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## Invited Review

# Future directions in breeding for disease resistance in aquaculture species

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**ABSTRACT** - Infectious disease is a major constraint for all species produced via aquaculture. The majority of farmed fish and shellfish production is based on stocks with limited or no selective breeding. Since disease resistance is almost universally heritable, there is huge potential to select for improved resistance to key diseases. This short review discusses the current methods of breeding more resistant aquaculture stocks, with success stories and current bottlenecks highlighted. The current implementation of genomic selection in breeding for disease resistance and routes to wider-scale implementation and improvement in aquaculture are discussed. Future directions are highlighted, including the potential of genome editing tools for mapping causative variation underlying disease resistance traits and for breeding aquaculture animals with enhanced resistance to disease.

Key Words: genome editing, genomic selection, selective breeding

## Introduction

Fish and shellfish production through aquaculture is a major source of high-quality protein for human diets, with a worldwide production of 73.8 million tonnes in 2014 (FAO, 2016). Improvements in the scale and efficiency of aquaculture are essential to meet the nutritional requirements of a rapidly growing global population, particularly in developing countries. Selective breeding programmes have great potential to help address this challenge via cumulative improvements in key production traits, such as resistance to disease. Currently, less than 10% of aquaculture production derives from selectively bred stocks (Gjedrem et al., 2012), lagging significantly behind the terrestrial animal and plant farming industries (Gjedrem et al., 2012; Yáñez et al., 2015; Robledo et al., 2017). Encouragingly, genetic gains for aquatic species are generally higher than that of terrestrial farm animals (Gjedrem et al., 2012; Nguyen, 2016; Gjedrem and Rye, 2016). However, the status of breeding programmes and the level of technology used for aquatic species production are wide-ranging, from use of wild seed stocks through to family-based selection incorporating genomic tools (Yáñez et al., 2015).

Infectious diseases present a major constraint on aquaculture production, causing high mortality levels and impaired growth due to infection. Particularly in marine aquaculture species that are exposed to the open-ocean environment, disease prevention through management and biosecurity is challenging (Lafferty et al., 2015). Indeed, many diseases in farmed hosts are transmitted from wild hosts in the surrounding waters and vice versa (Lafferty et al., 2015). For several farmed aquatic species, particularly finfish, there are vaccines and medicines which aid in the prevention and control of disease. However, these are often expensive and only partially effective and obtaining regulatory approval is often challenging (Lafferty et al., 2015). Further, blanket treatments are often used (e.g. in feed), which can lead to evolution of resistance in the pathogen. An example of this is the emergence of drug-resistant strains of ectoparasitic copepod sea lice, due to extensive use of medicines (Aaen et al., 2015). Therefore, a major and increasingly important component of disease control is selective breeding to produce stock with improved resistance to key pathogens, exploiting naturally-occurring genetic variation (heritability) for resistance in farmed aquaculture populations. Virtually all well-powered studies examining the genetic basis of disease resistance in aquaculture species have detected significant heritability for these traits (e.g. Yáñez et al., 2014; Gjedrem, 2015) Therefore, in conjunction with other prevention and control

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strategies, effective selective breeding programmes can offer cumulative and permanent improvements in host resistance (Bishop and Woolliams, 2010; Yáñez et al., 2014). This short review will highlight methods currently applied to tackle disease resistance by selective breeding and discuss future possibilities enabled by technological developments in genomics and genome-editing technologies.

## What is disease resistance?

Disease resistance is often used as a generic term to describe the ability of the host to limit infection, or the consequences of infection, by reducing pathogen replication (Råberg et al., 2007; Doeschl-Wilson et al., 2012; Bishop and Woolliams, 2014), and the opposite can be considered as susceptibility. However, several terms related to traits connected to broad-sense disease resistance have been defined and are typically context-dependent. For example, "tolerance" can refer to the ability of the host to reduce the impact of pathogens on performance (without necessarily affecting pathogen load) (Doeschl-Wilson et al., 2012) and "infectivity" is the propensity of transmitting infection upon contact with a susceptible individual (Lipschutz-Powell et al., 2012). For the purposes of this review, disease resistance will be used in the broadest sense, referring to all disease traits in which genetic improvement will lead to a reduction in disease incidence or severity. Disease resistance has been a target trait for aquaculture breeders for over 20 years and the first salmon breeding programmes have focused on disease resistance since 1993 (Gjoen and Bentsen, 1997). However, selective breeding for resistance to certain diseases is challenging; in part, due to the need for capturing accurate and informative disease resistance measures or correlates (Bishop and Woolliams, 2010; see below). To avoid compromising biosecurity within the breeding nucleus, advanced breeding schemes rely on disease data collected from relatives of the selection candidates (as opposed to the candidates themselves) as measured by experimental challenge or "field" data (Bishop and Woolliams, 2014).

Highly pathogenic viral and bacterial diseases impacting on aquaculture species are often the easiest to tackle from a practical breeding perspective by defining resistance as survival (and/or mortality) of individuals during an outbreak or a deliberate challenge (Ødegård et al. 2011). This binary trait has been shown to have a moderate to high heritability for a number of important infectious diseases (Ødegård et al. 2011, Yáñez et al. 2014; Gjedrem 2015). Therefore, disease-challenge testing can be applied to test relatives of the selection candidates in a breeding scheme, particularly for advanced finfish breeding programmes such as salmonids and tilapia (Ødegård et al., 2011; Yáñez et al., 2014; LaFrentz et al., 2016). These typically involve infecting tagged individual juvenile fish in a standardized tank environment with a pathogen strain that is similar to those causing disease outbreaks in the field. Mortality or survival until the end of the test (when mortality returns to baseline level) is recorded and this trait can be an excellent indicator of disease resistance in the field setting, as shown by high genetic correlations between trait measures in both environments (e.g. Ødegård et al., 2007). Alternative measures of disease resistance include pathogen or parasite load measured by cell culture or qPCR (e.g. for viral disease in shrimp; Phuthaworn et al., 2016) or biomarkers of the host immune response (Yáñez et al., 2014). For certain ectoparasites (e.g. salmon lice), simply counting the number of parasites attached to the fish represents the primary disease-resistance phenotype used for selection (e.g. Tsai et al., 2016).

An alternative to artificial challenge testing is collection of disease data and samples from field outbreaks, which can be used opportunistically to quantify genetic resistance to infectious diseases and calculate breeding values. A pre-requisite for this is the establishment of pedigree and family assignment in this scenario typically uses genetic markers. However, it is often difficult to discern the cause of mortality in natural outbreaks and obtaining high-quality samples from mortalities can be challenging. Furthermore, certain diseases (such as sea lice in salmon) are required to be controlled by other means (e.g. culling of stock for notifiable viral diseases or chemotherapeutants for parasites) before the fish become sufficiently infected to obtain meaningful resistance phenotypes.

## Current methods of breeding for disease resistance

The selective breeding techniques applied to improve resistance of aquaculture species to infectious diseases depend on the structure and technology used in the breeding programme. Due to the highly fecund nature of most aquaculture species, and the typically low economic value of juveniles, simple approaches such as mass selection can be applied. The resulting high selection intensity could enable rapid genetic progress for resistance traits (Gjedrem and Baranski, 2009). Mass selection produced greater than 60% increase in Oyster Herpes Virus survival compared with controls after four generations of selection (Dégremont, et al. 2015b) and has also been successfully applied to Taura Syndrome Virus in Panaeid shrimps (Cock et al., 2009). However, mass selection in advanced commercial breeding

schemes is not practical, because the risk of inbreeding depression (albeit this has not been widely observed in bivalve mass selection experiments; Dégremont et al. 2015b) and breeding from broodstock, which have previously been exposed to a disease outbreak, can present a biosecurity risk to hatcheries, particularly if the pathogen can be vertically transmitted.

The state of the art for the majority of advanced selective breeding schemes for aquaculture species is the use of family selection. Aquaculture species are particularly amenable to this structure due to the possibility of obtaining high numbers of full siblings and other close relatives of the selection candidates for testing (Gjedrem and Baranski, 2009). Family selection involves the maintenance of a breeding nucleus with candidate parental broodstock from a high number of genetically diverse families. Full siblings of these animals can be placed into field conditions or sent for experimental disease challenge testing to obtain family-level data on disease resistance. Accurate tracking of families and pedigree is achieved by tagging or genetic markers. Advances in genotyping technology, such as development of high-throughput genotyping for single-nucleotide polymorphism (SNP) multiplexes, have enabled rapid and accurate family assignment (Vandeputte and Haffray, 2014). Family selection for disease resistance has been highly successful for several species and diseases (Yáñez et al., 2014; Bishop and Woolliams, 2014). However, it does suffer some drawbacks, such as the cost of routine disease challenge data collection and the lack of opportunity to capitalise on half of the genetic variation (the within-family component). An additional challenge for breeding programmes of many aquaculture species is genotype by environment interaction, in which the performance of the selected animals can vary markedly across diverse production environments (e.g. in tilapia breeding; Sae-Lim et al., 2016). This results in re-ranking of genotypes across environments and effectively reduces the overall response to selection within a breeding programme (Sae-Lim et al., 2016).

Marker-assisted selection is one route to building on family selection and gaining information on the comparative disease resistance of selection candidates from within a full sibling family (i.e. the within-family genetic variation; Sonesson, 2007). Marker-assisted selection is based on the principle of detecting quantitative trait loci (QTL) affecting the trait of interest and selecting animals based on whether they carry favourable alleles at the QTL. Mapping of QTL has been a major goal for aquaculture genetics and breeding research and has yielded some successful practical results. Aquaculture species are typically close to their wild ancestors and the relatively new selection and disease pressures in the farm environment raise the possibility that major-effect loci segregate within the populations. A successful example of QTL analyses applied to selective breeding is the case of infectious pancreatic necrosis resistance in Atlantic salmon, in which a major QTL explains the majority of the genetic variance for resistance (Houston et al., 2008; Houston et al., 2010; Moen et al., 2009) and has been demonstrated as a successful means of controlling the disease (Moen et al., 2015). Selected other examples of QTL-affecting resistance to disease include the cases of salmonid alphavirus (Gonen et al., 2015), ISAV (Moen et al., 2007), and *Gyrodactylus salaris* (Gilbey et al., 2006) in salmon, lymphocystis disease in Japanese flounder (Fuji et al., 2006), Bonamiosis in the European Flat Oyster (Lallias et al., 2009), and *Flavobacterium psychrophilum* in rainbow trout (Vallejo et al., 2014). However, marker-assisted selection based on single QTL has not been routinely successful in animal breeding, partly because most economically important traits have a polygenic genetic architecture (Meuwissen et al., 2013). While recent domestication of aquaculture species may result in an oligogenic architecture for disease resistance traits, it is also important to consider that the effect of any given QTL may differ according to the environment and the genetic background of the population.

Genomic selection (GS) is the state-of-the-art for modern selective breeding schemes in aquaculture. In GS, genome-wide markers are used to calculated genomic breeding values without prior knowledge of the underlying QTL affecting the trait of interest (Meuwissen et al., 2001). The premise of GS is that marker effects are estimated in a "training" population, which has been measured for both phenotypes (e.g. disease resistance) and genotypes, and the developed model is then used to generate genomic breeding values on selection candidates with genotypes only. While the initial concept of GS was to detect and utilise population-wide linkage disequilibrium between genome-wide markers and QTL (Meuwissen et al., 2001), the benefits of genomic selection also include a more accurate estimate of the genetic relationship between any two individuals than could be given by pedigree records alone, particularly within families (Meuwissen et al., 2013). In all studies of aquaculture species to date, the use of GS has resulted in higher prediction accuracy of breeding values than the use of pedigree information alone (Odegård et al., 2014; Tsai et al., 2015; Dou et al., 2016). A prerequisite for genomic selection is a platform to generate high-density SNP marker genotypes across populations of animals and SNP arrays have been developed for several

aquaculture species, including Atlantic salmon (Houston et al., 2014; Yáñez et al., 2016), rainbow trout (Palti et al., 2015), common carp (Xu et al., 2014), and catfish (Liu et al., 2014). A major downside to GS is the cost, due to the expense of high-density genotyping in large numbers of individuals. In addition, while GS is effective wherein the training and test populations are closely related (e.g. within a year group of a breeding programme), the ability to predict breeding values in animals more distantly related to the training population is rather limited (Meuwissen et al., 2014; Tsai et al., 2016).

## Future directions

Due to the diversity of species that are grouped together as "aquaculture", both in terms of biology and production technology, it is challenging to make generalized predictions about the future of breeding for disease resistance. For example, the route to improved disease resistance in the vast majority of the farmed fish in the world is to work towards implementation of selective breeding (with ~90% of world aquaculture relying on unimproved stock). However, often the catalyst for driving the implementation or improvement of organised breeding schemes can be a major production issue, such as mortality due to disease. For example, previously uncontrollable outbreaks of viral disease have been an important driver for the establishment of selective breeding schemes for oyster species (Dégremont, et al. 2015a). For new and emerging aquaculture species, the steps taken to enable selective breeding for disease resistance may change with technological advances. For example, reference genome sequences, SNP genotyping platforms, and other genomic tools can now be generated rapidly from the beginning. This can inform the composition of the base population from which to begin a breeding scheme (Fernández et al., 2014) and can enable rapid progression to family or even marker-based selection techniques to ensure rapid gain and minimal inbreeding, once suitable selection goals have been established.

For certain aquaculture species with more advanced breeding schemes (e.g. based on family selection with sib-testing), improving response to selection in multiple environments will be a major goal. This will be particularly relevant for species such as tilapia (especially Nile Tilapia, *Oreochromis niloticus*), in which major breeding programmes are underway, and stock is typically disseminated to several countries and diverse farming systems (Sae-Lim et al., 2016; Omasaki et al., 2016). Therefore, it is important to quantify and incorporate G × E interaction when optimising a breeding programme for these species and the high fecundity may facilitate trait recording in multiple environments (Sae-Lim et al., 2016).

Genomic selection is routinely applied to target improvement of the most economically important traits in several aquaculture species. An obvious target trait in Atlantic salmon production is resistance to sea lice (*L. salmonis* in Europe and *Caligus spp.* in Chile). Progress in the next few years will be to tackle the aforementioned limitations of GS, namely cost and prediction accuracy in distant relatives. In aquaculture species with high fecundity and large full-sibling families, the marker density required for step changes in improvement in breeding value prediction over pedigree methods are relatively low (e.g. ~5 K genome-wide SNP in a typical salmon breeding programme) and even lower using within-family selection (Sonesson and Meuwissen, 2009; Lillehammer et al., 2013; Odegård et al., 2014; Tsai et al., 2015). The cost of generating SNP datasets of this magnitude will be driven lower by advances in genotyping by sequencing, which has great potential for genomic selection in farmed animals (Gorjanc et al., 2015; Robledo et al., 2017). Driven by the continuous reduction in cost per unit of next-generation sequencing data, allowing an increase in the number of animals that can be genotyped in a single lane of an Illumina sequencer, genotyping by sequencing is likely to overtake SNP arrays as the primary means of routine generation of population-level genotypes. While bioinformatics and data management challenges may hamper its routine implementation, technologies that combine targeted SNP probes with next-generation sequencing across many samples (e.g. Affymetrix's Eureka platform) can overcome this obstacle. Imputation techniques are also likely to play a key role in improving the cost-effectiveness of genomic selection for disease resistance and other key traits. With ever-improving reference genome sequences and genetic maps (e.g. Lien et al., 2016), the opportunity now exists to genotype selected animals (e.g. parents) at high density and the others (e.g. the offspring) at very-low density, but impute to high density – a technique that is relatively commonplace in terrestrial livestock breeding (e.g. Wellmann et al., 2013) and has shown promise in Atlantic salmon breeding (Tsai et al., 2017).

While there are clear routes to improve the cost-effectiveness of genomic prediction of disease resistance breeding values, improving the ability to predict across distantly related populations is likely to be more challenging. This is important for breeding for disease resistance in aquaculture, because it reduces the requirement for regular disease challenge and field testing. The current implementation of GS relies on a combination

of linkage disequilibrium between markers and causative variants and estimation of realised relationships between relatives (Daetwyler et al., 2012). As such, accuracy of genomic prediction is highly dependent on the degree of relationship between the training population and the validation population and this accuracy is not persistent across generations (Daetwyler et al., 2012). To improve genomic prediction in distantly related populations (such as separate year groups of a salmon breeding programme), identification and utilisation of causative variants and/or markers in linkage disequilibrium with causative variants is essential. For a typically polygenic trait, this is likely to require very large reference population sizes, genotyped at high density or fully sequenced (Hickey, 2013). Investment in gathering large-scale genetics datasets also leads to candidate genes and mutations for functional testing to inform the underlying biology of disease resistance. Further, functional annotation of the reference genomes will be key to prioritising putative causative variants and the recent Functional Annotation of All Salmonid Genomics initiative (MacQueen et al. 2017) will facilitate this.

Genome editing technology is likely to be a key tool in the identification of causative variation underlying resistance to disease in farmed animals. In simple terms, genome editing enables the deletion, change, or addition of base pairs at highly specific and targeted locations. The major techniques include zinc-finger nucleases, transcription activator-like effector nucleases, and clustered regularly interspaced short palindromic repeats and all involve the induction of double-strand breaks in the genome followed by repair (Sander and Joung, 2014). Genome editing can be applied to test hypotheses of putative causative variation from genetics studies or can be used to exploit knowledge of the biology underlying the trait to induce new mutations into selected target loci, i.e., the case of the CD163 locus conferring resistance to PRRS in pigs (Whitworth et al., 2015). The most obvious initial applications of GE in breeding for disease resistance are to increase the frequency of, and potentially fix, known resistance alleles at major effect loci. However, the advances in large-scale genetics studies may allow this to be extended to facilitate modulation of multiple loci with a more moderate effect size (Jenko et al., 2015). Published studies of genome editing in aquaculture species remain sparse, although the successful CRISPR-Cas9-mediated knockout of the *dnd* locus to induce sterility in the F0 generation of Atlantic salmon highlights its feasibility (Wargelius et al., 2016). For viral and bacterial disease resistance traits, genome editing in cell line models (e.g. Zhou et al., 2014) may be an important intermediate step to target and validate putative causative genes. While the practical application of genome editing technology in breeding is also subject to societal and regulatory approval, it has huge potential to tackle problematic aquaculture diseases and inform the biology underlying disease resistance.

## Conclusions

Aquaculture species are a diverse grouping and the majority of farmed fish and shellfish production is based on unimproved stocks. Disease resistance is almost universally heritable and is a key goal of existing selective breeding schemes. Several success stories of mass selection, family selection, and marker-assisted selection are evident. Gathering appropriate phenotypes from disease challenge or field experiments is pertinent for making genetic progress. Genomic selection is the state-of-the-art for modern aquaculture breeding schemes and offers substantial improvements in selection accuracy over pedigree-based methods. Driving down the cost of genomic selection, and specifically generation of genome-wide genetic marker datasets, is a major current goal. Genotype imputation and low-cost genotyping by sequencing are likely to contribute. Predicting disease resistance of distantly related animals to those with trait records is a major future challenge, which is directly related to the identification of causative variants. Genome editing technology is likely to play a key role in identifying causative variation and has potential for breeding disease-resistant animals in aquaculture.

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