelus coioides*) for a genome-wide association study on ammonia tolerance, Aquaculture 512 (2019) 734332.

[108] J.W. Wu, J.L. Zhao, Y. Zhao, M.K. Luo, Y. Wang, Y.H. Zhao, Change in ammonia metabolism gene expression of *Oreochromis niloticus* under the stress of high carbonate alkalinity, J. Fish. Sci. China 23 (2016) 1290–1299.

[109] E. Danulat, S. Kempe, Nitrogenous waste excretion and accumulation of urea and ammonia in *Chalcalburnus tarichi* (*Cyprinidae*), endemic to the extremely alkaline Lake Van (Eastern Turkey), Fish Physiol. Biochem. 9 (1992) 377–386.

[110] H.H. Su, D.M. Ma, H.P. Zhu, Z.G. Liu, F.Y. Gao, Transcriptomic response to three osmotic stresses in gills of hybrid tilapia (*Oreochromis mossambicus* female × *O. urolepis hornorum* male), BMC Genom. 21 (2020) 110.

[111] H. Selye, A syndrome produced by diverse nocuous agents, Nature 138 (1936) 32, 32.

[112] M.W.T. Tanck, T. Claes, H. Bovenhuis, J. Komen, Exploring the genetic background of stress using isogenic progenies of common carp selected for high or low stress-related cortisol response, Aquaculture 204 (2002) 419–434.

[113] S.E. Fevolden, T. Refstie, B. Gjerde, Genetic and phenotypic parameters for cortisol and glucose stress response in Atlantic salmon and rainbow trout, Aquaculture 118 (1993) 205–216.

[114] G.K. Iwama, Stress in fish, Ann. N. Y. Acad. Sci. 851 (1998) 304–310.

[115] M.L. Ruiz-Gómez, S. Kittilsen, E. Höglund, F. Huntingford, C. Sørensen, T. G. Pottinger, M. Bakken, S. Winberg, W.J. Korzan, Ø. Øverli, Behavioral plasticity

in rainbow trout (*Oncorhynchus mykiss*) with divergent coping styles: when doves become hawks, Horm. Behav. 54 (2008) 534–538.

[116] N.J. Bernier, R.E. Peter, The hypothalamic-pituitary-interrenal axis and the control of food intake in teleost fish, Comp. Biochem. Physiol. B Biochem. Mol. Biol. 129 (2001) 639–644.

[117] L. Hong, X.M. Zhang, Effects of environmental stress on physiological function of fish, Adv. Mar. Sci. 22 (2004) 114–121.

[118] M.W.T. Tanck, K.-J. Vermeulen, H. Bovenhuis, H. Komen, Heredity of stress-related cortisol response in androgenetic common carp (*Cyprinus carpio* L.), Aquaculture 199 (2001) 283–294.

[119] T.G. Pottinger, T.R. Carrick, Modification of the plasma cortisol response to stress in rainbow trout by selective breeding, Gen. Comp. Endocr. 116 (1999) 122–132.

[120] A. Madaro, F. Lai, P.G. Fjelldal, T. Hansen, V. Gelebart, B. Muren, I. Rønnestad, R. E. Olsen, L.H. Stien, Comparing physiological responses of acute and chronically stressed diploid and triploid Atlantic salmon (*Salmo salar*), Aquacult. Rep. 36 (2024) 102041.

[121] J.A. Calduch-Giner, G. Davey, A. Saera-Vila, B. Houeix, A. Talbot, P. Prunet, M. T. Cairns, J. Pérez-Sánchez, Use of microarray technology to assess the time course of liver stress response after confinement exposure in gilthead sea bream (*Sparus aurata* L.), BMC Genom. 11 (2010) 193.

[122] C. Tognoli, F. Rossi, F. Di Cola, G. Baj, E. Tongiorgi, G. Terova, M. Saroglia, G. Bernardini, R. Gornati, Acute stress alters transcript expression pattern and reduces processing of proBDNF to mature BDNF in *Dicentrarchus labrax*, BMC Neurosci. 11 (2010) 4.

[123] T.G. Pottinger, A.D. Pickering, M.A. Hurley, Consistency in the stress response of individuals of two strains of rainbow trout, Oncorhynchus mykiss, Aquaculture 103 (1992) 275–289.

[124] Ø. Øverli, T.G. Pottinger, T.R. Carrick, E. Overli, S. Winberg, Differences in behaviour between rainbow trout selected for high- and low-stress responsiveness, J. Exp. Biol. 205 (2002) 391–395.

[125] T.G. Pottinger, T.R. Carrick, Stress responsiveness affects dominant-subordinate relationships in rainbow trout, Horm, Beyond Behav. 40 (2001) 419–427.

[126] Ø. Øverli, C. Sørensen, A. Kiessling, T. Pottinger, H. Gjøen, Selection for improved stress tolerance in rainbow trout (*Oncorhynchus mykiss*) leads to reduced feed waste, Aquaculture 261 (2006) 776–781.

[127] G.M. Weber, R.L. Vallejo, S.E. Lankford, J.T. Silverstein, T.J. Welch, Cortisol response to a crowding stress: heritability and association with disease resistance to Yersinia ruckeri in rainbow trout, J. Aquacult. 70 (2008) 425–433.

[128] X.X. You, X.X. Shan, Q. Shi, Research advances in the genomics and applications for molecular breeding of aquaculture animals, Aquaculture 526 (2020). Not Available.

[129] M. Sodeland, M. Gaarder, T. Moen, M. Thomassen, S. Kjøglum, M. Kent, S. Lien, Genome-wide association testing reveals quantitative trait loci for fillet texture and fat content in Atlantic salmon, Aquaculture 408 (2013) 169–174.

[130] M.J. Shi, W.T. Zhang, Y.Y. Cheng, X.Q. Xia, Fish breeding technology based on whole genome alalysis and its application, J. Agric. Sci. Technol. 24 (2022) 33–41.

[131] B. Hussain, Modernization in plant breeding approaches for improving biotic stress resistance in crop plants, Turk. J. Agric. For. 39 (2015) 515–530.

[132] Y.X. Wang, N. Zafar, Q. Ali, H. Manghwar, G.Y. Wang, L. Yu, X. Ding, F. Ding, N. Hong, G.P. Wang, et al., CRISPR/Cas genome editing technologies for plant improvement against biotic and abiotic stresses: advances, limitations, and future perspectives, Cells 11 (2022) 3928.

[133] H.C. Zhu, C. Li, C.X. Gao, Applications of CRISPR-Cas in agriculture and plant biotechnology, Nat. Rev. Mol. Cell Biol. 21 (2020) 661–677.