



Adaption to extreme environments: a perspective from fish genomics

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Abstract Fishes exhibit greater species diversity than any other group of vertebrates. They are found in most bodies of water, including those that pose extreme challenges, such as sulfide springs, rivers contaminated with heavy metals and organic pollutants, and caves without light. Adaptation to these extreme environments usually occurs rapidly, which has stimulated much interest in uncovering the genetic basis of such rapid adaptation. Since the sequencing of the zebrafish genome in 2001, rapid development of high-throughput sequencing technology has facilitated the additional sequencing of ~ 210 ray-finned fish genomes to date. As a result of this wealth of resources, much attention has been focused on the genetic basis of adaptation in fishes, particularly in extreme environments. The goal of this review is to summarize recent advances in fish genomics, with a specific focus on the use of genomic data to understand the genetic basis of adaptation to extreme

environments in fishes. The results highlight that fishes often adapt to extreme environments through phenotypic and physiological changes that have a confirmed or inferred genetic basis. Moreover, such changes are usually rapid and repeated when parallel adaptation to similar extreme environments occurs. Specifically, parallel genetic changes are usually observed at both the intra- and interspecific level. The advances in fish genomics provide the opportunity to understand how evolutionary changes feed back into ecosystems that are facing extreme environmental changes, as well as to advance our understanding of the repeatability and predictability of evolutionary response (of fishes) to extreme environmental changes.

Keywords Adaptation · Comparative genomics · Extreme environment · Parallelism · Population genomics

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Extreme aquatic environments: an introduction

Approximately 36,000 species of fish are recognized globally, and new species continue to be identified each year. Accounting for more than half of the named vertebrates on the planet, fishes exhibit greater species diversity than any other group of vertebrates. Fishes are abundant in most bodies of water, and occupy nearly all types of aquatic environments, both

naturally occurring and manmade, even those which pose extreme challenges for survival.

There is a vast diversity of biotic and abiotic factors in aquatic ecosystems. Some conditions can reach extremes and hence impose great challenges for adaptation. For example, hydrogen sulfide (H_2S) produced by both geochemical and biological processes is a potential respiratory toxicant for fishes, as it interferes with oxidative phosphorylation by directly inhibiting cytochrome c oxidase (COX) of the mitochondrial respiratory chain (Cooper and Brown 2008; Tobler et al. 2018). In addition, H_2S can also reduce the oxygen affinity of oxygen transporters, leading to their loss of function (Pietri et al. 2011). This physiological stress can be further exacerbated by hypoxic conditions that are often correlated with sulfidic conditions, which also challenge blood oxygen transport and metabolism (Plath et al. 2015). Nevertheless, some species of fish are found in H_2S -rich (and oxygen-poor) environments, such as hagfishes (*Eptatretus* and *Rochina crassa*) and sablefish (*Anoplopoma fimbria*) in deep-sea hydrothermal vents, pupfish (*Cyprinodon bobmilleri*) and killifish (*Aphanius dispar*) in cold springs, and *Poecilia* in caves (Engel 2007; Greenway et al. 2014; Levin 2005; Smith and Baco 2003; Van Dover 2000).

Water pH represents another extreme condition that some fishes have adapted to. Although most fishes can only survive in neutral water (or close to; i.e. pH \sim 7.0), some have adapted to highly acidic (e.g. dace, Kaneko et al. 1999; bluegill and largemouth bass, Graham 1993) or alkaline (e.g. tilapia, Randall et al. 1989; terek, Danulat and Kempe 1992; Amur ide, Xu et al. 2013a, b) lakes. Similar to H_2S , pH can also impair blood oxygen affinity and transport (Ye and Randall 1991). In addition, pH can alter ammonia excretion and challenge ionoregulation by creating a net loss of essential monovalent ions (Wright and Wood 1985). Ionoregulation can also be challenged by hypersalinity—another extreme aquatic condition found in some landlocked saline lakes and mangrove swamps. In these environments, large salt loads are absorbed across the gills, kidneys and intestine, which causes a constant loss of body water and accumulation of electrolytes (Evans 2008). Yet, some fishes have established biochemical adaptations to overcome these challenges (see Kavembe et al. 2016a for list of fishes adapted to saline lakes).

In addition to chemical stresses, physical stress can also pose extreme physiological and behavioural challenges for fishes. For example, the lightless, silent, biotically simple and stable environment of dark caves and subterranean aquatic habitats can constrain orientation and navigation, which has significant implications for survival (i.e. finding food) and reproduction (i.e. finding a mate; Soares and Niemiller 2013). Interestingly, other than salamanders, fishes are the only vertebrate group that has successfully colonized—and become completely restricted to—subterranean habitats. Indeed, cavefishes exhibit considerable phylogenetic and geographical diversity; over 300 cavefish species are represented by 10 orders and 22 families, and occur on every continent except Antarctica (Soares and Niemiller 2013).

Finally, anthropogenic activities, such as mining, discharging pharmaceuticals and pesticides from factories, and improper wastewater treatment can create or compound extreme environmental stressors in aquatic habitats (Jurgens et al. 2016; Larsson 2014; Rolshausen et al. 2015; Williams et al. 2009). For example, pollutants arising from heavy metal contamination (copper, zinc, cadmium, nickel, arsenic, lead, iron, mercury, silver and selenium) and organic compounds [polychlorinated dibenzo-*p*-dioxins/furans (PCDD/Fs), polychlorinated biphenyl (PCBs), polycyclic aromatic hydrocarbons (PAHs), and Lindane] can pose major toxicity threats via disruption of ion homeostasis and generation of reactive oxygen species (Wood 2011; Valko et al. 2005). Moreover, organic pollutants have disruptive effects on the neuroendocrine and immune systems (Denison et al. 2011), can interrupt cardiovascular and embryonic development, and interfere with reproductive functions (Barron et al. 2004; Cherr et al. 2017). Surprisingly, some fish species are found in highly polluted environments, for example brown trout (*Salmo trutta*) in the Hayle River in South-West England (Uren Webster et al. 2013), Atlantic killifish (*Fundulus heteroclitus*) in urban estuaries in the USA (Reid et al. 2016), and North Atlantic eels (*Anguilla*) exposed to high concentrations of selenium and organic pollutants in the Gironde and St. Lawrence systems (Laporte et al. 2016).

Adaptations to extreme environments: a brief overview

Regardless of the source of environmental stressor, fishes have evolved various morphological, biochemical, behavioural, life-history, and physiological mechanisms in order to adapt to extreme conditions. Perhaps one of the most well-known and conspicuous morphological adaptations to extreme environments is the loss of eyes and pigment in cave-dwelling fish such as the Mexican tetra (*Astyanax mexicanus*; Avise and Selander 1972; Bradic et al. 2012; Coghill et al. 2014) and *Sinocyclocheilus* cavefish (Borowsky 2018; Yang et al. 2016). Other phenotypic adaptations to extreme conditions include changes in the brain, head, mouth, jaw and lip size and shape observed in fishes adapted to sulfuric and hypoxic conditions (Chapman and Hulen 2001; Palacios et al. 2013; Tobler et al. 2011). Similarly, changes in gills, such as morphology (i.e. size and shape) and cellular arrangement (i.e. remodelling) are common modifications in response to hypersaline, hypoxic, or sulfuric conditions (Chapman and Hulen 2001; Friedman et al. 2012; Nilsson 2007; Sollid et al. 2003; Sollid and Nilsson 2006; Tobler et al. 2011). For example, the gill chloride cells of acid-tolerant dace have been rearranged in a follicular structure and contain high concentrations of $\text{Na}^+\text{-K}^+\text{-ATPase}$, carbonic anhydrase II, type 3 Na^+/H^+ exchanger, type 1 $\text{Na}^+\text{-HCO}_3^-$ cotransporter, and aquaporin-3, in order to prevent acidification of plasma and sodium loss (Hirata et al. 2003; Kaneko et al. 1999). Other physiological adaptations include production of ornithine-urea cycle enzymes in the liver of tilapia adapted to the alkaline Lake Magadi, in which the urea is excreted across the gills into the surrounding alkaline habitat (Randall et al. 1989). In addition, oscar (*Astronotus ocellatus*) adapted to hypoxia demonstrate activation of anaerobic metabolism (Sloman et al. 2006). In most cases, such morphological and physiological mechanisms are not modified in isolation; rather, they are accompanied by additional changes—either in succession or simultaneously—in other behavioural or life-history traits, in order to achieve heritable adaptation at the organismal level, which is passed down to future generations. Of course, non-genetic (i.e. plastic) modifications can also occur in response to extreme environments, but these do not fall under the focus of this review.

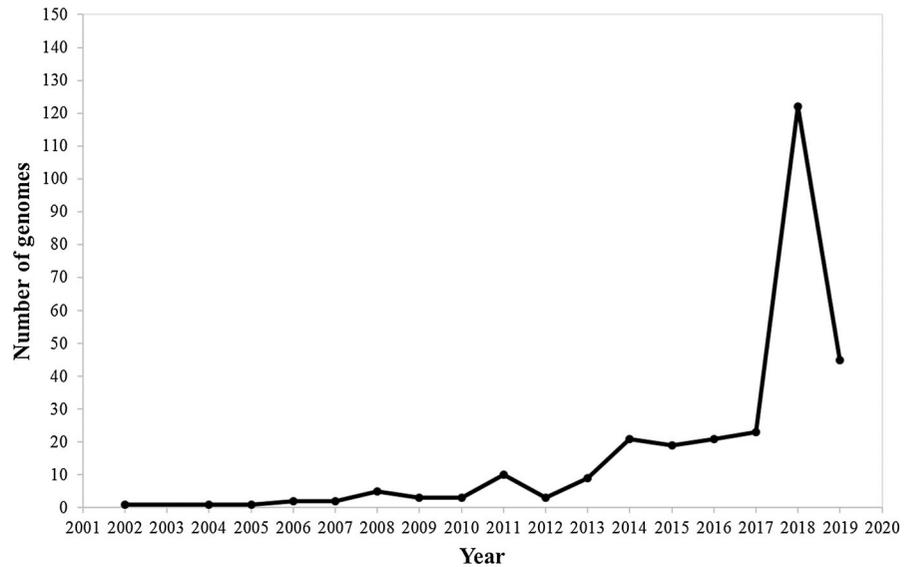
Genetic insights into adaptations to extreme environments

As the examples of adaptations to extreme environments continue to grow, so too does the interest in their genomic basis. The first fish genome to be fully sequenced was that of the zebrafish (*Danio rerio*), which was initiated in 2001. Since then, the number of sequenced fish genomes has continued to increase each year, which has been greatly facilitated by the development and refinement of high-throughput sequencing technologies. As of June 2019, over 200 ray-finned fish genomes have been sequenced (Fig. 1). Such advances in technology have allowed deeper investigations into the genomic basis of adaptations to extreme aquatic habitats. In order to highlight some of the important studies exploring this issue, academic databases (Google Scholar, ISI Web of Science) were searched using keywords including fish, extreme environment, adaptation, and genomics. In what follows, we summarize the main approaches (candidate gene sequencing, quantitative trait locus (QTL) mapping, comparative population genomics and transcriptomics), and findings in regards to the amount, type, and interactions between mutations that contribute to adaptation in extreme environments (Table 1).

Identifying genetic adaptations to extreme environments

Although adaptive responses to extreme environments can be achieved through plastic or evolutionary changes (or a combination of the two), the focus of this review is on studies exploring modifications that are strictly genetic (i.e. selection that causes an alteration in allele frequencies and/or arises from de novo mutations). Traditional studies began with sequence analysis of candidate genes, for example opsins and crystallins, to identify specific nucleotide substitutions associated with loss of eyes in cave-dwelling fish (Langecker et al. 1993; Yokoyama and Yokoyama 1990), and functional comparisons of metallothionein genes to explore the arrangement of metal-responsive elements that contributes to cadmium tolerance in pike and stone loaches (Olsson and Kille 1997). Another classical approach towards understanding the genomic basis of extremophile adaptation has been QTL mapping, as applied for

Fig. 1 The number of publicly available ray-finned fish genomes by June 30, 2019



example by Yoshizawa et al. (2013) and Kowalko et al. (2013) to explore the genomic basis of complex behavioural traits associated with adaptation to caves, tolerance to dioxin-like compounds (DLCs) in killifish (Nacci et al. 2016), and hypoxia tolerance in Nile tilapia (Li et al. 2017). By studying multiple loci simultaneously, these studies have provided important insights into the number of genes involved in adaptation, and their potential interaction. Further understanding of the polygenic nature of adaptation has been facilitated by approaches that explore patterns across the genome, such as restriction-site associated DNA sequencing (RAD-seq) or whole genome resequencing. For example, Laporte et al. (2016) performed genome-wide analysis in two species of North Atlantic eels (American eel, *Anguilla rostrata* and European eel, *Anguilla anguilla*) exposed to high concentrations of selenium and organic pollutants, and found that both species had a significant number of covarying markers. Similar results were also reported by Nacci et al. (2016), who noted the high explanatory power (44%) of the interactions between independent QTLs associated with DLC tolerance in killifish. Interestingly, the Pool-Seq strategy employed by Pfenninger et al. (2015) highlighted a difference in the degree of polygenetic adaptation when comparing independent populations of *Poecilia*; higher polygenic adaptation was detected in the population with the key mitochondrial adaptation that led to an H₂S-insensitive COX (Pfenninger et al. 2014; Pfenninger et al.

2015), indicating that stochastic differences can exist even within closely related populations of the same species.

Population genomic approaches using high-density markers have also been useful in screening for selective sweeps. For example, when comparing populations of Amur ide from the alkaline Lake Dali Nor with those from lakes with neutral pH, Xu et al. (2017) identified selective sweeps in a number of genomic regions that harbor genes involved in ion homeostasis, acid-base regulation, unfolded protein response, reactive oxygen species elimination, and urea excretion. High-throughput techniques allow patterns of genome-wide differentiation to be probed with increased power and resolution, sometimes uncovering many divergent genomic regions in wild populations of fishes adapted to extreme environments. In comparisons between guppy populations from polluted and unpolluted rivers, Hamilton et al. (2017) found 1600 RAD loci (5%) that had F_{ST} values greater than 0.75; among these highly differentiated loci, roughly 36% fell within genes that were significantly enriched for gene ontology terms associated with cellular processes and metal ion binding. Similarly, despite the high levels of panmixia across the radiation of *Alcolapia* in East African alkaline lakes, peaks of differentiation were identified in several genomic locations, suggesting that the radiation is undergoing adaptive divergence (Ford et al. 2015). However, in some cases such as the tilapia (*Alcolapia*

Table 1 Examples of genomics-based studies of adaptation to extreme environments in fishes

Species	Environment	Methodology	Genetic mechanisms and main finding	References
<i>Poecilia mexicana</i> ; <i>Poecilia sulphuraria</i>	High H ₂ S	Mitochondrial genome sequencing	Non-synonymous nucleotide substitutions in <i>cox1</i> and <i>cox3</i> caused reduced H ₂ S susceptibility of COX Amino acid substitutions in <i>cox1</i> and <i>cox3</i> were shared between two populations; a different adaptive mechanism is implicated in the third population	Pfenninger et al. (2014)
<i>Poecilia mexicana</i>	High H ₂ S	Pool-seq	Many small de novo mutations distributed across the genome of sulfide-adapted populations Genes involved in the H ₂ S detoxification pathway show strong signals of positive selection; parallelism strongest at the metabolic pathway level	Pfenninger et al. (2015)
<i>Poecilia mexicana</i> ; <i>Poecilia sulphuraria</i>	High H ₂ S	RNA-seq	Changes in expression of many genes associated with enzymatic H ₂ S detoxification and transport of oxidized sulfur species, oxidative phosphorylation, energy metabolism, and pathways involved in responses to oxidative stress Little evidence for convergence among the three independent population pairs	Kelley et al. (2016)
<i>Leuciscus waleckii</i>	High alkalinity	De novo genome sequencing; genome re-sequencing	Presence of expanded long terminal repeats with high nucleotide substitution rates Expansion of genes associated with providing protective barriers to eggs and regulating acid-base balance 79,004 synonymous and 138,725 non-synonymous SNPs	Xu et al. (2017)
<i>Lateolabrax maculatus</i>	High salinity	RNA-seq	Identified 455 differentially expressed genes (DEG) in response to salinity challenge (184 upregulated and 241 downregulated) DEGs categorized into functional categories including metabolites and ion transporters, energy metabolism, signal transduction, immune response and structure reorganization	Zhang et al. (2017)
<i>Salmo trutta</i>	Heavy metals	RNA-seq	Changes in expression of genes in the metal- and ion-homeostasis pathways	Uren Webster et al. (2013)
<i>Fundulus heteroclitus</i>	Organic pollutants	Genome re-sequencing; RNA-seq	Many small and few large genomic outliers; deletions and duplications are common variants Strongest selection on the aryl hydrocarbon receptor (AHR) signaling pathway, including regulatory genes and transcriptional targets Rapid and repeated adaptation to toxic organic pollution likely achieved through standing genetic variation	Reid et al. (2016)
<i>Fundulus heteroclitus</i>	Organic pollutants	RAD-seq	Eight genomic regions of increased divergence distributed across the genome, mainly in regions harboring genes in the AHR signaling pathway	Osterberg et al. (2018)
<i>Anguilla anguilla</i> ; <i>Anguilla rostrata</i>	Selenium and organic pollutants	RAD-seq	Less than 1% of loci identified as important outliers Little genomic convergence in important outliers among independent population pairs; stronger convergence at the pathway level, particularly in sterol regulation	Laporte et al. (2016)

Table 1 continued

Species	Environment	Methodology	Genetic mechanisms and main finding	References
<i>Astyanax mexicanus</i>	Cave	De novo genome sequencing; RNA-seq; QTL-mapping	15 non-overlapping QTL underlying eye-related phenotypes (some with pleiotropic effects), enriched for genes involved in congenital eye abnormalities Reduced expression in several candidate genes of cave-dwelling fish Differences in eyes between cave and surface fish driven by a combination of regulatory and non-synonymous coding changes	McGaugh et al. (2014)
<i>Astyanax mexicanus</i>	Cave	Sequence comparisons of insulin genes	Change in coding region of insulin receptor gene (<i>insra</i>)	Riddle et al. (2018)
<i>Astyanax mexicanus</i>	Cave	cDNA sequence comparisons of <i>Oca2</i> gene	Non-synonymous changes in conserved residues Deleted exons	Protas et al. (2006)
<i>Sinyclocheilus anophthalmus</i>	Cave	RNA-seq	Downregulation of photoreceptor genes in cave fish Several regulatory changes in retinal cell development and maintenance genes Genetic mechanisms underlying eye reduction are different in different cave species	Meng et al. (2013)
<i>Sinyclocheilus anshuiensis</i>	Cave	De novo genome sequencing; RNA-seq; QTL-mapping	Loss and downregulation of opsin genes, pseudogeneization of crystallin genes may promote the loss of eyes Deletion of <i>Mpv17</i> and mutation of <i>Tyr</i> contribute to the Albino phenotype Deletion of two copies of <i>Skp1</i> leads to the loss of diurnal rhythm Deletion of <i>Edar</i> and loss of <i>Lamb3</i> and <i>Col7a</i> may lead to the degradation of scales Loss of <i>creb34</i> may promote decreased fecundity Expansion of taste-related genes may lead to an increased the number of taste buds	Yang et al. (2016)

grahami) adapted to the hot, alkaline and hypersaline Lake Magadi, genome-wide scans of multiple East African populations detected only one locus putatively under selection (Kavembe et al. 2016b). In general, increasing the number of loci screened offers insights into the number and distribution of genomic regions underlying adaptation. A common finding is that many genomic regions distributed across the genome have putatively contributed to adaptation (see Table 2). In one case, their relative contribution to a particular phenotypic or physiological trait was small (< 10%; Li et al. 2017). On the other hand, albinism in the Mexican cave tetra mapped to a single mutation that explained nearly 50% of the variance in this trait (Protas et al. 2006). Clearly more studies of this nature

are needed to further understand the effect of loci underlying adaptation.

Finally, strategies such as whole genome (re)sequencing and de novo assembly have led to the identification of expansions of genes associated with alkalinity adaptation in Amur ide, including the zona pellucida domain-containing protein gene, vitelline membrane outer layer protein 1 gene, natriuretic peptide receptor gene, and the solute carrier family 12 gene (Xu et al. 2017). These genes are thought to provide protective barriers to eggs and regulate acid-base balance in response to the alkaline stress of Lake Dali Nor. Similarly, de novo assembly of the cave-dwelling *A. mexicanus* provided refinement of mapping known candidate genes associated with eye

Table 2 List of genome/transcriptome scans with reported outlier SNPs/windows/scaffolds/QTL/differentially expressed genes

Species	Methodology	Average number of clean reads/coverage	Number of loci screened	Number of outlier SNPs/windows/scaffolds/QTL/differentially expressed genes (DEGs)	References
<i>Poecilia mexicana</i>	Pool-seq	157,278,951	3,104,200 SNPs	Puy: 19,063 SNPs; Tac: 26,809 SNPs	Pfenninger et al. (2015)
<i>Leuciscus waleckii</i>	Genome re-sequencing	10× coverage	6,477,849 SNPs	3760 windows	Xu et al. (2017)
<i>Oreochromis niloticus</i>	RAD-seq; QTL-mapping	10× coverage	924 SNPs	59 QTL associated with hypoxia	Li et al. (2017)
<i>Fundulus heteroclitus</i>	RAD-seq	1,330,973	12,071 SNPs	AWvKC: 14 scaffolds; AWvMC: 13 scaffolds; KCvMC: 14 scaffolds	Osterberg et al. (2018)
<i>Anguilla anguilla</i> ; <i>Anguilla rostrata</i>	RAD-seq	Not reported	23,659; 14,755 SNPs	142 SNPs; 141 SNPs	Laporte et al. (2016)
<i>Salmo trutta</i>	RNA-seq	66.5 M	202,994 transcripts	998 differentially expressed transcripts	Uren Webster et al. (2013)
<i>Fundulus heteroclitus</i>	Genome re-sequencing; RNA-seq	0.6–7-fold coverage	37,065 scaffolds	6414 scaffolds	Reid et al. (2016)
<i>Astyanax mexicanus</i>	QTL-mapping	Not reported	178	48 QTL associated with eye-related phenotypes	Protas et al. (2007)
<i>Sinocyclocheilus anophthalmus</i>	RNA-seq	132,682,597	52,915–52,656 contigs	1658 DEGs	Meng et al. (2013)
<i>Alcolapia grahami</i>	RAD-seq	770,618	7171 SNPs	1 SNP	Kavembe et al. (2016a, b)
<i>Poecilia reticulata</i>	RAD-seq	2,653,012–14,849,446	30,423 RAD loci	1623 SNPs	Hamilton et al. (2017)

degeneration and other cave-adapted traits, as well as identification of novel regulators of eye development (McGaugh et al. 2014). Yang et al. (2016) sequenced the genomes of three *Sinocyclocheilus* species (cave-dwelling *Sinocyclocheilus anshuiensis*, semi-cave-dwelling *Sinocyclocheilus rhinoceros*, and surface-dwelling *Sinocyclocheilus grahami*), and identified several molecular mechanisms contributing to the troglomorphic characteristics of *Sinocyclocheilus* cavefishes. These included the loss of opsin genes and pseudogenization of crystallin genes, which may promote the degradation of the lens and retina; the deletion of *Mpv17* and mutation of *Tyr*, which may play an important role in generating the Albino

phenotype; the deletion of two copies of *Skp1*, which leads to the loss of diurnal rhythm; the deletion of *Edar* and loss of *Lamb3* and *Col7a*, which may lead to the degradation of scales; the loss of *creb34*, which may decrease fecundity; and the expansion of taste-related genes, which may lead to an increased number of taste buds (Yang et al. 2016). In spite of the plethora of information this technology can offer, these large datasets nevertheless rely on complex analytical approaches that may inevitably overlook key candidate genes.

In addition to variation at the genomic level, changes at the transcriptomic level have long been thought to underlie phenotypic responses to

environmental changes (King and Wilson 1975). Early studies of gene expression tended to focus on very few specific candidate genes, for example AQP3, which has been studied extensively in the gills of fishes adapted to hypersaline environments (Lavery and Skadhauge 2015). In addition, gene expression studies that have targeted the gene encoding sulfide:quinone oxidoreductase found that it is consistently upregulated in natural sulfide spring populations of *Poecilia* (Kelley et al. 2016). Common garden experiments even confirmed that lab-reared individuals retained constitutive expression of this gene regardless of the H₂S concentration, suggesting evolutionary divergence at the level of gene regulation. However, recent technological advances have provided the opportunity to screen the entire transcriptome. This has led to the identification of tens to thousands of genes that were differentially expressed between cave- and surface-dwelling *Sinocyclocheilus* (Meng et al. 2013), between alkaline tolerant and sensitive Amur ide (Xu et al. 2013a, b), and between metal tolerant and sensitive brown trout (Uren Webster et al. 2013). For a list of main studies and their key findings, see Table 1.

Parallel versus non-parallel genetic modifications

There has been a longstanding interest in determining whether parallel environmental stressors evoke the same or different genetic pathways to generate specialized adaptations when independent populations are exposed to the same extreme environmental conditions. One of the most common strategies for assessing the degree of parallelism is to compare several independent populations that have become adapted to an extreme condition with the ancestral population found in normal environments. For example, Pfenninger et al. (2014) compared three independent lineages of *Poecilia* adapted to dark caves, and found that reduced H₂S susceptibility of COX was achieved through the same amino acid substitutions in *cox1* and *cox3* genes in two of these lineages. However, decreased H₂S susceptibility was not detected in a third lineage, suggesting that different genetic mechanisms to H₂S resistance can evolve even in closely related lineages. Similarly, Riddle et al. (2018) found that a mutation in the insulin receptor gene that causes insulin resistance—beneficial for cave fish adapted to long periods of starvation—was present in most, but not all, populations of the Mexican

cave tetra (*Astyanax mexicanus*). Another example of non-parallel genetic evolution is in the pigmentation gene *Oca2*, known to cause albinism in the Mexican tetra (Protas et al. 2006). Although the same gene was under selection in two independent cave populations, the loss of function in the pigmentation protein OCA2 occurred through different deletions. Interestingly, a later study identified a frameshift mutation in another independent gene that also contributed to depigmentation in the same species (*Mc1r*; Gross et al. 2009). Moreover, in the *Sinocyclocheilus* cavefish, yet another set of genes are responsible for loss of pigmentation—Yang et al. (2016) discovered a deletion in *Mpv17* and an amino acid mutation in *Tyr* that led to the same cave-adapted phenotype as *A. mexicanus*, providing evidence for non-parallelism on an interspecific level. A striking example of parallelism was documented in Atlantic killifish (*Fundulus heteroclitus*) that have become tolerant to otherwise lethal levels of pollution: when screening pairs of pollution-tolerant and sensitive (reference) populations, Reid et al. (2016) found that the strongest outliers—genes relating to the aryl hydrocarbon (AHR) signaling pathway—were shared across the four population pairs. Nevertheless, most of the outliers were unique to each tolerant population, indicating that while parallel genetic changes can contribute to repeated adaptation, non-parallel modifications are more common. Similar findings were reported by Osterberg et al. (2018) in a follow-up study of the same species, who also found very few shared outliers—again, genes relating to the AHR pathway—in pollution/clean population comparisons. Interestingly, an AHR gene has also been identified as contributing to PCB resistance in Atlantic tomcod from the Hudson River (Wirgin et al. 2011). Hence, unlike the interspecific cavefish example, parallel genetic changes can occur between divergent species when populations are exposed to the same extreme environmental conditions.

The occurrence of parallelism has also been investigated at the transcriptomic and pathway level. Since adaptation usually involves changes in expression in several genes, advances in technology have facilitated studies of the degree of parallelism across the entire transcriptome. For example, Kelley et al. (2016) compared genome-wide gene expression patterns of gills from closely related pairs of *Poecilia* populations, some of which were adapted to H₂S-rich environments and some were not. Although the large-

scale gene expression pattern was only weakly parallel across independent H₂S-adapted *Poecilia* species/populations, a small number of genes were consistently differentially expressed in the same direction in all H₂S-adapted population pairs. Notably, these up-regulated genes were associated with enzymatic H₂S detoxification and transport of oxidized sulfur species, oxidative phosphorylation, energy metabolism, and pathways involved in responses to oxidative stress. Similarly, transcriptomic analysis confirmed that the AHR pathway is repeatedly desensitized in multiple pollution-tolerant populations of killifish, as evidenced by the up-regulation of AHR-pathway genes in sensitive—but not tolerant—populations exposed to a pollution challenge (Reid et al. 2016). Comparative transcriptomics have also been used to investigate the degree of interspecific parallelism underlying convergent eye loss in cavefishes (*Sinocyclocheilus* and *Astyanax*). With the exception of few genes such as rhodopsin, which is downregulated in both species (Yang et al. 2016), the loss of eyes in each species appears to result from the expression of different sets of genes, or in the case of crystallin genes, expression in opposite directions (Meng et al. 2013).

The role of demographic processes in shaping adaptive responses

The probability of convergent phenotypes having a shared molecular basis can be influenced by four primary determinants: natural selection, historical phylogenetic history, population demography (and the extent of contemporary gene flow between ancestral (reference) and derived (adapted) populations/species), and genetic constraints (Rosenblum et al. 2014). Among these, all but phylogenetic history can have direct effects on the degree of parallelism, whereas phylogenetic history has an indirect influence through shaping other factors. As such, the amount and direction of gene flow has been studied at both inter- and intraspecific levels. For example, mitochondrial analysis confirmed the independent colonization and adaptation to H₂S-rich environments among Poeciliidae (Tobler et al. 2018), a pattern that was also revealed at the species-level within the *Poecilia mexicana* species complex (Pfenninger et al. 2014). Independent colonization of caves was found in the Mexican tetra; Bradic et al. (2012) found evidence for at least five separate evolutionary origins of the cave

and surface *Astyanax* populations that were distributed across three geographically distinct regions. Similarly, species of another iconic cavefish *Sinocyclocheilus* have also been shown to colonize caves independently and repeatedly (Li et al. 2008; Xiao et al. 2005; Zhao and Zhang 2009). Phylogenetic analyses suggest that the *Sinocyclocheilus* genus originated ~ 10 million years ago, and diversified into six major clades—five of which contain cave species (Li et al. 2008). Interestingly, some studies that have explored contemporary gene flow have found low overall divergence between populations inhabiting extreme environments and those in “reference” habitats. For example, Williams and Oleksiak (2011) reported high gene flow between killifish populations inhabiting polluted and unpolluted rivers, as did Lind and Grahn (2011) in a study of stickleback from polluted and unpolluted sites in the Baltic Sea. Similarly, Ford et al. (2015) and Kavembe et al. (2016b) found evidence for ongoing gene flow and hybridization between cichlid species in African alkaline lakes. In spite of the low genome-wide levels of differentiation in these contrasts, high levels of divergence were found at specific loci/genomic regions, suggesting that selection in these extreme aquatic conditions is strong and populations can adapt to local environments. On the other hand, high levels of genome-wide population divergence have been detected—even over small spatial scales—such as among *Poecilia* populations from various caves (Tobler et al. 2008), and tomcod populations from the polluted Hudson River and nearby estuaries (Wirgin et al. 2011). Hence, selection appears to shape adaptive responses to extreme environments regardless of the level of neutral population structuring. Moreover, as advised by Rosenblum et al. (2014), the best practice is to link phenotypes with genotypes while accounting for phylogenetic interference in inferences of selection, such that all systems and hierarchical levels are integrated in studies aimed at exploring the genetic basis underlying repeated adaptation at different molecular levels.

Challenges and future directions

Great progress has been made towards understanding the genomic basis of adaptation in fishes inhabiting extreme aquatic environments, and as more teleost

genomes continue to become available (e.g. Earth BioGenome Project; Lewin et al. 2018), insights into these important and complex molecular mechanisms should deepen. Nevertheless, increased resources and sample sizes do not come without limitations. For example, while sequencing to greater coverage and depth can increase the amount and reliability of polymorphic loci identified, this of course comes with increased financial expenses. Additionally, more data can generate more background noise, hence refinement of analytical approaches would also be necessary. Greater statistical strength can be gained by increasing sample size, for example when screening population pairs for the degree of parallelism; as well, including more populations can provide additional support for candidate loci. However, all of these improvements increase computational time, which is another limiting factor to be considered when applying NGS approaches. QTL mapping remains a robust approach for identifying the genetic basis of particular traits, but this requires the use of artificial crosses, which may be impractical (or impossible) to generate in some species (e.g. *Sinocyclocheilus*). Similarly, controlled laboratory experiments offer the possibility to address questions related to heritability, trans-generational, and epigenetic effects. In addition, single environmental stressors can be isolated and manipulated, or several can be combined to explore their interactive effects. However, the associated costs—in terms of finances, space, time, etc.—pose extreme challenges for studies requiring laboratory experiments. While transcriptional studies have greatly advanced our understanding of the regulatory changes that underlie adaptation, this approach provides information that is relevant only to a specific tissue at a specific point in time. Hence, important changes in expression can easily be overlooked due to sampling strategy. Overall, while genomic approaches have offered unprecedented access to information about adaptation to extreme environments, they are not sufficient to fully understand the complexity of the molecular mechanisms involved and hence need to be complimented with experiments that explore adaptation at the organismal level.

Interestingly, of the ~ 210 published ray-finned fish genomes, only few have been studied extensively enough to fit the criteria of this review. However, the genomes of several deep-sea fishes are available (e.g. *Acanthochaenus luetkenii*, *Bathygadus*

melanobranchus, *Melanonus zugmayeri*, *Mora moro*, *Pseudoliparis swirei*, *Rondeletia loricata*, *Stylephorus chordates*, *Trachyrincus scabrous*), which could be used to explore the genomic basis of adaptation to the various stressors of deep-sea life (Wang et al. 2019), such as high pressure, low/no oxygen, and darkness. Not only could these deep-sea fish genomes be compared among each other, but they could also be compared with those from other extreme environments that pose similar challenges—for example, cavefishes that are also adapted to darkness, or the *Nile tilapia* adapted to hypoxia. In addition, the available genomes of air-breathing fishes (e.g. *Arapaima gigas*, *Boleophthalmus pectinirostris*, *Channa argus*, *Clarias batrachus*, *Monopterus albus*, *Periophthalmus magnuspinnatus*) could be used to further our understanding of the genomics of acid-base balance, ionoregulation, and nitrogenous waste excretion. Similarly, comparative genomics of polar fishes adapted to nearly freezing temperatures (e.g. *Lota lota*, *Notothenia coriiceps*, *Arctogadus glacialis*, *Boreogadus saida*, *Chaenocephalus aceratus*) could offer insights into the adaptive evolution of antifreeze proteins and hemoglobin genes. Although there are other species of cavefish—including *Typhlichthys subterraneus*, whose genome has been sequenced—most of the in-depth population genomics studies thus far have only focused on *Poecilia*, *Sinocyclocheilus*, and *Astyanax*. Hence, at the moment there seems to be a publication bias, but hopefully this will soon be overcome with the increased availability of various genomic and bioinformatic resources.

Thus far, both intra-specific comparisons of derived vs. ancestral populations and inter-specific comparisons of species with similar adaptations have facilitated the identification of genomic regions under selection. Further analytical approaches can be applied to explore, for example, the rate of evolution in adaptive genes, and how this compares to other species tolerant to (and found in) the same extreme environments, in order to assess the potential for a particular species to evolve more rapidly and hence out-compete other species. In addition, more robust models could be developed to test for different types of selection (e.g. polygenic adaptation, adaptation with admixture), as well as estimate the effect size of divergent loci. Despite the fact that the number of sequenced genomes continues to increase, most of these resources have been generated using short-read

sequencing technology (e.g. Illumina platforms). However, new technologies that provide longer reads and single-molecule sequencing (e.g. PacBio SMRT, Nanopore, 10× Genomics) offer a powerful option to refine genome assembly and better identify novel DNA modifications and their associations with adaptive traits, which are overlooked by short-read techniques. This can also be applied to the transcriptome, which can then be further investigated more thoroughly with genome editing to explore the link between gene variants and expression, and their consequence on protein structure. Similarly, although other omics approaches have not been applied to extremophile fishes yet, integrating studies of the proteome and metabolome can provide a multi-dimensional, integrative way of pinpointing the mechanisms underlying adaptation. Of course, generation of such complex data requires the generation of complex computing techniques. Perhaps machine learning applications could become more commonly used in genomics in order to more rapidly and robustly identify the drivers of adaptation.

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