Genetic and epigenetic regulation of growth, reproduction, disease resistance and stress responses in aquaculture

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Major progress has been made with genomic and genetic studies in aquaculture in the last decade. However, research on epigenetic regulation of aquaculture traits is still at an early stage. It is apparent that most, if not all, aquaculture traits are regulated at both genetic and epigenetic levels. This paper reviews recent progress in understanding of genetic and epigenetic regulation of important aquaculture traits such as growth, reproduction, disease resistance, and stress responses. Although it is challenging to make generalized statements, DNA methylation is mostly correlated with down-regulation of gene expression, especially when at promoters and enhancers. As such, methylation of growth factors and their receptors is negatively correlated with growth; hypomethylation of genes important for stress tolerance is correlated with increased stress tolerance; hypomethylation of genes important for male or female sex differentiation leads to sex differentiation into males or females, respectively. It is apparent that environmental regulation of aquaculture traits is mediated at the level of epigenetic regulation, and such environment-induced epigenetic changes appeared to be intergenerationally inherited, but evidences for transgenerational inheritance are still limited.

KEYWORDS
DNA methylation, epigenetic regulation, genome, QTL, fish, shellfish, aquaculture

1 Introduction

Important performance and production traits for aquaculture include growth rate, feed conversion efficiency, disease resistance, stress tolerance such as low oxygen tolerance, reproductive success, harvestability, and processing yields, among many others (Gjedrem, 2012; Boyd, 2015; Abdelrahman et al., 2017; Zhong et al., 2017; Li et al., 2019; Houston et al., 2020; Xu et al., 2022). Of these traits, disease resistance continues to be the top priority for aquaculture production because disease problems constitute the largest single cause of economic losses in aquaculture (Mzula et al., 2021; Naylor et al., 2021). Most, if not all, of these traits are regulated at both genetic and
epigenetic levels, and as such, understanding of genetic and epigenetic regulation of aquaculture traits is of high priority for aquaculture genomics and genetics research (Abdelrahman et al., 2017; Granada et al., 2018; Rexroad et al., 2019; Roy et al., 2021; Ren et al., 2022).

The central dogma has guided biological research for over half of a century. However, research advances in the last 20 years have provided information for the more complete interpretation of the central dogma. These included the huge regulatory functions of non-coding and small RNAs, epigenetic regulation through DNA methylation, and epigenetic regulation through histone modifications. This review will focus on DNA methylation and its regulation of genomic expression related to aquaculture traits. While research is very active with non-coding RNAs and histone modifications with aquaculture species, systematic knowledge of how such mechanisms are involved in the control of aquaculture traits is yet to be published, and as such, we will only briefly discuss epigenetic regulation through histone modifications.

In eukaryotic organisms, cytosine methylation is the primary form of DNA methylation, and 5 mC is the major methylated form of cytosine. As shown in Figure 1, DNA methylation can insert its roles in the regulation of genome expression at the level of transcription through activation or repression of transcription, thereby having an impact on the types of transcripts and their amounts, or at the level of posttranscription. At the organismal level, DNA methylation is involved in gamete production, embryonic and later development, and differentiation.

In the last decade, drastic progress has been made in aquaculture genomics and genetics research. Major milestones included the production of whole genome sequences for many aquaculture species. Many of these genome sequences are of high quality. The availability of high-quality genome sequence assemblies allowed mapping of QTLs controlling important performance and production traits to chromosomal locations, with information of tightly linked markers, especially sequence-tagged single nucleotide polymorphic (SNP) markers. Such high-quality genome sequence assemblies also allowed mapping of methylated bases to genome locations in relation to performance traits. At the same time, high throughput RNA-Seq has allowed
qualitative as well as quantitative assessment of genome-wide transcription in relation to genomic sequence variations and epigenomic regulation. This review will summarize recent studies of aquaculture traits at genetic and epigenetic levels, with a focus of DNA methylation.

2 DNA methylation and epigenetic regulation

DNA methylation is catalyzed by DNA methyltransferases, and its regulation of gene expression is materialized by the differential binding affinities of methylated DNA to various transcriptional factors and methylated DNA binding proteins, as compared to those of unmethylated DNA. Most often, methylation at the transcriptional regulatory sequences such as the promoters has a negative impact to the transcription of the involved gene(s). Therefore, significantly lower levels of CpG methylation have been observed around transcriptional start sites (TSS). This section reviews general information of DNA methylation and its regulation at various levels.

2.1 DNA methyltransferases and methylated DNA binding proteins

DNA methyltransferases (DNMTs) regulate the transfer of methyl groups from S-adenosylmethionine to cytosine residues on genomic DNA. In mammals there are four members of the DNMT family, including DNMT1, DNMT3A, DNMT3B, and DNMT3L, of which DNMT3L does not harbor any transferase activities (Jin and Robertson, 2013), but is essential for establishment of maternal genomic imprints in the growing oocyte and at dispersed repeated sequences. In addition, DNMT2 exists in most, if not all, eukaryotic organisms as a homologue of DNA methyltransferase. It has all the sequence characteristics of a cytosine methyltransferase but has not been demonstrated to carry any methyltransferase activities. DNMT1 has greater methyltransferase activity than DNMT3B. DNMT3B, and DNMT3, DNMT5, and DNMT7 are unique in fishes (Balasubramanian et al., 2019). DNA methyltransferases have also been studied in other fishes such as Japanese rice fish (Dasmahapatra and Khan, 2015), mandarin fish (Zhou et al., 2021), fathead minnow (Wood et al., 2016), and goldfish (Zhang et al., 2014).

Several methylated DNA binding proteins have been identified, whose expression is involved in the epigenetic regulation through DNA methylation. These included methyl-CpG binding protein 2 (MeCP2), and methyl-CpG-binding domain proteins 1 (MBD1) and 2 (MBD2). MeCP2 is believed to be a global repressor of methylated promoters (Cross et al., 1997), and MBD1 and MBD2 have also been reported to bind with higher affinity to methylated CpG sites than to unmethylated sites (Goll and Bestor, 2005). To date, methylated DNA binding proteins have been studied with aquatic animals only in model species such as zebrafish (Gao et al., 2015; Nozawa et al., 2017).

2.2 DNA demethylation

The reverse of DNA methylation is DNA demethylation that can happen passively or actively. Functional deficiency in maintenance of methylation can lead to replication-dependent dilution of 5 mC, which is known as passive DNA methylation (for a review, see Zeng and Chen, 2019). Active DNA demethylation involves rapid loss of DNA methylation by removal of the methyl group from 5 mC. The first step of active demethylation involves oxidation of 5 mC by the ten-eleven translocation (TET) family of enzymes, TET1, TET2, and TET3, which oxidizes 5 mC into 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC), and 5-carboxylcytosine (5caC) (Tahiliani et al., 2009; Ito et al., 2010, 2011; He et al., 2011). These oxidized products serve as intermediates of DNA demethylation. They are repaired into unmodified C, achieving demethylation (reviewed by Zeng and Chen, 2019).

2.3 Major methylation sites in the context of genomic DNA

Although methylation of adenine can also happen, we will focus this review on methylation of cytosine. Depending on the sequence context where base C is situated, the chances of being methylated vary greatly (Figure 2). The position of C in a sequence can be in three different situations: 1) CG motifs; 2) CHG motifs where H is A, C, or T; and 3) CHH, where H is A, C, or T. In many fish species studied to date, approximately 70%–80% CpG sites were found to be methylated. For
instance, 74.5%–78.4% of all C’s at the CpG sites were methylated in channel catfish (Yang et al., 2022). This is similar to those observed in other vertebrate animal species, slightly higher than that seen in mice (74%) (Feng et al., 2010) and tilapia (69.60%) (Wan et al., 2016), but slightly lower than that in zebrafish (80.3%) (Feng et al., 2010). Methylation rate at CHG and CHH sites are much less frequent, at only miniscule scale as compared to methylation at CpG sites. For example, only 0.3%–0.4% of Cs within the CHG and CHH context were methylated in channel catfish (Yang et al., 2022). Similarly, only 1.22% and 0.91% of Cs within CHG and CHH context were methylated in zebrafish (Feng et al., 2010), 0.47% and 0.57% of Cs within CHG and CHH were methylated in tilapia (Wan et al., 2016). However, methylation rates at CHG and CHH sites is much higher in plants (Kenchanmane Raju et al., 2019).

In contrast to the situations with teleost fish, methylation in invertebrate aquaculture species such as mollusks and crustaceans appeared to be quite different in two aspects: 1) the levels of methylation in crustaceans and bivalves appear to be much lower than those in teleost fish; and 2) DNA methylation in these invertebrate species appears to be predominantly found in gene bodies (Gavery and Roberts, 2013; Gavery and Roberts, 2014). For example, about 15% of CG (1.8% total cytosines) in the Pacific oyster Crassostrea gigas genome are methylated (Gavery and Roberts, 2013), which is similar to those in gastropod (snails have ~2% of cytosines being methylated) (Fneich et al., 2013), but much lower than those observed with vertebrate animals. With marbled crayfish, Procambarus virginalis, the global 5-methylcytosine level was 2.78% at mid-embryonic development and decreased slightly to 2.41% in 2-year-old adults (Vogt, 2022). Methylation levels are even lower with micro-crustaceans. Average percentage CpG methylation was below 1% (Kvist et al., 2018) or just slightly above 1% with Daphnia magna (Hearn et al., 2021). Using whole genome bisulfite sequencing, Kvist et al. (2018) demonstrated that DNA methylation in Daphnia is mainly enriched within the coding regions of genes, with the highest methylation levels observed at exons 2–4, in contrast to the situations of vertebrates whose genomes are globally methylated. Significant negative correlation between gene family size and the degree of methylation was observed with Daphnia, suggesting that gene body methylation may help regulate gene family expansion and functional diversification of gene families leading to phenotypic variations (Asselman et al., 2016).

### 2.4 Regulation of gene expression through DNA methylation

Epigenetics refers to heritable changes in gene expression and phenotype that arise “on top of” or “in addition to” primary DNA sequence. After almost half a century since the term was published, epigenetics has now become one of the
hottest research areas in biology because it is involved in essentially all biological processes and often serves as a mechanism of control and regulation. These processes span from life to death involving embryonic development, cell cycle control, growth and development, differentiation, responses to diseases and other environmental factors (Venney et al., 2021), and regulation of aging and cancer (for review, see Skvortsova et al., 2018; Zeng and Chen, 2019; Vidaurre and Chen, 2021; Fu et al., 2020).

A well-established concept of epigenetic regulation is that DNA methylation regulates gene expression by inhibiting the binding of transcription factor(s) to DNA or recruiting proteins involved in gene repression, thereby repressing transcription (Jones, 2012; Moore et al., 2013). Because this is well established and almost over-used concept, we will not further elaborate on this. However, regulation of gene expression by DNA methylation is more complex than this simple notion. In fact, DNA methylation can not only repress transcription, but also activate transcription. For example, transcriptional anti-silencing factors SUVH1 and SUVH3 bind to methylated DNA and recruit the DNAJ proteins to enhance proximal gene expression, thereby encountering the repressive effects of transposon insertion near genes (Harris et al., 2018).

How DNA methylation regulates transcription is complex depending on where and when DNA methylation occurs in relation to gene structure and development. The promoter-region hypermethylation events are especially critical and can frequently serve as alternative mechanisms for coding-region mutations for loss of key gene function (Herman and Baylin, 2000). CpG methylation in promoters are negatively correlated with transcription. As such, most CpG islands when located at transcription start sites are not methylated (Jones, 2012). Hypermethylation of the promoter and coding region can inhibit gene expression, while demethylation of the promoter and coding region can activate gene expression (Han et al., 2021a). However, intragenic methylation of CpG sites can activate transcription (Jones, 2012), but such positive correlation of intragenic methylation and transcriptional activation may be tissue specific. Intragenic methylation at CH sites is positively correlated with gene expression in human embryonic cells but is negatively correlated with gene expression in the brain (Luo et al., 2018).

2.5 Regulation of recombination through DNA methylation

Genes are not distributed evenly in the genome. Instead, genomes are divided into gene-rich euchromatin regions and repeat-rich heterochromatin regions. Typically, chromosome regions such as centromeres, telomeres are composed almost purely of repetitive sequences. In addition, ribosomal (rRNA) and transfer RNA (tRNA) loci are composed of tandem repeats of these structural RNA genes. Transposable elements can be highly repetitive but in teleost fish, the most abundant types of transposable elements are Tc1/mariner type of transposons that are dispersed throughout the genomes. Repeat-containing regions undergo little or no meiotic crossover recombination.

DNA methylation is a widespread epigenetic mark of repeat sequences associated with heterochromatin in eukaryote genomes. DNA methylation repress meiotic recombination. Recombination rates in heterochromatin regions are generally very low. For instance, genomic regions surrounding the centromeres are generally enriched in DNA methylation and histone modifications such as H3K9me2 (Simon et al., 2015), and there is no recombination in centromeric regions (Termolino et al., 2016). However, the causal relationship of DNA methylation and recombination is not fully demonstrated. The repressive roles of methylation on meiotic recombination in euchromatic regions have been demonstrated, but additional factors may be involved in controlling the suppression of recombination in heterochromatin. For instance, in Arabidopsis, deficiency in DNA methylation increased meiotic crossover rates in euchromatic but not in heterochromatic regions (Melamed-Bessudo and Levy, 2012).

2.6 Regulation of alternative splicing through DNA methylation

Alternative splicing is an evolutionarily conserved mechanism that increases transcriptome diversity by producing multiple mRNA products from a single gene. In humans, >90% of genes have alternatively spliced transcripts (Wang et al., 2008). In fish species, the proportion of genes with alternative splicing is probably lower. In channel catfish, approximately 39% of genes were found with alternative splice transcripts after infection with Edwardsiella ictaluri (Tan et al., 2018a). Methylation levels in exons are higher than in introns, and alternative exons display lower levels of DNA methylation than constitutively spliced exons, suggesting methylation is involved in alternative splicing (Lev Maor et al., 2015). Such regulation of alternative splicing is believed to be mediated by CCCTC-binding factor (CTCF). Intragenic CTCF binding sites, particularly those proximal to splice junctions, influence pre-mRNA splicing decisions, and thus mediate alternative exon or intron inclusion (for a review, see Alharbi et al., 2021). DNA methylation at CpG sites within CTCF target sites can prevent CTCF binding, thereby regulating alternative splicing. Such regulatory processes also involve MeCP2 and TET1. DNA methylation mediates opposing effects on the role of CTCF and MeCP2 binding to DNA and subsequently regulation of pre-mRNA splicing, although the detailed mechanisms are not fully understood (Alharbi et al., 2021).
3 Review of recent progress of genetic and epigenetic studies of aquaculture traits

Most of the studies of epigenetic regulation were conducted in humans, rodents, and model organisms. Epigenetic research with aquaculture species, compared to those in model species, are relatively recent and limited, but more and more researchers are turning their attention to this hot research area (Metzger and Schulte, 2016). Understanding of epigenetic regulation of various traits will lead to practical applications in aquaculture with various approaches such as epigenomic editing (for a recent review, see Nakamura et al., 2021), environmental manipulation, and epigenetic selection (Metzger and Schulte, 2016).

3.1 Reference genome sequences as resources for genetic and epigenetic studies

According to FAO (https://www.fao.org/documents/card/en/c/ca9229en/), aquaculture produced an annual total of over 82 million metric tons of seafood, with finfish contributing over 54 million tons, crustaceans contributing over 9.3 million tons, and molluscs contributing over 17.5 million tons. The major
3.2 Genetic and epigenetic regulation of growth

Growth is among the most important traits for aquaculture production. However, because growth can be selected readily by phenotypes, genetic and genomic work on growth QTL was limited. Nonetheless, genomic work allowed identification of novel growth controlling genes (for review, see Abdelrahman et al., 2017). For example, significant growth QTL have been identified from tilapia (Liu et al., 2014), channel catfish (Li et al., 2018), and Asian seabass (Wang et al., 2019). Interestingly, in eastern oysters, Zeng and Guo (2022) identified a set of genes that are both important for biomineralization and growth. With triploid sea cucumber Apostichopus japonicus, the term ribosome production was enriched in fast growing sea cucumbers, and a set of 11 significant differential metabolites were found to be associated with growth advantage (Xie et al., 2022).

A few studies of epigenetic regulation of growth trait have been conducted with fish and shellfish species. Methylation differences were observed between slow and fast muscle in Takifugu rubripes (Wang et al., 2021). In allotriploid carps, heterosis and growth are regulated by DNA methylation (Ren et al., 2022). However, the detailed relationship between DNA methylation and gene expression can be complicated. With large yellow croaker, dynamic alterations of methylation of growth-related genes and their expression were observed after starvation treatment, but the correlation of methylation and expression was not consistently observed (Zhang et al., 2019). Increased growth in the interspecific hybrid of snakehead fish was found to be correlated with reduced methylation in the hybrid fry (Ou et al., 2019). In tilapia, increased methylation was observed at the promoter of growth hormone (GH) gene in females, but not in males, correlated with expression of the GH gene and growth performance (Zhong et al., 2014), suggesting epigenetic regulation of growth differences between males and females (Podgorniak et al., 2019). In triploid sea cucumber Apostichopus japonicus, 23 genes (such as Guf1, SGT, Col5a1, HAL, HPS1, etc.) exhibited correlation between levels of promoter methylation and levels of expression, suggesting functional interactions of promoter methylation and growth in triploid sea cucumbers (Han et al., 2021a). DNA methylation is believed to regulate gene expression in polyploid organisms (for a review, see Osborn et al., 2003), and such regulation by DNA methylation was a part of the regulatory mechanism for allelic silencing in allopolyplody fish (Matos et al., 2016). In a study with tilapia, Konstantinidis et al. (2021) showed tissue-specific differential methylation of genes involved in somatic growth, such as growth factors and their receptors, with hypomethylation in the muscle tissues. All these studies demonstrated the involvement of DNA methylation in regulation of fish growth. With Giant freshwater prawn, Macrobrachium rosenbergii, increased levels of genomic methylation were observed with the “iron prawn”, prawns with serious growth retardation (Jiang et al., 2020). This is similar to the situation in Japanese flounder, where increased methylation of MyoD and IGF genes are correlated with reduced growth (Huang et al., 2018).

3.3 Genetic and epigenetic regulation of disease resistance

Great efforts have been made to understand the molecular basis for disease resistance. Studies on genetic basis have focused on identification of QTL controlling disease resistance or susceptibility, and determination of causal genes (Table 2). A good example is the determination of resistance for the infectious pancreatic necrosis virus (IPNV) in Atlantic salmon (Houston et al., 2008; Houston et al., 2010; Moen et al., 2015; Pavelin et al., 2021). In a series of studies, these researchers identified a single QTL fully responsible for the disease resistance, and such information has been applied in the aquaculture industry to control IPNV. Interestingly, earlier studies seemed to indicate that a cellular receptor for the virus, cadherin 1, was the causal gene (Moen et al., 2015). However, further analysis of whole genome sequencing and functional annotation, knockout, and differential expression analysis of homologous resistant and susceptible fish after infection allowed the identification of NEDD-8 activating enzyme 1 (nae1) as the causal gene (Pavelin et al., 2021). As summarized in a recent white paper (Abdelrahman et al., 2017), QTL studies have been conducted to identify genetic variants and genomic regions associated with disease resistance in various aquaculture species, including channel catfish, Atlantic salmon, rainbow trout, Asian seabass, and Japanese flounder, among many other aquaculture species (Table 2). Moreover, transcriptomic analyses after disease infection and stress challenges were conducted in aquaculture...
species (Qian et al., 2014; Jin et al., 2022), providing insights into differentially expressed genes, and their involved gene pathways. Genes important for immune response were identified in Atlantic salmon using RNA-Seq (Fu et al., 2022). With catfish, Jin et al. (2022) applied the bulk segregant analysis and RNA-Seq (BSR-Seq) to determine genes involved in QTLs important for ESC resistance. Such analysis allowed identification of potential candidate genes for ESC resistance. As summarized in Table 2, one of the major characteristics of disease resistance in aquaculture species is that just one or few genes control disease resistance in aquatic species. This has been demonstrated with viral diseases, as well as bacterial diseases.

In contrast to extensive genetic studies, studies of epigenetic regulation of disease resistance are still limited. In grass carp, hypermethylation of GC island upstream of the RIG-I gene in the susceptible fish led to reduced expression of RIG-I gene, which in turn accounted for the observed susceptibility for the grass carp reovirus (Shang et al., 2016). With brine shrimp (Artemia franciscana), biological control treatment with a plant-based phenolic compound resulted in transgenerational inherited increased resistance against Vibrio parahaemolyticus, the pathogen for acute hepatopancreatic necrosis (Roy et al., 2019, 2022), and DNA methylation was involved in the elevated expression of innate immune genes.

### Table 2 Some examples of genetic studies of disease resistance in several major aquaculture fish species.

| Species          | Diseases                                      | QTL and candidate genes                                                                 | References                                                                 |
|------------------|----------------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Atlantic salmon  | Infectious pancreatic necrosis (IPN), viral | A single QTL on chromosome 26 explains all the resistance, and NEDD-8 activating enzyme 1 was the candidate causal gene | Moen et al. (2009); Moen et al. (2015); Houston et al. (2010); Pavelin et al. (2021) |
|                  | Pancreas disease (PD), viral                | QTL mapped to chromosome 3 and chromosome 7                                             | Gonen et al. (2015); Hillestad et al. (2020a)                            |
|                  | Infectious salmon anemia (ISA), viral       | QTL mapped to chromosome 15                                                             | Moen et al. (2007); Li et al. (2011); Gervais et al. (2021)              |
|                  | Cardiomyopathy syndrome, viral              | QTL mapped to chromosome 27                                                             | Hillestad and Moghadam, (2019); Hillestad et al. (2020b)                 |
| Rainbow trout    | Arnobic gill disease (AGD), parasitic       | QTL mapped to various chromosomes 1, 2, 5, 4, 9, 13                                      | Boison et al. (2019); Aslam et al. (2020)                                |
|                  | Sea lice, parasitic                         | QTL mapped to chromosomes 3, 18, 21                                                     | Robleto et al. (2019)                                                    |
|                  | Bacterial coldwater disease                 | QTL for resistance was mapped to chromosome 19, 8 and 25                                  | Wiera et al. (2013); Vallejo et al. (2014); Liu et al. (2015); Palti et al. (2015); Fraslin et al. (2019); Liu et al. (2022) |
|                  | Whirling disease                            | A major QTL was identified on chromosome 9 for resistance                                | Baerwald et al. (2011)                                                  |
|                  | Columnaris disease (CD), bacterial          | Major QTL were mapped to chromosomes 3 and 5                                           | Calboli et al. (2022); Fraslin et al. (2022)                             |
|                  | White spot disease (WSD), parasitic         | Two QTL were identified on chromosome 16 and 17                                         | Jaafar et al. (2020)                                                    |
| Common carp      | RNA-Seq                                      | DEGs related to CyHV-3 disease resistance were identified                               | Tadmor-Levi et al. (2019a)                                              |
| Common carp      | Cyprinid herpes virus disease               | QTL mapped to chromosome 14, 30, 43, 44, and 46                                          | Palaokostas et al. (2018); Tadmor-Levi et al. (2019b)                   |
| Grass carp       | Grass carp reovirus                         | Resistance against GCRV has high heritability                                           | Huang et al. (2015)                                                     |
| Catfish          | Enteric septicemia of catfish (ESC) disease, bacterial | QTL were mapped to chromosome 1, 12, and 16                                             | Zhou et al. (2017); Shi et al. (2018); Tan et al. (2018b); Jin et al. (2022) |
|                  | Columnaris disease, bacterial               | QTL mapped to linkage group 7, 12, and 14 in genomic hubs                                | Geng et al. (2015)                                                     |
|                  | Aeromonas septicemia disease, bacterial     | QTL mapped to linkage groups 2, 26, and 29                                               | Zhang et al. (2020); Wang et al. (2019)                                 |
| Asian seabass    | Viral nervous necrosis disease (VNN or NNV) | QTL and suggestive QTL were identified                                                   | Liu et al. (2016); Yang et al. (2020)                                   |
| Gilthead seabream| Pasteurellous disease                       | Two significant QTL were identified                                                     | Massault et al. (2011)                                                 |
| Japanese flounder| Lymphocystis disease, viral                 | Marker-assisted selection                                                                | Fuji et al. (2007)                                                     |
| Turbot           | Aeromonas disease, bacterial                | QTLs were identified                                                                     | Rodríguez-Ramilo et al. (2011)                                          |
3.4 Genetic and epigenetic regulation of heat stress

Heat stress is increasingly a problem for aquatic organisms with the trend of climate change. Heat stress tolerance is particularly important for cold- and cool-water species. As such, much work has been conducted with salmonids. QTL for upper temperature tolerance (UTT) have been identified (Jackson et al., 1998; Perry et al., 2001; Somorjai et al., 2003). Genes associated with UTT have been identified; small heat shock proteins, along with hsp90, were found to be associated with UTT (Quinn et al., 2011). Strains were developed to have enhanced upper temperature tolerance for rainbow trout (Chen et al., 2015; Tan et al., 2016). Similarly, QTL for UTT were identified in turbot (Ma A. et al., 2021).

Genetic research of heat stress tolerance with warmwater fish is rare. While temperature may not be a major factor for survival with warmwater fish, the adverse impacts of high temperature on growth, disease resistance and sex reversal (see below) make it important to study heat stress tolerance with warmwater fish as well. Jin et al. (2017) identified three significant loci associated with tolerance to heat stress in channel catfish, a warmwater species. Genes included in these QTL regions included those involved in protein folding, protein degradation and protein synthesis, as well as those for iron transport and cytoskeletal reorganization.

Temperature is probably a single most frequent and most important environmental factor for poikilothermic animals such as fish. With just a few degrees of temperature change, thousands of genes are differentially expressed (e.g., Liu et al., 2013). The question is how such expression is regulated. Although the detailed mechanisms await to be elucidated, it is apparent that DNA methylation is intensely involved. Several studies have been conducted with epigenetic regulation of heat stress resistance. These studies provided strong evidence for intergenerational inheritance of acquired traits that were epigenetically regulated. With an Artemia model, Norouzitallab et al. (2014) conducted common garden experiments, where the Artemia was exposed to nonlethal heat shocks. The parental population was observed with increased expression of heat shock protein 70, and they are more tolerant to lethal heat stress, and more resistant against pathogenic Vibrio campbellii. Most interestingly, they found that the acquired phenotypic traits were transmitted to three successive generations without any additional exposure to heat stress. However, in this study, the measurement was levels of global DNA methylation and acetylated histones H3 and H4, not specific epigenetic marks (Norouzitallab et al., 2014). In a separate study, Robinson et al. (2019) demonstrated that early developmental stress can affect subsequent gene expression response to an acute stress in Atlantic salmon. Using reduced representation bisulfite sequencing, they found differences in methylation in the genomic neighborhood of the response genes, but the patterns of methylation was complicated (Robinson et al., 2019). Similarly, a study using zebrafish demonstrated complex interactions of temperature, DNA methylation and other environmental factors (Pierron et al., 2021). In that work, they found strong correlation of heat and methylation level of cyp19a1a gene with population masculinization.

High temperature stress may be a real threat to many aquatic species in the face of global climate change. Adaptive phenotypic response through epigenetic regulation may be particularly important for K-strategy species, where the species population is maintained at its maximal capacity as allowed by the environment, as demonstrated with winter skate (Leucoraja ocellata) (Lighten et al., 2016). Such adaptive responses are believed to be regulated by epigenetic regulation. DNA methyltransferase 3a was shown to mediate developmental thermal plasticity in zebrafish (Loughland et al., 2021) as its knockout led to decreased survival and increased deformed larvae under cold temperatures. High temperature stress caused a significant increase of de novo DNA methyltransferase genes although it did not cause global cytosine methylation levels during reprogramming of DNA methylation (Dorts et al., 2016). There is a clear gender-specific response to temperature stress, as demonstrated by the work with Chinese tongue sole (Cynoglossus semilaevis), where approximately a quarter of the differentially expressed genes were shared among males, females, and pseudo-males (Wang et al., 2020). Although the literature is still limited at present, it is apparent that high temperature stress may have a fundamental impact on fish and shellfish species, affecting their growth, development, and sex phenotypes, mostly through the mechanisms of epigenetic regulation, especially with global climate change scenarios. With European seabass, increases of even 2°C in larvae significantly changed global DNA methylation and the expression of ecologically-relevant genes related to DNA methylation, stress response, muscle and organ formations (Anastasiadi et al., 2017). Similarly, with marine stickleback (Gasterosteus aculeatus), parental acclimation to ocean warming led to dynamic and temperature-sensitive re-programming throughout offspring development (Fellous et al., 2022).

3.5 Genetic and epigenetic regulation of tolerance to low oxygen

Aquatic organisms face frequent variations in dissolved oxygen in water. Under aquaculture conditions, hypoxia can be caused by natural phenomena (e.g., weather, temperature, or water flow rate), water pollution and eutrophication, high stocking density, and improper use of aeration. Aquatic species are often encountered with hypoxia (low oxygen) or even anoxia (no oxygen) environments. During the normal production cycle, aquaculture species experience great levels of variation in dissolved oxygen; even during a 24-h day and night shift, oxygen in the water vary greatly. In aquaculture ponds,
oxygen levels are high during the sunny hours of the day and start to decline in the evening, related to the photosynthesis activities of algal species. As a result, aquaculture species must cope with such variations in dissolved oxygen concentrations. In the face of climate change and potential global warming, aquatic organisms are facing unprecedented challenges. While responses to high temperature can be different types of responses as compared to responses to hypoxia, temperature and oxygen conditions are much interwoven for aquatic organisms. Most often, high temperature could be related to reduced dissolved oxygen (Breitburg et al., 2018). In addition, exposure to hypoxia can also cause depression of the immune system in fish such as catfish, leading to increased susceptibility to diseases (Kvamme et al., 2013; Geng et al., 2014).

Much genetic and genomic research has been conducted to identify genes underlying low oxygen tolerance. With catfish, QTL analyses were conducted to localize low oxygen tolerance genes with both intra- and inter-specific systems (Wang et al., 2017c; Zhong et al., 2017). Selection signatures in the domestication processes that involved low oxygen conditions have been identified (Sun et al., 2014). Through RNA-Seq and gene expression studies, Yang et al. (2018) identified a large number of differentially expressed genes under hypoxic conditions in the swim bladder. Several gene pathways were involved in response to low oxygen including HIF signaling pathway, MAPK signaling pathway, PI3K/Akt/mTOR signaling pathway, Ras signaling pathway, and signaling by VEGF in the catfish swim bladder. A common set of genes important to both hypoxia and disease responses were identified, suggesting a common linkage of disease and hypoxia responses, such as claudin gene (Sun et al., 2015), CC chemokines (Fu et al., 2017), and their receptors (Fu et al., 2017c, Bcl-2 (Yuan et al., 2016), as well as hypoxia-specific responses such as hypoxia inducible factors 1 alpha (HIF-1) and hypoxia inducible factor inhibiting factor (FIH-1) (Geng et al., 2014). Similarly, hypoxia tolerance QTL have been identified in tilapia (Li et al., 2017), and in Pelteobagrus vachelli (Zhang et al., 2020). HIF-1 was found important for hypoxia in red swamp cray fish (Xu et al., 2022).

With bighead catfish, Ma et al. (2021) identified 26 candidate genes involved in air-breathing development and function.

Good progress has been made in understanding of the involvement of DNA methylation in tolerance of hypoxia and anoxia. DNA methylation has regulatory functions in the Pacific oyster (Crassostrea gigas), particularly in gene families that have inducible expression, including those involved in the stress and environmental responses (Gavery and Roberts, 2010). Beemelmanns et al. (2021) used a set of biomarker genes for temperature stress (cirrbp, serpinh1), oxidative stress (prdx6, ucp2), apoptosis (jund), and metabolism (pdk3), and uncovered distinct CpG methylation profiles under high temperature and low oxygen. With freshwater turtle, Wijenayake and Storey (2016) determined expression of four DNA methyltransferases, DNMT1, DNMT2, DNMT3A, and DNMT3B, and two methyl-binding domain proteins, MB1 and MB2, and found upregulated expression of these genes in the liver and white muscles under anoxic submergence of the organism, suggesting increased DNA methylation under hypoxic conditions. With rainbow trout, hypoxia treatment induced expression of BCL2 interacting protein 3 (bnip3) and its related genes. Such induced expression was found to be regulated by DNA methylation (Veron et al., 2018). Similarly, reduced levels of methylation in the promoter regions of STAT3 and VEGFA genes were found to be correlated with their increased expression under hypoxic conditions (Li et al., 2022a).

3.6 Genetic and epigenetic sex determination and regulation of sex differentiation

Teleost fish exhibit a tremendous level of diversity and plasticity in sex determination. Not only genotypes are important for sex determination, in many cases the environment, especially the temperature, can exert its effect on sex determination. Thus, genetic sex determination (GSD) and temperature-dependent sex determination (TSD) may be operating in the same or different species of lower vertebrates.

Extensive research has been conducted with sex determination and differentiation. The first sex determination gene in fish was identified from medaka, where DMY gene, a duplicate gene of DMRT1 on the Y chromosome, was identified as the sex determination gene in medaka fish Oryzias latipes (Matsuda et al., 2002). This gene was found as the sex determination gene in closely related medaka species of O. curvinotus (Table 3). However, in a different medaka species of O. luzonensis, GsdY, the gonadal soma derived growth factor on the Y chromosome, was found to be the master sex determination gene, suggesting rapid evolution of master sex determination genes among teleost fish (Myosho et al., 2012).

However, new master sex determination genes are generally recruited from genes involved in the downstream of the sex determination regulatory genetic network. These included DMRT1, Gsdf, AMH, Amhr2, and Hsd17b1 (Table 3). The only exception is Sdy, the master sex determination gene in rainbow trout and Atlantic salmon (Yano et al., 2012, 2013). Sdy is a duplicated immune-related gene that became integrated in the classical vertebrate sex differentiation cascade by interacting with the Forkhead box domain of the female-determining transcription factor, Foxl2 (Bertho et al., 2018). In the presence of Foxl2, SdY is translocated to the nucleus where the SdY:Foxl2 complex prevents activation of the aromatase (cyp19a1a) promoter, thereby disrupting the female differentiation pathway, consequently allowing testicular differentiation to proceed (Bertho et al., 2018). In channel catfish, we have identified an epigenetically marked locus
within the sex determination region (SDR), where hypermethylation was found on the X chromosomes but hypomethylation was found on the Y chromosome, leading to differential expression of the sex determination gene (Yang et al., 2022). Similarly, with the Siamese fighting fish (Betta splendens), genetic sex is determined by an X/Y system with dmrt1 gene as the master sex determination gene, but the expression of the dmrt1 gene on the X chromosome is down-regulated by changes in DNA methylation caused by transposon-induced epigenetic silencing, where a transposon, drbx1, inserted into the fourth intron of the X-linked dmrt1 allele (Wang et al., 2022). Extensive studies have been conducted with epigenetic regulation of sex determination and/or differentiation. These studies have focused on the following aspects of epigenetic regulation: 1) Sexual dimorphism in DNA methylation patterns; 2) Epigenetic regulation through DNA methylation of key genes involved in the sex determination regulatory genetic network and/or sex differentiation; and 3) Involvement of epigenetic regulation in temperature (or other factors)-induced sex reversal. Sexual dimorphism of methylation patterns was observed with several fish species. Some examples are summarized in Table 4. Detailed examination of the sex differences in methylation patterns differentiates the sexual methylation pattern dimorphism into two categories: 1) The difference is concentrated on sex chromosome, and 2) the differences are general. In this regard, there are many similarities between the situations of three spine stickleback (Metzger and Schulte, 2018) and channel catfish (Wang et al., 2022; Yang et al., 2022), where sex dimorphism in DNA methylation is concentrated on the sex chromosome. In both cases, hypermethylation was observed on the X chromosome and hypomethylation was observed on the Y chromosome. In channel catfish, such differential methylation was observed within the SDR, suggesting the importance of DNA methylation in sex determination and differentiation.

Many studies have focused on the relationship between expression of key genes involved in sex determination regulatory genetic network and DNA methylation. Table 5 shows many examples of such research. In general, key genes for female gonadal differentiation such as cyp19a are differentially expressed and differentially methylated, with higher expression and lower levels of methylation in females than in males. In contrast, key genes for male gonadal differentiation such as dmrt1 are differentially expressed and differentially methylated, with higher expression and lower levels of methylation in males than in females. However, in most cases,
only the promoter regions were under investigation, and the definition of the promoter vary among studies. In addition, the correlation is generally not linear. The traditional notion that DNA methylation suppress gene expression may have its limitations (see Section 2.4). Whatever the detailed mechanisms are, the ultimate difference it makes is the difference in gene expression, which is the core of the central dogma of molecular biology, but the key modification here is at the level of DNA methylation, i.e., epigenetic regulation, rather than being coded in DNA sequences.

From the studies conducted to date (with some examples shown in Table 6), it is apparent that DNA methylation is involved in the temperature-dependent sex determination. However, high temperature apparently had opposite sex ratio shift with different species. In zebrafish, tilapia, and half-smooth tongue sole, high temperature induced masculinization, while

### TABLE 5 Differential DNA methylation of key genes involved in sex determination and/or differentiation.

| Species                        | Major findings                                                                 | References                           |
|-------------------------------|--------------------------------------------------------------------------------|--------------------------------------|
| European sea bass             | Juvenile males have double the DNA methylation levels of females in the promoter of gonadal aromatase Cyp19a whose methylation is involved in temperature-dependent sex ratio shift | Navarro-Martín et al. (2011)         |
| Japanese flounder             | High expression of dmr1 and cyp19a in males and females, respectively, which are negatively correlated with methylation of their promoters | Wen et al. (2014)                    |
| Zebrafish                     | Differential CpG methylated in the brain                                       | Chatterjee et al. (2016)             |
| Nile tilapia                  | Cyp19a1 is important for high temperature-induced masculinization               | Wang et al. (2017b)                  |
| Japanese flounder             | Hypomethylation of esr1 promoter and overexpression in females, sex-specific patterns of transcription with dmr1, dmr3, and hdac1 | Laing et al. (2018)                  |
| Hermaphrodite barramundi      | Cyp19a1 and amh were more methylated in males, whereas dmr1 and nr3a2 were more methylated in females | Domingos et al. (2018)               |
| Chinese sea perch             | Hypomethylated cyp19a1a promoter region in females                               | Chen et al. (2018b)                  |
| Culter alburnus               | Dmr1 gene hypomethylated and highly expressed in males                          | Jia et al. (2019)                    |
| Large yellow croaker          | Key genes of sex determination are differentially methylated in males, females, and neonales | He et al. (2020a)                    |
| Schizothorax kozlovi           | High expression and low methylation of dmr1 in males                            | He et al. (2020b)                    |
| Pelvicachromis pulcher         | Sex-specific hypomethylation and expression in females of copy A of cyp19a1 gene | Driscoll et al. (2020)               |
| Orange-spotted grouper        | Hypomethylated cyp19a1a promoter region in females                              | Guo et al. (2021)                    |
| Olive flounder                | Global methylation was higher in testis than in ovary                           | Liu et al. (2021)                    |

### TABLE 6 Methylation/demethylation of specific genes and their involvement in sex reversal/sex ratio shift.

| Species                        | Major findings                                                                 | References                           |
|-------------------------------|--------------------------------------------------------------------------------|--------------------------------------|
| Tilapia                       | Upregulation of CYP11B2 and DMRT1 during high temperature-induced masculinization | Li et al. (2014)                     |
|                               | High temperature induced sex reversal to males is accompanied with higher methylation levels in the gonads | Sun et al. (2016)                    |
| Half-smooth tongue sole       | Heat induced sex reversal into pseudomales are regulated by DNA methylation of key genes in sex determination pathway, and transgenerational inheritance after heat treatment was observed | Shao et al. (2014)                   |
| Zebrafish                     | Treatment of DNA methyltransferase inhibitor 5-Aza-4C feminizes zebrafish, with permanent alterations of gonadal transcriptome, with increased expression of key genes of female gonadal development | Ribas et al. (2017)                  |
|                               | High temperature induced sex shift toward males of parental families and F1 fish, but not F2 fish. Methylation was lower in F1, but not in P and F2 fish | Valdivieso et al. (2020)             |
|                               | Sox90 and esr1 are down-regulated in high temperature-induced masculinization  | Han et al. (2021b)                   |
| Channel catfish               | Key genes for female gonadal development and male gonadal development were upregulated, and down-regulated, respectively, during hormone-induced feminization, but the methylation patterns were complex. These are independent from the sex determination region. High temperature induces sex reversal to females | Wang et al. (2022)                   |
|                               |                                                                                         | Zhou et al., unpublished data        |
high temperature induced feminization in channel catfish. These systems, therefore, provide a great comparative platform to determine the relationship of high temperature, DNA methylation, gene expression and phenotypic sex differentiation.

4 Histone modifications and their regulation of genome expression

There are numerous types of histone modifications, but several types of histone modifications are better understood as to how they are related to genome expression. These include histone methylation, acetylation and phosphorylation (Zhang et al., 2021). Histone methylation, usually at the lysine (K) residues of histone H3 and H4, are best understood in their roles for regulation of gene expression. The methylation is catalyzed by histone methyltransferase, which uses S-adenosylmethionine as the substrate to transfer methyl groups onto the lysine residues of histones. The lysine residues of histones can be mono-, di-, and tri-methylated to act as the active or repressive marks of gene expression. Gene activation has been correlated with H3K4me3, H3K36me3, and H3K79me3, while H3K9, H3K27, and H4K20 are known as repressive marks that are usually associated with the silenced gene expression and heterochromatin (Zhang et al., 2021). It is important to note that multiple histone modifications may occur, and they collectively affect genome expression. Table 7 summarizes the general pattern of histone modifications and their correlated gene expression.

Histone modifications can be most efficiently studied by chromatin immunoprecipitation with high-throughput sequencing (ChIP-Seq). ChIP-Seq is a powerful technology to locate regulatory elements, as indicated by association of histone modifications such as H3K4me3 with actively transcribed gene promoters, and H3K27ac with enhancers. It is also very useful to locate sites involved in gene silencing, as indicated by association of some histone modifications with repression of gene expression such as H3K9me3 and H3K27me3 (Table 7). ChIP-Seq has been well demonstrated with human and mouse research with over a dozen different histone modifications being assayed, but less so with agricultural animals. However, as histone proteins are so highly conserved, the antibodies for mammalian species should, for the most part, work for various fish species.

Among teleost fish, ChIP-Seq has been primarily conducted in model systems. For example, Zhu et al. (2019) studied histone modification patterns with H3K4m3 and H3K27me3 early during development. In zebrafish, ChIP-Seq after infection of spring viremia of carp virus (SVCV) allowed identification of key immune genes of interferon signalling pathway and c-reactive protein genes, and demonstrated the importance of epigenetic modifications in response to viral infections (Medina-Gali et al., 2018). As a proof of concept, ChIP-Seq was conducted with tilapia (Kratochwil and Meyer, 2015). With common carp, increased H4K12ac was found to be associated with aging oocytes (Waghmare et al., 2021).

5 Intergenerational and transgenerational epigenetic inheritance

One of the most interesting questions is if the environmentally induced epigenetic changes and their regulated gene expression are inherited. For this discussion, we would like to differentiate intergenerational and transgenerational epigenetic inheritance. Intergenerational epigenetic inheritance refers to inheritance of epigenetic marks and/or their related phenotypes from one generation (F0) to the next (F1), while transgenerational epigenetic inheritance refers to the passage of information from grandparents to grandchild (F2) or later generations if paternal grandparent was exposed or F3 if maternal grandparent was exposed (Skinner and Guerrero-Bosagna, 2009; Lacal and Ventura, 2018).

Like the situation with mammalian species, where intergenerational epigenetic inheritance is not uncommon, but transgenerational epigenetic inheritance has not been fully demonstrated (For a review, see Cavalli and Heard, 2019), most studies with aquatic species have clearly supported
TABLE 8 Examples of studies of intergenerational and transgenerational epigenetic inheritance.

| Species                     | Treatment                                      | Epigenetic marks or phenotypic analysis                                                                 | References                      |
|-----------------------------|------------------------------------------------|---------------------------------------------------------------------------------------------------------|---------------------------------|
| Half-smooth tongue sole     | High temperature induced sex reversal to pseudomales | Pseudomales produced F1 pseudomales without temperature treatment                                     | Intergenerational               |
| Zebrafish                   | Crude oil containing diet                      | Global methylation of F1 was decreased as exposed parents                                              | Intergenerational               |
| Atlantic salmon             | Captivity                                      | Differential methylation in F1 with exposed parents                                                    | Intergenerational               |
| Pipidaria                   | Heat-killed bacteria                            | Expression of genes involved in DNA methylation                                                       | Intergenerational and transgenerational |
| Zebras                     | benzo[a]pyrene exposure of F0 fish              | F2 fish exhibited altered phenotypes                                                                  | Transgenerational               |
| Zebrafish                   | Mercury exposure of F0                          | F2 fish exhibited altered phenotypes                                                                  | Transgenerational               |
| Zebrafish                   | Permethrin exposure of F0                       | F2 fish exhibited altered phenotypes                                                                  | Transgenerational               |
| Zebras                     | F0 exposure to mono(2-ethylhexyl) phthalate and 5-azacytidine | Differential methylation in F1 and F2                                                                | Transgenerational and transgenerational |
| Medaka                      | F0 exposure to bisphenol A and 17α-ethynlestradiol | Changed gene expression in F2                                                                      | Transgenerational               |
| Atlantic molly              | Exposure of F0 fish to hydrogen sulfide         | 80% overlap of epigenetic profiles of F2 of treated F0 fish                                           | Transgenerational               |
| Daphnia fransiscana         | Phloroglucinol Treatment                        | Elevated methylation was observed in F1, and in cysts in F2 but not in F2 nor F3 of juveniles         | Intergenerational and perhaps Transgenerational       |
| Daphnia magna               | Vibrio challenge or injection                   | Treated progenies had transgenerational immune memory                                                   | Roy et al. (2019)               |
| Daphnia magna               | Zinc exposure                                   | Significant reduction of cytosine methylation in F1 but not in F2                                      | Intergenerational               |
| Daphnia magna               | Exposure to 5-azacytidine                       | Changes of DNA methylation were observed in F2 and F1, but not very specific                          | Transgenerational               |
| Daphnia magna               | Chronic external γ-irradiation                  | Changes of DNA methylation were observed in exposed F0 and unexposed F1, F2, and F3 animals         | Transgenerational               |
| Daphnia magna               | High salinity                                   | Differeential methylation of a set of specific genes were observed in F0 and unexposed F1, F2, and F3 | Transgenerational               |

intergenerational epigenetic inheritance. For example, with Atlantic salmon, captive rearing of adult caused intergenerational differential methylation in F1 (Wellband et al., 2021). However, it is not concretely solid with transgenerational epigenetic inheritance. Some examples of intergenerational and transgenerational epigenetic studies are provided in Table 8. Most of these studies were conducted with model species zebrafish, or microcrustacean Daphnia or Artemia species.

As shown in Table 8, most of these studies were conducted for just two generations, and in some cases for three generations. In addition, in many of these cases, the measurements were general performance traits, rather than specific molecular patterns. Even when DNA methylation was determined, demonstration of transgenerational epigenetic inheritance with specific patterns of DNA methylation is very limited. Perhaps a best example is from a recent study with Atlantic molly (Poecilia mexicana), where the epigenetic alterations under hydrogen sulfide are inherited to laboratory-reared, non-exposed F2 fish (Kelley et al., 2021). When epigenetic changes in response to hydrogen sulfide were examined in red blood cells, there was over 80% overlap in differentially methylated regions (DMRs) across generations, suggesting that DMRs have stable generational inheritance in the absence of the sulfide environment.

With D. magna, treatment with 5-azacytidine reduced the level of DNA methylation, and such reduced level of methylation was stably transferred to two subsequent non-exposed generations (Vandegehuchte et al., 2010a). A reduced level of methylation was observed after exposure to zinc, and such patterns of reduced methylation and correlated gene expression was observed in F1 animals, but not in F2 animals (Vandegehuchte et al., 2010b), suggesting intergenerational epigenetic inheritance. γ-irradiation-induced DNA methylation patterns were found to be inheritable, as common methylation patterns were observed from unexposed F2 and F3 individuals, but specific patterns of methylation were not reported (Trijau et al., 2018). High levels of salinity led to hypomethylation of treated F0 animals, and such
hypomethylation was transgenerationally inherited to three consequent nonexposed generations (F₁, F₂, and F₃) (Jeremias et al., 2018).

With brine shrimp (Artemia franciscana), phloroglucinol treatment significantly enhanced the expression of a core set of innate immune genes and resistance against bacterial infections of Vibrio parahaemolyticus and V. harveyi. Such enhanced resistance was observed in their progeny in three subsequent generations (Roy et al., 2019, 2022). In a separate study, Norouzitallab et al. (2014) exposed Artemia to nonlethal heat shocks, which increased the expression of Hsp70. The treated Artemia exhibited increased levels of tolerance for lethal heat stress, and resistance against pathogenic Vibrio campbellii. These acquired phenotypic traits were transmitted to three successive generations, none of which were exposed to the parental stressor. This transgenerational inheritance of the acquired traits was associated with altered levels of global DNA methylation and acetylated histones H3 and H4 in the heat-shocked group compared to the control group, where both the parental and successive generations were reared at standard temperature. These results indicated that epigenetic mechanisms, such as global DNA methylation and histones H3 and H4 acetylation, have particular dynamics that are crucial in the heritability of the acquired adaptive phenotypic traits across generations.

6 Future perspectives

Although DNA methylation is perhaps the most studied of epigenetic regulation of aquaculture performance and production traits, the exact mechanisms of epigenetic regulation requires great attention. The studies of histone modifications and their relations with aquaculture performance and production traits are so limited to date, but this apparently demands research efforts, especially in understanding of transcriptional activation and inactivation. Finally, the regulation by ncRNAs is extremely important and likely is involved in expression of aquaculture performance and production traits; although this review intentionally left this out because systematic knowledge of epigenetic regulation of aquaculture traits is very limited at this time, but the importance of research in these areas cannot be overstated.

In addition to understanding epigenetic regulation, precise epigenome editing technologies have become available (for reviews, see Laufer and Singh, 2015; Goell and Hilton, 2021; Nakamura et al., 2021). Applications of epigenome editing technologies will deepen our understanding of epigenetic regulation from the level of correlation to the level of establishing causal effect relationships between epigenome modifications and performance traits. More directly, epigenome editing will also allow “engineering” of desired traits, based on information of epigenetic regulation.

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ZL wrote the manuscript, DG and TZ reviewed and revised the manuscript, prepared the tables and references.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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columnar in a farmed rainbow trout population. Aquaculture 557, 738332. doi:10.1016/j.aquaculture.2022.738332
Fu, Q., Yang, Y., Li, C., Zeng, Q., Zhou, T., Li, N., et al. (2017a). The chemokine superfamily. II. The 64 CC chemokines in channel catfish and their involvement in disease and hypoxia responses. Dev. Comp. Immunol. 73, 97–108. doi:10.1016/j.devimim.2017.03.012
Fu, Q., Yang, Y., Li, C., Zeng, Q., Zhou, T., Li, N., et al. (2017b). The CC and CXC chemokine receptors in channel catfish (Ictalurus punctatus) and their involvement in disease and hypoxia responses. Dev. Comp. Immunol. 77, 241–251. doi:10.1016/j.devimim.2017.08.012
Fu, Q., Zeng, Q., Li, Y., Yang, Y., Li, C., Liu, S., et al. (2017c). The chemokine superfamily in channel catfish. I. CXC subfamily and their involvement in disease defense and hypoxia responses. Fish. Shellfish Immunol. 60, 380–390. doi:10.1016/j.fsi.2016.12.004
Fu, X., Zhang, C., and Zhang, Y. (2020). Epigenetic regulation of mouse preimplantation embryo development. Curr. Opin. Genet. Dev. 64, 13–20. doi:10.1016/j.gde.2020.03.015
Fuji, K., Hasegawa, O., Honda, K., Kumasaka, K., Sakamoto, T., and Okamoto, N. (2007). Marker-assisted breeding of a lymphocystis disease-resistant Japanese flounder (Paralichthys olivaceus). Aquaculture 272 (1–4), 291–295. doi:10.1016/j.aquaculture.2007.07.210
Gao, H., Bu, Y., Wu, Q., Wang, X., Chang, N., Lei, L., et al. (2015). MeCP2 regulates neural cell differentiation by suppressing the ID1 to Her2 axis in zebrafish. J. Cell Sci. 128 (11), 2340–2350. doi:10.1242/jcs.167974
Gao, Z., You, X., Zhang, X., Chen, J., Xu, T., Huang, Y., et al. (2021). A chromosome-level genome assembly of the striped catfish (Pangasianodon hypophthalmus). Genomics 113 (5), 3349–3356. doi:10.1016/j.ygeno.2021.07.026
Gavery, M. R., and Roberts, S. B. (2014). A context dependent role for DNA methylation in bivalves. Brief. Funct. Genomics 13 (5), 217–222. doi:10.1093/bfgp/elv054
Gavery, M. R., and Roberts, S. B. (2017). Epigenetic considerations in aquaculture. Peerf 5, e4147. doi:10.7717/peerj.4147
Gavery, M. R., and Roberts, S. B. (2010). DNA methylation patterns provide insight into epigenetic regulation in the Pacific oyster (Crassostrea gigas). BMC Genomics 11 (1), 483. doi:10.1186/1471-2164-11-483
Geng, X., Feng, J., Liu, S., Wang, Y., Arias, C., and Liu, Z. (2014). Transcriptional regulation of hypoxia inducible factors α (HIF-α) and their inhibiting factor (HIF-α) and their involvement in disease and hypoxia responses. Fish. Shellfish Immunol. 60, 380–390. doi:10.1016/j.fsi.2016.12.004
Geng, X., Sha, J., Liu, S., Bao, L., Zhang, J., Wang, R., et al. (2015). A genome-wide cDNA expression profiling of genetic loci associated with higher resistance to piscine myocarditis virus in Atlantic salmon (Salmo salar L). BMC Genomics 21 (1), 388. doi:10.1186/s12862-020-06788-4
Hearns, J., Penderleith, F., and Little, T. J. (2021). DNA methylation differs extensively between strains of the same geographical origin and changes with age in Daphnia magna. Epigenetics Chromatin 14 (1), 4. doi:10.1186/s13072-020-00397-z
Herman, J. G., and Baylin, S. B. (2000). Promoter hypermethylation and gene silencing in human cancer. Curr. Top. Microbiol. Immunol. 249, 35–54. doi:10.1007/3-540-42197-4_3
Herpin, A., Schartl, M., Depinaci’, A., Guiguenn, Y., Bohe, J., Hua-Van, A., et al. (2021). Allecic diversification after transposable element exaptation promoted gdf5 as the master sex determining gene of bumblebee. Genome Res. 31 (8), 1366–1380. doi:10.1101/gr.724266.120
Hillestad, B., Kristjánsson, Ó., Makvandi-Nejad, S., and Moghadam, H. K. (2020a). Genome-wide association study confirms previous findings of major loci affecting resistance to piscine myocarditis virus in Atlantic salmon (Salmo salar L). Genes (Basel) 11 (6), 608. doi:10.3390/genes11060608
Hillestad, B., Makvandi-Nejad, S., Krasnov, A., and Moghadam, H. K. (2020b). Identification of genetic loci associated with higher resistance to pancreas disease (PD) in Atlantic salmon (Salmo salar L). BMC Genomics 21 (1), 388. doi:10.1186/s12862-020-06761-6
Hillestad, B., and Moghadam, H. K. (2019). Genome-wide association study of piscine myocarditis virus (PMCV) resistance in Atlantic salmon (Salmo salar). J. Hered. 110 (6), 720–726. doi:10.1093/jhered/est040
Houston, D. R., Bean, T. P., Macqueen, D. J., Gundappa, M. K., Jin, Y. H., Jenkins, T. L., et al. (2020). Darwin Kaluga. Nat. Rev. Genet. 21 (7), 389–409. doi:10.1038/s41576-020-0227-y
Houston, D. R., Haley, C. S., Hamilton, A. G., Dotta-Velasco, J. C., Gheyas, A. A., et al. (2010). The susceptibility of Atlantic salmon fry to freshwater infection with infectious pancreatic necrosis is largely explained by a major QTL. Heredity 105 (3), 311–319. doi:10.1038/hdy.2009.137
Ito, S., Shen, L., Dai, Q., Wu, S. C., Collins, L. B., Swenberg, J. A., et al. (2008). Major quantitative trait loci affect resistance to infectious pancreatic necrosis in Atlantic salmon (Salmo salar). Genetics 178 (2), 1109–1115. doi:10.1534/genetics.107.082974
He, Y., Wu, X., Zhu, Y., and Yang, D. (2020b). Expression profiles of dmrt1 in Schizothorax kozlowi, and their relation to CpG methylation of its promoter and tissue. Zool. Sci. 37 (2), 140–147. doi:10.2108/zs190054
He, Y. F., Li, B. Z., Li, Z., Liu, P., Wang, Y., Tang, Q., et al. (2011). Tet-mediated formation of 5-carboxylcytosine and its excision by TDG in mammalian DNA. Science 333 (6047), 1303–1307. doi:10.1126/science.1210994
Ito, S., Daza, A., Nakamura, K., Dai, Q., Wu, S. C., Collins, L. B., Swenberg, J. A., et al. (2008). The susceptibility of Atlantic salmon fry to freshwater infection with infectious pancreatic necrosis is largely explained by a major QTL. Heredity 105 (3), 311–319. doi:10.1038/hdy.2009.137
Ito, S., Shen, L., Dai, Q., Wu, S. C., Collins, L. B., Swenberg, J. A., et al. (2011). Tet proteins in 5mC to 5hmC conversion, ES-cell self-renewal and inner cell mass specification. Nature 466 (7310), 1129–1133. doi:10.1038/nature09303
Ito, S., Shen, L., Dai, Q., Wu, S. C., Collins, L. B., Swenberg, J. A., et al. (2011). Tet proteins can convert 5-methylcytosine to 5-formylcytosine and 5-carboxylcytosine. Science 333 (6047), 1300–1303. doi:10.1126/science.1210997
Kvamme, B. O., Gadan, K., Finne-Frieldt, F., Niklasson, L., Sundh, S., Sundell, K., et al. (2013). Modulation of innate immune responses in Atlantic salmon by chronic hypoxia-induced stress. Fish. Shellfish Immunol. 34 (1), 55–65. doi:10.1016/j.fsi.2012.10.006

Krist, I., Gonzáles Athanásio, C., Shams Solari, O., Brown, J. B., Colbourne, J. K., Pfender, M. E., et al. (2018). Pattern of DNA methylation in Daphnia: Evolutionary perspective. Genome Biol. Evol. 10 (8), 1988–2007. doi:10.1093/gbe/eyv115

Liu, J., Viana, J., Dempster, E. L., Uren Webster, T. M., van Aarle, R., Mill, J., et al. (2018). Sex-specific transcription and DNA methylation profiles of reproductive and epigenetic associated genes in the gonads and livers of breeding zebrafish. Comp. Biochem. Physiol. A Mol. Integr. Physiol. 222, 26–16. doi:10.1016/j.cbpa.2018.04.004

Lauf, B. I., and Singh, S. M. (2015). Strategies for precise modulation of gene expression by epigenome editing: An overview. Epigenetics Chromatin 8, 34. doi:10.1186/s13072-015-0023-7

Lev Maor, G., Yarmim, A., and Ast, G. (2015). The alternative role of DNA methylation in splicing regulation. Trende Genet. 31 (5), 274–280. doi:10.1016/j.tig.2015.03.002

Li, C. G., Wang, H., Chen, H. J., Zhao, Y., Fu, P. S., and Lui, X. S. (2014). Differential expression analysis of genes involved in high-temperature induced sex differentiation in Nile tilapia. Comp. Biochem. Physiol. B Biochem. Mol. Biol. 177, 37–45. doi:10.1016/j.cbpb.2014.08.006

Li, H. L., Liu, G. X., Li, B. J., Chen, C. H., Liu, H. R., and Xiu, J. H. (2017). Genome-wide QTL analysis identified significant associations between hypoxia tolerance and mutations in the GPR132 and ARCG genes in Nile Tilapia. Mar. Biol. (195), 441–453. doi:10.1007/s00228-016-3078-7

Li, J., Borosovich, K. A., Koop, B. F., and Davidson, W. S. (2011). Comparative genomics identifies candidate genes for infectious salmon anemia (ISA) resistance in Atlantic salmon (Salmo salar). Mar. Biol. (NY) (173), 232–241. doi:10.1007/s00227-010-1928-4

Li, M., Sun, Y., Zhao, J., Shi, H., Zeng, S., Ye, K., et al. (2015). A tandem duplicate of anti-mullerian hormone with a misense SNP on the Y chromosome is essential for male sex determination in Nile Tilapia, Oryzias latipes. PLoS Genet. 11 (11), e1005678. doi:10.1371/journal.pgen.1005678

Li, N., Zhou, T., Geng, X., Jin, Y., Wang, X., Liu, S., et al. (2018). Identification of novel genes significantly affecting growth in catfish through GWAS analysis. Mol. Genet. Genomics 299 (3), 587–599. doi:10.1007/s00439-017-1406-1

Li, P., Chen, J., Zhu, C., Pan, Z., Li, Q., Wei, H., et al. (2022A). DNA methylation difference between female and male ussuri catfish (pseudobagrus ussuriensis) in brain and gonad tissues. Life (Basel) 12 (6), 874. doi:10.3390/ lifedi02060874

Li, X., Liu, B., Yang, J., Li, G., Wen, H., Zhang, M., et al. (2022B). DNA methylation in promoter region of immune related genes STAT3 and VEGFA and biochemical parameters change in muscle of Japanese flounder under acute hypoxia. Dev. Comp. Immunol. 129, 104295. doi:10.1016/j.dci.2021.104295

Li, Y., Zhang, B., Yang, Y., and Chen, S. (2019). Estimationmodel genetic parameters for juvenile growth performance traits in olive flounder (Paralichthys olivaceus). Aquac. Fish. Sci. 4 (2), 48–52. doi:10.1007/s41010-019-0021-8

Lién, S., Koop, B. F., Sandre, S. R., Miller, J. R., Kent, M. P., Nome, T., et al. (2016). The Atlantic salmon genome provides insights into redlipidization. Nature 533 (7602), 200–205. doi:10.1038/nature17614

Lighton, J., Incarnato, D., Ward, B. J., van Oosterhout, C., Bradbury, I., Hanson, M., et al. (2016). Adaptive phenotypic response to climate enabled by epigenetics in a K-strategy species, the fish Leucoroccus occulta (Rajidae). R. Soc. Open Sci. 3 (10), 160299. doi:10.1098/rsos.160299

Liu, F., Sun, F., Xiu, J. H., Li, J., Pu, G. H., Lin, G., et al. (2014). A genome scan revealed significant associations of growth traits with a major QTL and GHR2 in tilapia. Sci. Rep. 4, 7256. doi:10.1038/srep07256

Liu, H., Chen, C. L., Xu, L., Liu, N., Hu, Y., Zhang, H., et al. (2021). A chromosome-level assembly of blunt stout nseum (Magurhuluma amblechymella) genome reveals an expansion of olfactory receptor genes in freshwater fish. Mol. Biol. Evol. 38 (10), 4238–4251. doi:10.1093/molbev/msab152

Liu, P., Wang, L., Wong, S. M., and Yue, G. H. (2016). Fine mapping QTL for resistance to VNN disease using a high-density linkage map in Asian seabass. Sci. Rep. 6, 23122. doi:10.1038/srep23122

Liu, S., Martin, K. E., Gao, G., Long, R., Evenhuis, J. P., Leeds, T. D., et al. (2022). Identification of haplotyping and association of resistance to bacterial cold water disease in rainbow trout using whole-genome resequencing. Front. Genet. 13, 936806. doi:10.3389/fgene.2022.936806
Liu, S., Vallejo, R. L., Palti, Y., Gao, G., Maranck, D. P., Hernandez, A. G., et al. (2015). Identification of single nucleotide polymorphism markers associated with bacterial cold water disease resistance and spleen size in rainbow trout. *Front. Genet.* 6, 298. doi:10.3389/fgen.2015.00298

Liu, S., Wang, X., Sun, F., Zhang, J., Feng, J., Liu, H., et al. (2013). RNA-Seq reveals expression signatures of genes involved in oxygen transport, protein synthesis, folding, and degradation in response to heat stress in catfish. *Physiol. Genomics* 45 (12), 462–476. doi:10.1152/physiogenomics.00006.2013

Liu, Y., Wang, W., Liang, S., Wang, L., Zou, Y., Wu, Z., et al. (2021). Sexual dimorphism of DNA and histone methylation profiles in the gonads of the olive flounder *Paralichthys olivaceus*. *Fish. Physiol. Biochem.* 47 (3), 1341–1352. doi:10.1007/s10695-021-00986-x

Liu, Z., Liu, S., Yao, J., Bao, L., Zhang, J., Li, Y., et al. (2016). The channel catfish genome sequence provides insights into the evolution of scale formation in teleosts. *Nat. Commun.* 7, 11757. doi:10.1038/ncomms11757

Loughland, I., Little, A., and Seebacher, F. (2021). DNA methyltransferase 3a mediates developmental thermal plasticity. *BMC Biol.* 19 (1), 11. doi:10.1186/s12915-020-00942-w

Luo, C., Hajkova, P., and Ecker, J. R. (2018). Dynamic DNA methylation: In the right place at the right time. *Science* 361 (6409), 1336–1340. doi:10.1126/science.aat6806

Ma, A., Huang, Z., Wang, X. A., Xu, Y., and Guo, X. (2021). Identification of quantitative trait loci associated with upper temperature tolerance in turbot, *Brama argus*. *Anim. Genet.* 52 (1), 191–203. doi:10.1111/age.12655

Ma, X., Su, B., Bangs, M., Alston, V., Backenstose, N. J. C., Simora, R. M., et al. (2021). Comparative genomic and transcriptomic analyses revealed twenty-six candidate genes involved in the air-breathing development and function of the bighead catfish *Clarias macrocephalus*. *Mar. Biotechnol.* 23 (1), 90–105. doi:10.1007/s10276-022-10005-4

Marchione, A. D., Thompson, Z., and Kathrein, K. L. (2021). DNA methylation and histone modifications are essential for regulation of stem cell formation and differentiation in zebrafish development. *Brief. Funct. Genomics* elab022. doi:10.1093/bfgp/elab022

Massault, C., Franch, R., Halee, C., de Koninck, D. J., Bovenhuis, H., Pelizzari, C., et al. (2011). Quantitative trait loci for resistance to fish pasturelessness in gilthead sea bream (*Sparus aurata*). *Anim. Genet.* 42 (2), 191–203. doi:10.1111/j.1365-2052.2010.02110.x

Matsuda, M., Nagahama, Y., Shinozaki, A., Tanaka, H., and Ohshima, T. (2017). Zebrafish MeCP2 is required for proper axonal elongation of motor neurons and synapse formation. *Dev. Neurobiol.* 77 (9), 1101–1113. doi:10.1002/dneu.22498

Ma, A., Huang, Z., Wang, X. A., Xu, Y., and Guo, X. (2021). DNA methyltransferase 3a mediates developmental thermal plasticity. *BMC Biol.* 19 (1), 11. doi:10.1186/s12915-020-00942-w

Moore, L. D., Le, T., and Fan, G. (2013). DNA methylation and its basic function. *Neuropsychopharmacology* 38 (1), 23–38. doi:10.1038/npp.2012.112

Miyoshi, T., Okate, H., Masuyama, H., Matsuda, M., Kuroki, Y., Fujimura, Y., et al. (2012). Tracing the emergence of a novel sex-determining gene in medaka, *Oryzias latipes*. *Genetics* 191 (1), 163–179. doi:10.1534/genetics.111.137497

Mzala, A., Wambura, P. N., Mdegela, R. H., and Shirima, G. M. (2021). Present status of aquaculture and the challenge of bacterial diseases in freshwater farmed fish in Tanzania: A call for sustainable strategies. *Aquac. Fish. 6* (3), 247–253. doi:10.16166/2020.05.083

Nakamura, M., Gao, Y., Dominguez, A. A., and Qi, L. S. (2021). CRISPR technologies for precise epigenome editing. *Nat. Cell Biol.* 23 (11), 12–22. doi:10.1038/s41594-022-01567-3

Naylor, R. L., Hardy, R. W., Buschmann, A. H., Bush, S. R., Gao, L., Klinger, D. H., et al. (2021). A 20-year retrospective review of global aquaculture. *Nature* 591 (7851), 551–563. doi:10.1038/s41586-021-03086-8

Norouzitallab, P., Barah, K., Van deheukele, M., Vanden Bussche, J., Catania, F., Vanden Bussche, J., et al. (2014). Environmental heat stress induces epigenetic transgenerational inheritance of robustness in parthenogenetic Artemia. *Development* 141 (28), 3552–3563. doi:10.1242/dev.124094

Nakamura, M., Gao, Y., Dominguez, A. A., and Qi, L. S. (2021). CRISPR technologies for precise epigenome editing. *Nat. Cell Biol.* 23 (11), 12–22. doi:10.1038/s41594-022-01567-3

Ogaw, O., Inoue, A., Kageyama, S., Akiyama, T., Nagata, M., and Aski, F. (2008). Changes in H3K7 methylation during reprogramming of zebrafish parthenogenetic embryos. *Proc. Natl. Acad. Sci. U. S. A.* 105 (3), 10438–10443. doi:10.1073/pnas.0707266105

Ogaw, O., Inoue, A., Kageyama, S., Akiyama, T., Nagata, M., and Aski, F. (2008). Changes in H3K7 methylation during reprogramming of zebrafish parthenogenetic embryos. *Proc. Natl. Acad. Sci. U. S. A.* 105 (3), 10438–10443. doi:10.1073/pnas.0707266105

Okami, R. K., Lin, T., Lee, J. E., Kang, Y. J., and Shin, H. Y. (2019). *BioMed* 19 (3), e1007327. doi:10.1111/b ALLOWEDしていないかです。
Potok, Magdalena E., Nix, David A., Parmelli, Timothy J., and Cairns, Bradley R. (2013). Reprogramming the maternal zebrafish genome after fertilization to match the paternal methylation pattern. Cell 153, 739–772. doi:10.1016/j.cell.2013.04.030

Qian, X., Bai, Y., Zhuang, Q., and Zhong, G. (2014). RNA-Seq technology and its application in fish transcriptomics. OMICS 18 (2), 98–110. doi:10.1089/omi.2013.0110

Quinn, N. L., McGowan, C. R., Cooper, G. A., Koop, B. F., and Davidson, W. S. (2011). Identification of genes associated with heat tolerance in Arctic char exposed to acute thermal stress. Physiol Genomics 43 (1), 685–696. doi:10.1152/physiolgenomics.00008.2011

Ren, Z., Li, Z., Yan, L., Liao, K., Kong, F., Zhang, L., et al. (2019). Chromosome-level genome assembly of the razor clam Sinonovacula constricta (Lamarck, 1818). Mol. Ecol. Resour. 19, 1647–1658. doi:10.1111/1755-0998.13086

Ribas, L., Vanezis, K., Imuès, M. A., and Piferrer, F. (2017). Treatment with a DNA methyltransferase inhibitor feminizes zebrafish and induces long-term expression changes in the gonads. Epigenetics Chromatin 10 (1), 59. doi:10.1186/s13072-017-0045-6

Robins, W. H., McVean, G., and Durbin, R. (2008). A flexible and accurate method for genome-wide association studies. Nat. Genet. 40 (1), 62–69. doi:10.1038/ng.166

Roy, S., Kumar, V., Behera, B. K., and Das, B. K. (2021). “Epigenetics: Perspectives and potential in aquaculture,” in Advances in Fisheries Biotechnology, 2021. Editors P. K. Pandey and J. Parha (Singapore: Springer). doi:10.1007/978-981-16-3216-9_9

Roy, S., Kumar, V., Bossier, P., Vanrooyen, D., and Norozitallab, P. (2022). Induction of transgenerational innate immune memory against Vibrio infections in a brine shrimp (Artemia francicana) model. Aquaculture 537, 738309. doi:10.1016/j.aquaculture.2022.108458

Saito, Y., Kajirai, T., Arai, R., Asakawa, H., Ohtsuki, C., Horikoshi, N., et al. (2016). A genetically encoded probe for live-cell imaging of H4K20 monomethylation. J. Mol. Biol. 428 (20), 3885–3892. doi:10.1016/j.jmb.2016.08.010

Shang, X., Wang, S., Su, J., and Su, J. (2016). DNA methylation of GRI-G1 gene notably relates to the resistance against GCRV and negatively-regulates mRNA expression changes in the gonads. BMC Genomics 12, 541. doi:10.1186/1471-2164-12-541

Shao, C., Yao, B., Xiao, Z., Chen, X., Li, B., Jia, X., et al. (2017). The genome and transcriptome of Japanese flounder provide insights into flatfish asymmetry. Nat. Genet. 49 (1), 119–124. doi:10.1038/ng.3732

Shao, C., Li, Q., Chen, S., Zhang, P., Lian, J., Hu, Q., et al. (2014). Epigenetic modification and inheritance in sexual reversal of fish. Genome Res. 24 (4), 604–615. doi:10.1101/gr.121722.113

Sha, H., Zhou, T., Wang, X., Yang, Y., Wu, C., Liu, S., et al. (2018). Genome-wide association analysis of intra-specific QTL associated with the resistance for enteric septicaemia of carp. Mol. Genet. Genomics 299 (6), 1365–1378. doi:10.1007/s00438-018-1463-0

Simon, J. M., Parker, J. S., Liu, F., Rothbard, S. B., Ait-Si-Ali, S., Shaikh, B. D., et al. (2011). A role for widely interspersed zinc finger (WIZ) in retention of the α9α11 methyltransferase on chromatin. J. Biol. Chem. 290 (43), 26088–26092. doi:10.1074/jbc.M111.565459

Skvortsova, K., Iovino, N., and Bogdanovic, O. (2018). Functions and mechanisms of genetic inheritance in animals. Nat. Rev. Mol. Cell Biol. 19 (12), 774–780. doi:10.1038/s41580-018-0074-2

Somorjai, J. M., Danzmann, R. G., and Ferguson, M. M. (2003). Distribution of temperature tolerance quantitative trait loci in Arctic char (Salvelinus alpinus) and inferred homologies in trout (Oncorhynchus mykiss). Genetics 163 (3), 1443–1456. doi:10.1093/genetics/163.3.1443

Song, W., Xie, Y., Sun, M., Li, X., Fitzpatrick, C. K., Vaux, F., et al. (2021). A duplicated amh is the master sex-determining gene for Sebastes rockfish in the Northeast Pacific. Open Biol. 11 (7), 210063. doi:10.1098/rsob.210063

Sun, D., Yu, H., and Li, Q. (2022). Genome-wide differential DNA methylomes provide insights into the infertility of tilapia oysters. Mar. Biotechnol. 24 (1), 18–31. doi:10.1007/s10204-021-00838-y

Sun, L., Liu, S., Bao, L., Li, Y., Feng, J., and Liu, Z. (2015). Claudine multigene family in channeled catfish and their expression profiles in response to bacterial infection and hypoxia as revealed by meta-analysis of RNA-Seq datasets. Comp. Biochem. Physiol. Part D Genomics Proteomics 13, 60–69. doi:10.1016/j.cbd.2015.01.002

Sun, L., Liu, S., Wang, R., Jiang, Y., Zhang, Y., Zhang, J., et al. (2014). Identification and analysis of genome-wide SNPs provide insight into signatures of selection and domestication in channel catfish (Ictalurus punctatus). PLoS one 9 (10), e109666. doi:10.1371/journal.pone.0109666

Tan, X., Wang, Y. Y., Zhao, Y., Wang, H., Li, N., and Ji, S. X. (2016). Global DNA methylation changes in Nile Tilapia gonads during high temperature-induced masculinization. PLoS ONE 11 (8), 0158483. doi:10.1371/journal.pone.0158483

Tadmor-Levi, R., Doron-Faigenboim, A., Marcos-Hadad, E., Petit, J., Hulata, G., Forlenza, M., et al. (2019a). Different transcriptional response between susceptible and resistant common carp (Cyprinus carpio) fish hints on the mechanism of CyHV-3 disease resistance. BMC Genomics 20 (1), 1019. doi:10.1186/s12864-019-4691-9

Takayama, K., Shimoda, N., Takanaga, S., Horumi, S., and Kikuchi, Y. (2014). Expression patterns of dunlinshk, dunlin and dromit during development and fin regeneration in zebrafish. Gene Expr. Patterns 14 (2), 105–110. doi:10.1016/j.gep.2014.01.005

Tao, W., Cao, J., Xiao, H., Zhu, X., Dong, J., Kocher, T. D., et al. (2021). A chromosome-level genome assembly of Mozambique Tilapia (Oreochromis mossambicus) reveals the structure of sex determining regions. Front. Genet. 12, 796211. doi:10.3389/fgene.2021.796211

Termolino, P., Cremona, G., Conaglion, M. F., and Conicella, C. (2016). Insights into epigenetic landscape of recombinant-free regions. Front. Genet. 125 (2), 301–308. doi:10.1016/j.ijbiolres.2012.01.005

Thayil, A. J., Wang, X., Bhardari, P., Vom Saal, F. S., Tilted, D. E., and Bhardari, R. K. (2020). Bisphenol A and 17α-ethinylestradiol-induced transgenerational gene expression differences in the brain-pituitary-testis axis of medaka, Oryzias latipes. Biol. Reprod. 103 (6), 1324–1335. doi:10.1093/biolre/ioa169

Triaus, M., Asselman, J., Armant, O., Adam-Guillermin, C., De Scampheleaere, K. A. C., and Alonzo, F. (2018). Transgenerational DNA methylation changes in Daphnia magna exposed to chronic γ irradiation. Environ. Sci. Technol. 52 (7), 4331–4339. doi:10.1021/acs.est.7b05669

Ungewittert, T., Pootakham, W., Nookaew, I., Sinthrod, C., Angbong, P., Sittikankaew, K., et al. (2021). A chromosome-level assembly of the black tiger shrimp (Penaeus monodon) genome facilitates the identification of growth-associated genes. Mol. Ecol. Resour. 21 (5), 1620–1640. doi:10.1111/1755-0998.13357
Valdivieso, A., Ribas, L., Monlór-Gutino, A., Orbiñ, L., and Piérfer, F. (2020). Exposure of zebrafish to elevated temperature induces sex ratio shifts and alterations in the testis epithelial gene expression of unexposed offspring. Env. Res. 186, 109601. doi:10.1016/j.envres.2020.109601

Vallejo, R. L., Palti, Y., Liu, S., Maranick, D. P., and Wiens, G. D. (2014). Validation of linked QTL for bacterial cold water disease resistance and spleen size on rainbow trout chromosome Omy19. Aquaculture 432, 139–143. doi:10.1016/j.aquaculture.2014.05.003

Vandegehuchte, M. B., De Coninck, D., Vandenbrouck, T., De Coen, W. M., and Venney, C. J., Wellband, K. W., and Heath, D. D. (2021). Rearing environment during evolution and domestication. Mar. Biotechnol. 23 (1), 50. doi:10.1007/s10695-015-0112-3

Vandegehuchte, M. B., Lemière, F., and Janssen, C. R. (2010a). Gene transcription profiles during sex determination and validating QTL for fatty acid compositions and growth traits in Asian seabass. Fish. Sci. 76, 3329–3340. doi:10.1007/s12265-010-0969-x

Vandegehuchte, M. B., Lemière, F., Vanhacker, L., Vanden Berghe, W., and Janssen, C. R. (2010b). Direct and transgenerational impact on Daphnia magna of chemicals with a known effect on DNA methylation. Comp. Biochem. Physiol. C. Toxicol. Pharmacol. 151 (3), 278–285. doi:10.1016/j.cbpc.2009.11.007

Venney, C. J., Wellband, K. W., and Heath, D. D. (2021). Rearing environment affects the genome architecture and plasticity of DNA methylation in Chinsook salmon. Heredity 126 (1), 38–49. doi:10.1038/s41437-020-0346-4

Verne, V., Marandell, L., Liu, J., Vélez, E. J., Lepais, O., Pansaret, S., et al. (2018). DNA methylation of the promoter region of bnp3 and bnp3l genes induced by metabolic programming. BMC Genomics 19 (1), 677. doi:10.1186/s12864-018-5048-4

Verrier, E. R., Dorson, M., Mauger, S., Torhy, C., Ciobotaru, C., Hervet, C., et al. (2012). Resistance to a rhadinovirus (VHSV) in rainbow trout: Identification of a major QTL related to innate mechanisms. PLoS One 8 (2), e53502. doi:10.1371/journal.pone.005302

Vidalurie, V., and Chen, X. (2021). Epigenetic regulation of drosophila germline stem cell maintenance and differentiation. Dev. Biol. 473, 105–118. doi:10.1016/j.ydbio.2021.02.003

Vogt, G. (2022). Studying phenotypic variation and DNA methylation across development, ecology and evolution in the clonal marbled crayfish. A paradigm for investigating epigenotype-phenotype relationships in micro-invertebrates. Sci. Nat. 109 (1), 16. doi:10.1111/sin.0121-0782-6

Waghmare, S. G., Samarim, A. M., Samarim, A. M., Danielsen, M., Müller, H. S., Pelcar, T., et al. (2021). Histone acetylation dynamics during in vivo and in vitro oocyte aging in common carp Cyprinus carpio. Int. J. Mol. Sci. 22 (11), 6036. doi:10.3390/ijms22116036

Wang, Z. Y., Xia, J. H., Lin, G., Wang, L., Lin, V. C., and Yue, G. H. (2016). Genome-wide methylation analysis identified sexually dimorphic methylated regions in hybrid tilapia. Sci. Rep. 6, 35903. doi:10.1038/srep35903

Wang, E. T., Sandberg, R., Luo, S., Khrebtukova, I., Zhang, L., Mayr, C., et al. (2011). Reference genome of the armadillo glyptodontemyca. Mar. Biotechnol. 13 (11), 1212–1219. doi:10.1007/s10695-011-9330-2

Wang, L., Chua, E., Sun, F., Wan, Z. Y., Ye, B., Pang, H., et al. (2019). Mapping and validating QTL for fatty acid compositions and growth traits in Asian seabass. Mar. Biotechnol. 21 (5), 643–654. doi:10.1111/mbt.12990

Wang, L., Sun, F., Wan, Z. Y., Yang, Z., Tay, Y. X., Lee, M., et al. (2022). Transposon-induced epigenetic silencing in the Xin chromosome as a novel form of dmrt1 expression regulation during sex determination in the fighting fish. BMC Biol. 20 (1), 5. doi:10.1186/s12864-020-02715-y

Wang, Q., Hao, X., Wang, X., Li, J., Liu, G., Kuang, Y., et al. (2014). Genome-wide methylation reprogramming during sex determination and transition in zebra danio. Genomics Proteomics Bioinforma. 12 (11), 1205–1211. doi:10.1089/geno.2013.05471

Yang, Y., Zhao, M., Wu, X., Li, J., Liu, G., Kuang, Y., et al. (2014). Genome sequence and genetic diversity of the common carp, Cyprinus carpio. Nat. Genet. 46 (11), 1212–1219. doi:10.1038/ng.3098

Yao, A., Gubardin, J., Corrier, G., and Vignolles, A. (2021). Long-term transcriptional response of the FSH and TSH genes in rainbow trout: Identiﬁcation of a master gene for the regulation of the reproductive axis. Genes 12 (6), 770. doi:10.3390/genes12060770

Yao, A., Nicol, B., Jouanno, E., Quillet, E., Fostier, A., Guyomard, R., et al. (2012). An endogenous genomic region in a region of a rainbow trout sex chromosome region. Nat. Ecol. Evol. 6 (6), 1428–1436. doi:10.1038/ngeo1735

Yao, Z., Gao, T., Xu, Y., Li, X., Li, J., Liu, H., et al. (2021). A chromosome-level reference genome of red swamp crayfish Procambarus clarkii provides insights into the gene families regarding growth or development in crustaceans. Genomics 113 (3), 3274–3284. doi:10.1089/geno.2021.07.017

Yang, X., Fu, Q., Wang, X., Liu, Y., Zeng, Q., Li, Y., et al. (2018). Comparative transcriptome analysis of the swimbladder reveals expression signatures in response to low oxygen stress in channel catfish, Ictalurus punctatus. Physiol. Genomics 50 (8), 636–647. doi:10.1152/physiogenomics.00125.2017

Yang, Y., Zhou, T., Liu, Y., Tian, C., Bao, L., Wang, W., et al. (2022). Identiﬁcation of an epigenetically marked locus within the sex determination region of channel catfish. Int. J. Mol. Sci. 23 (10), 451. doi:10.3390/ijms2310451

Yang, Z., Wong, S. M., and Yue, G. H. (2020). Characterization of GAB3 and its association with NNN resistance in the Asian seabass. Fish. Shellfish Immunol. 104, 18–24. doi:10.1016/j.fsi.2020.05.035

Yano, A., Guymard, R., Nicol, B., Josann, E., Quillet, E., Kopp, C., et al. (2012). An immune-related gene evolved into the master sex-determining gene in rainbow trout, Oncorhynchus mykiss. Curr. Biol. 22 (15), 1423–1429. doi:10.1016/j.cub.2012.05.045

Yano, A., Nicol, B., Josann, E., Quillet, E., Fostier, A., Guymard, R., et al. (2013). The sexually dimorphic on the Y-chromosome gene (sdY) is a conserved male-specific Y-chromosome sequence in many salmonids. Evol. Appl. 6 (3), 486–496. doi:10.1111/eva.12032

Liu et al. 10.3389/fgene.2022.99471
Yuan, Z., Liu, S., Yao, J., Zeng, Q., Tan, S., and Liu, Z. (2016). Expression of Bcl-2 genes in channel catfish after bacterial infection and hypoxia stress. *Dev. Comp. Immunol.* 65, 79–90. doi:10.1016/j.dci.2016.06.018

Zeng, D., and Guo, X. (2022). Mantle transcriptome provides insights into biomineralization and growth regulation in the eastern oyster (*Crassostrea virginica*). *Mar. Biotechnol.* 24 (1), 82–96. doi:10.1007/s10126-021-10088-7

Zeng, Y., and Chen, T. (2019). DNA methylation reprogramming during mammalian development. *Genes (Basel).* 10 (4), 257. doi:10.3390/genes10040257

Zhang, B., Zheng, H., Huang, B., Li, W., Xiang, Y., Peng, X., et al. (2016). Allelic reprogramming of the histone modification H3K4me3 in early mammalian development. *Nature* 537 (7621), 553–557. doi:10.1038/nature19361

Zhang, G., Fang, X., Guo, X., Li, L., Luo, R., Xu, F., et al. (2012). The oyster genome reveals stress adaptation and complexity of shell formation. *Nature* 490 (7418), 49–54. doi:10.1038/nature11413

Zhang, G., Li, J., Zhang, J., Liang, X., Wang, T., and Yin, S. (2020). A high-density SNP-based genetic map and several economic traits-related loci in *Pelteobagrus vachelli*. *BMC Genomics* 21 (1), 700. doi:10.1186/s12864-020-07115-7

Zhang, J. (2004). Evolution of DMY, a newly emergent male sex-determination gene of medaka fish. *Genetics* 166 (4), 1887–1895. doi:10.1534/genetics.166.4.1887

Zhang, T., Cooper, S., and Brockdorff, N. (2015). The interplay of histone modifications - writers that read. *EMBO Rep.* 16 (11), 1467–1481. doi:10.15252/embr.201540945

Zhang, X., Li, H., Qiu, Q., Qi, Y., Huang, D., and Zhang, Y. (2014). 2, 4-Dichlorophenol induces global DNA hypermethylation through the increase of S-adenosylmethionine and the upregulation of DNMTs mRNA in the liver of goldfish *Carassius auratus*. *Comp. Biochem. Physiol. C. Toxicol. Pharmacol.* 160, 54–59. doi:10.1016/j.cbpc.2013.11.008

Zhang, X., Yuan, J., Sun, Y., Li, S., Gao, Y., Yu, Y., et al. (2019). Penaeid shrimp genome provides insights into benthic adaptation and frequent molting. *Nat. Commun.* 10 (1), 356. doi:10.1038/s41467-018-08197-4

Zhang, Y., Liu, Z., and Li, H. (2020). Genomic prediction of columnaris disease resistance in catfish. *Mar. Biotechnol.* 22 (1), 145–151. doi:10.1007/s10126-019-09941-7

Zhang, Y., Shen, W., Cao, M., Li, J., Zheng, B., Lou, Z., et al. (2019). Dynamic alterations in methylation of global DNA and growth-related genes in large yellow croaker (*Larimichthys crocea*) in response to starvation stress. *Comp. Biochem. Physiol. B Biochem. Mol. Biol.* 227, 98–105. doi:10.1016/j.cbpb.2018.09.006

Zhong, H., Xiao, J., Chen, W., Zhou, Y., Tang, Z., Guo, Z., et al. (2014). DNA methylation of pituitary growth hormone is involved in male growth superiority of Nile tilapia (*Oreochromis niloticus*). *Comp. Biochem. Physiol. B Biochem. Mol. Biol.* 171, 42–48. doi:10.1016/j.cbpb.2014.03.006

Zhou, M., Zhao, Z., Zhao, J., Wu, M., and Chen, X. (2021). Gene expression profiling of DNA methyltransferase genes in *Siniperca chuatsi* based on transcriptome sequencing. *J. Fish. Biol.* 99 (5), 1755–1760. doi:10.1111/jfb.14862

Zhong, X., Wang, X., Zhou, T., Jin, Y., Tan, S., Jiang, C., et al. (2017). Genome-wide association study reveals multiple novel QTL associated with low oxygen tolerance in hybrid catfish. *Mar. Biotechnol.* 19 (4), 379–390. doi:10.1007/s10126-017-9757-5

Zhou, M., Zhao, Z., Zhao, J., Wu, M., and Chen, X. (2021). Gene expression profiling of DNA methyltransferase genes in *Siniperca chuatsi* based on transcriptome sequencing. *J. Fish. Biol.* 99 (5), 1755–1760. doi:10.1111/jfb.14862

Zhou, T., Liu, S., Geng, X., Jin, Y., Jiang, C., Bao, L., et al. (2017). GWAS analysis of QTL for enteric septicemia of catfish and their involved genes suggest evolutionary conservation of a molecular mechanism of disease resistance. *Mol. Genet. Genomics* 292 (1), 231–242. doi:10.1007/s00438-016-1269-x

Zhu, W., Xu, X., Wang, X., and Liu, J. (2019). Reprogramming histone modification patterns to coordinate gene expression in early zebrafish embryos. *BMC Genomics* 20 (1), 248. doi:10.1186/s12864-019-5611-7