Positive Genetic Correlation between Resistance to Aeromonasis and Streptococcosis in Nile Tilapia *Oreochromis niloticus* (Linnaeus, 1758)

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ABSTRACT

We estimated genetic parameters for resistance to two bacterial diseases, aeromonasis and streptococcosis, in Nile tilapia, evaluating whether genetic correlation exists between these traits. A total of 43 families were produced using a partial factorial design. At 30 days post-hatch, 120 fish from each family were divided into two groups and were subjected to bath challenge in *Aeromonas hydrophila* (AH) or *Streptoccoccus agalactiae* (SA) solutions at median lethal concentration (96 h LC_{50}). Survival was measured as a binary trait (dead/alive) at day 14 post-challenge. Variance components were estimated using two statistical models. Heritability estimates were low and comparable between the threshold and the linear animal models for both traits, being 0.17±0.04 and 0.18±0.05 for AH; and 0.15±0.03 and 0.15±0.04 for SA. For each trait, the accuracy of the linear model in predicting estimated breeding values (EBVs) was slightly higher than that for the threshold model. Spearman rank correlation between models was almost unity (r~1), indicating similar rankings of families by these models. Genetic correlations between resistance to AH and SA were moderately positive (r_{EBVs} = 0.41) for both threshold and linear models. This positive correlation is favorable for the genetic improvement of tilapia fry, as selection for increased resistance in one of the traits would result in a correlated response for the other.

Keywords: *Aeromonas hydrophila*, Genetic correlation, Heritability, Model accuracy, *Streptococcus agalactiae*

INTRODUCTION

Aeromonasis and streptococcosis are among the bacterial diseases that affect the production of tilapia fry and fingerlings in Thailand. *Aeromonas hydrophila* (AH), a causative agent of aeromonasis, is well known as an opportunistic but important pathogen in freshwater environments (Camus *et al*., 1998; Cipriano, 2001). Streptococcosis, a disease caused by a Gram-positive bacterium, *Streptococcus agalactiae* (SA), is highly devastating and responsible for economic losses in tilapia culture worldwide (Suanyuk *et al*., 2008; Ye *et al*., 2011; Anshary *et al*., 2014; Zamri-Saad *et al*., 2014; Asencios *et al*., 2016; Leal *et al*., 2019). Although *A. hydrophila* is not considered a serious threat to tilapia farming, infection of *A. hydrophila* can cause mass mortality in early life stages (Camus *et al*., 1998). These diseases are often associated with high temperatures during summer months from April to July when water temperature increases to 30 ºC (Rodkhum *et al*., 2011; Kayansamruaj *et al*., 2014). Prevention and control of infectious diseases have relied mostly on the applications of antibiotics and vaccines. However, the use of antibiotics is increasingly becoming limited due to the impacts on fish performance and welfare, as well as on the environment.

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Selective breeding provides an effective way to control infectious diseases, limiting the use of antibiotics and reducing production costs. The economic benefit of selection is that genetic gain is cumulative and permanent (Gjedrem, 2015). Breeding for disease resistance has been successful in key species, including salmonids (reviewed by Yáñez *et al*., 2014), shrimps (Argue *et al*., 2002; Huang *et al*., 2012) and tilapias (Shoemaker *et al*., 2017; Sukhavachana *et al*., 2019; Suebsong *et al*., 2019). Resistance to different pathogens has been reported to be genetically correlated, which can be either favorable or unfavorable, depending upon the breeding goal. The objective of this study was to determine whether genetic correlation exists between resistance to AH and SA in Nile tilapia at the fry stage. Two statistical models, threshold and linear animal models, were used to estimate variance components. In addition, models were compared in terms of the accuracy of breeding value prediction.

MATERIALS AND METHODS

Mating design and production of families

Nile tilapia used in this study were derived from the 9th generation of the GIFT (Genetically Improved Farmed Tilapia) strain and had undergone two generations of selection to improve growth by the Thai Department of Fisheries (DOF). Broodstock were kept at the tilapia breeding center located in Pathum Thani Province, Thailand. Sixty males and 60 females were selected and tagged using passive integrated transponders (PIT). A single-pair mating scheme based on the partial factorial design (Berg and Henryon, 1998) was used to produce families. Each pair was stocked in a 3 m×2 m×1 m concrete tank and was allowed to spawn naturally. Eggs were collected from the mouths of females after seven to ten days and transferred to 2-L incubating trays with flow-through water and continuous aeration. Fry were obtained after approximately 10 days of incubation. Fry from 43 families were transferred to 2 m×1 m×1 m hapas and reared separately for 20 days. At approximately 30 days post-hatch, they were transferred to the Department of Aquaculture, Kasetsart University, Bangkok, for a challenge test.

Bacterial challenges

Bacterial strains, including *Aeromonas hydrophila* (AH: AQAH01) and *Streptococcus agalactiae* (SA: AQSA01), were isolated from infected tilapia fry at a private hatchery during an outbreak of the disease in Thailand in 2013, and were provided for this study by Dr. Prapansak Srisapoome at the Department of Aquaculture, Kasetsart University. Fry (28±7 days post-hatch) from each family were stocked separately in 1,000-L fiberglass tanks and acclimated for seven days. The median lethal concentration of the pathogen (LC_{50}) at 96 h for bath challenge was determined as follows. Fish were divided into five groups of 10 individuals, each group with three replicates, and were placed in 10-L glass aquaria. Five concentrations of pathogenic bacteria ranging from 1×10^{10} to 1×10^{14} CFU·mL^{-1} were prepared from an initial concentration of 1×10^{8} CFU·mL^{-1} for AH and SA. Mortality was observed at 24, 48, 72 and 96 h.

Two days before the challenge trials, 20 fish were sampled from each family to diagnose any external parasite or bacterial infections. One-hundred-twenty fish from each family were divided into two batches of 60 fish each for AH and SA challenges. The sixty fish from each batch were distributed equally among three replicate glass aquaria (10 L) with aeration and acclimated for two days. Fish from each batch were subjected to bath challenge with either AH or SA solution at the LC_{50} of 4.5×10^{13} or 1.0×10^{13} CFU·mL^{-1}, respectively. A control group comprising 60 fish sampled from all families was treated with sterile phosphate buffered saline (PBS). Mortality was recorded every three hours until 20 days post-challenge. Dead fish were examined for clinical signs of disease. Bacteria were re-isolated from the liver to verify the cause of infection.

Data analyses

Kaplan-Meier survival

Resistance to AH and SA was measured as a binary trait (0/1 for dead/surviving fish). Also, the number of days from challenge to death for individuals (i.e., survival time) was used to calculate

the Kaplan-Meier survival estimator for families (Kaplan and Meier, 1958), using the survival package in R (Therneau and Grambsch, 2000). The estimated Kaplan-Meier survival function is

$$\hat{S}(t) = \Pi t_i < t \left(1 - \frac{d_i}{n_i}\right)$$

where t_i is the time of death at day i; d_i is the number of dead fish at t_i, and n_i is the number of fish that survive before t_i. Fish that survived at each time interval and at the end of the challenge period were recorded as censored. The log-rank test was used to test the equality of survival functions among families.

Statistical models

A generalized linear model was used to analyze the binary survival traits after the disease challenge. Wald's F test, which is similar to an ANOVA, was used to evaluate the fixed effects of days post-hatch (age), batch (challenge date) and aquarium, using ASReml version 4.1 (Gilmour *et al*., 2015). Only batch was significant, and age was included as a covariate in the models. A log-likelihood ratio test (Lynch and Walsh, 1998) was used to determine the significance of the additive effects for the animal and the confounding effects of shared environment within full-sib families. Only the additive effects of the animals were significant. Two models were applied as follows:

The threshold model (THR): a probit link function was used for estimation of variance components as $Pr(y_{ij}) = \phi\,(\mu + \beta g_j + b_i + a_j)$, where y_{ij} is the phenotype (0=dead; 1=surviving) of fish j; $\phi(\cdot)$ is the standard normal cumulative distribution function, μ is the constant; β is the regression coefficient for days post-hatch; g_j is the covariate effect of days post-hatch; b_i is the fixed effect of challenge date; and a_j is the additive effect of fish j.

Binary data also were analyzed using a linear animal model (LIN) as $y_{ij} = \mu + \beta g_j + b_i + a_j + e_{ij}$, where y_{ij} is the phenotype (0=dead; 1= surviving) of fish j; e_{ij} is the random error of fish j and the other parameters are as described for the THR model.

Models were fitted using ASReML version 4.1 (Gilmour *et al*., 2015) to obtain variance and covariance components by a restricted maximum likelihood (REML) procedure. Heritability was estimated as:

$$h^2 = \sigma_a^2 / \left(\sigma_a^2 + \sigma_e^2\right)$$

where σ_a^2 is the additive genetic variance and σ_e^2 is the residual variance. For the THR model, $\sigma_e^2 = 1$.

Models were compared based on their accuracies (r_{EBV}) in predicting the breeding value of individuals as:

$$r_{EBV} = \sqrt{1 - \frac{SE_i^2}{(1+f_i)\sigma_a^2}}$$

where SE_i is the standard error of the predicted breeding value of fish i; f_i is the inbreeding coefficient of fish i; $1 + f_i$ is derived from the diagonal of the numerator relationship matrix, and σ_a^2 is the estimated additive genetic variance (Gilmour *et al*., 2015). The agreement of genetic predictions between models was assessed using the Spearman's rank correlation coefficients between the full-sib family estimated breeding values (EBVs).

Because disease resistance traits for AH and SA were measured on different sibs within families, the cross-environment genetic correlation was used as an approximation for the genetic correlation between traits (Falconer and Mackay, 1997; Astles *et al*., 2006). In this case, pathogen infections by AH and SA were treated as two different environments (Sae-Lim *et al*., 2015). The genetic correlation (r_g) was calculated as the Pearson correlation between mid-parent breeding values for resistance to AH and SA in the same model as

$$r_g = \frac{Cov_{x,y}}{\sqrt{V_x V_y}}$$

where $Cov_{x,y}$ is the covariance between family EBVs for resistance to AH and SA; V_x is the variance of EBVs for resistance to AH and V_y is the variance of EBVs for resistance to SA.

RESULTS

The AH-challenged fish showed clinical signs of septicemic infection, including bilateral exophthalmia, ulcerations, and reddening of the skin. The SA-infected fish exhibited skin hemorrhaging, unilateral or bilateral exophthalmia, as well as whirling behavior. Re-isolation of bacteria from the livers of moribund fish confirmed either AH or SA infection as a cause of death. After 20 days of bath challenge, survival of 43 families (5,160 fish) comprising 19 paternal and 11 maternal half-sib families ranged from 5 to 75 % (mean survival= 33 %) and 0 to 80 % (mean survival = 34 %) for AH and SA, respectively (Figure 1). In the challenge groups, no mortalities were observed after day 14. No mortality occurred in the control groups during the challenge test period.

The estimates of Kaplan-Meier survival functions across families were nearly identical for both resistance traits (Figure 2).

Variance components, estimates of heritability (h^2) and model accuracy for resistance to these two diseases are presented in Table 1.

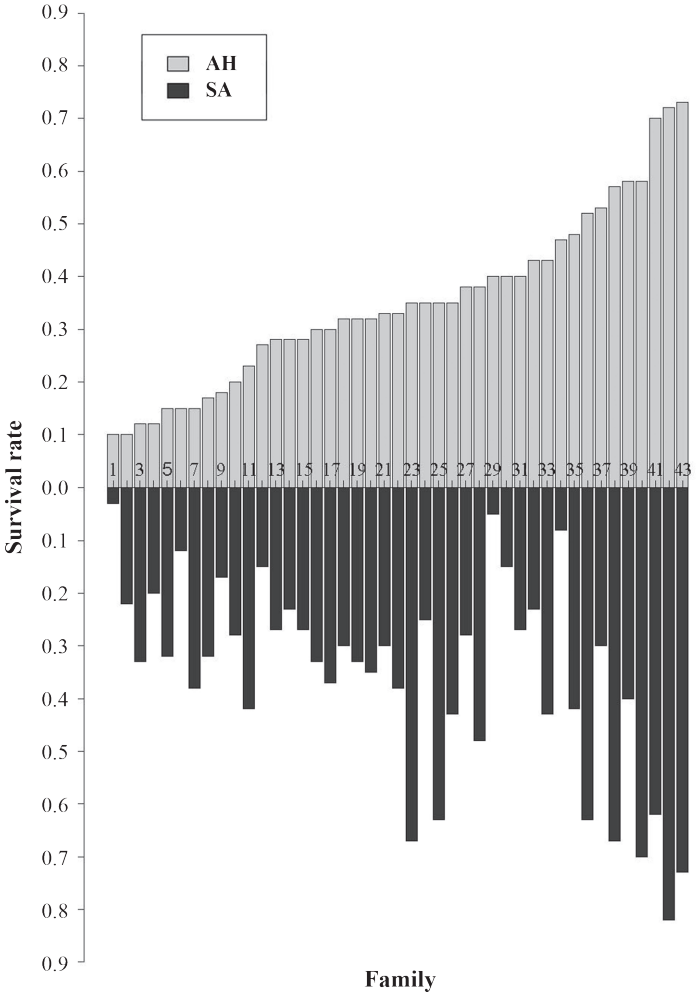

Figure 1. Comparison of survival rates of 43 families after 20 days of bath challenge with *Aeromonas hydrophila* (AH) and *Streptococcus agalactiae* (SA).

Heritability estimates were comparable between threshold and linear animal models for both traits, i.e., 0.17±0.04 and 0.18±0.05 for AH; and 0.15± 0.03 and 0.15±0.04 for SA. When models were compared in terms of accuracy in predicting breeding values for resistance to diseases, the linear model was somewhat more accurate (r_{EBV} = 0.62 and 0.61) than the threshold model (r_{EBV} = 0.58 and 0.57).

Estimates of Spearman rank correlation coefficients between full-sib family EBVs between models were almost unity (~1) for both traits, indicating similar rankings of families in these models (Figure 3).

Genetic correlations (r_{EBV}) between disease resistance traits were identical (0.41) and favorable for both the threshold and linear models (Figure 4).

Table 1. Estimates of additive genetic variance (σ_a^2), residual variance (σ_e^2), heritability (h^2) and accuracy of the model (r_{EBV}) for resistance to *Aeromonas hydrophila* and *Streptococcus agalactiae*. The models used were threshold animal model (THR) and linear animal model (LIN).

Trait	Model	$\sigma_a^2 \pm SE$	$\sigma_e^2 \pm SE$	$h^2 \pm SE$	r_{EBV}
Aeromonas hydrophila	THR	0.22±0.05	1	0.17±0.04	0.58
	LIN	0.04±0.01	0.18±0.01	0.18±0.05	0.62
Streptococcus agalactiae	THR	0.18±0.05	1	0.15±0.03	0.57
	LIN	0.04±0.01	0.19±0.01	0.15±0.04	0.61

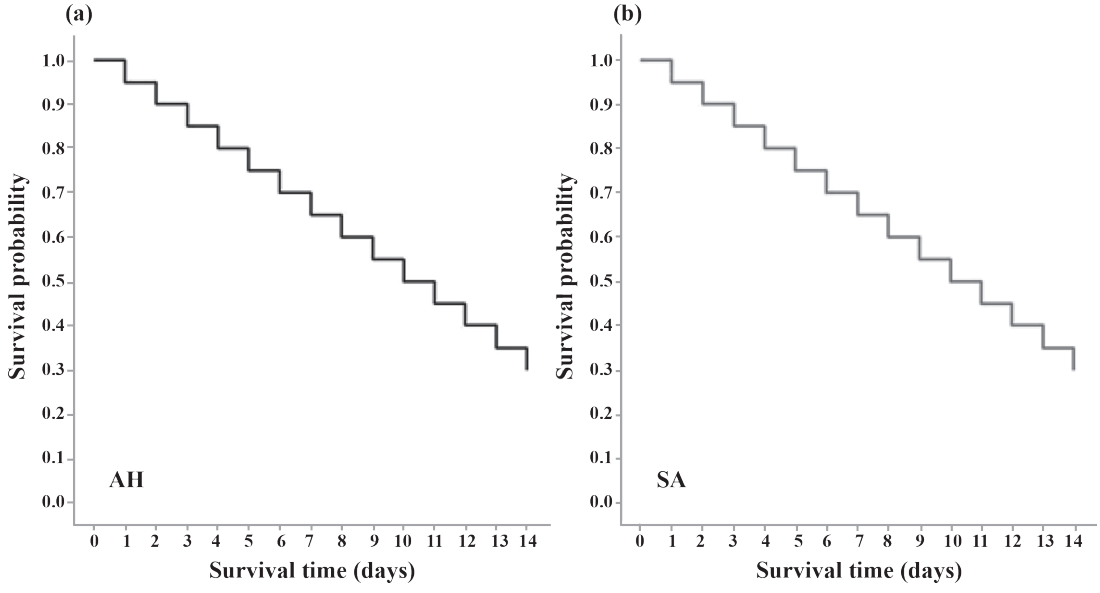

Figure 2. Kaplan-Meier survival curves across families of tilapia fry challenged with: *Aeromonas hydrophila*: AH (a) and *Streptococcus agalactiae*: SA (b).

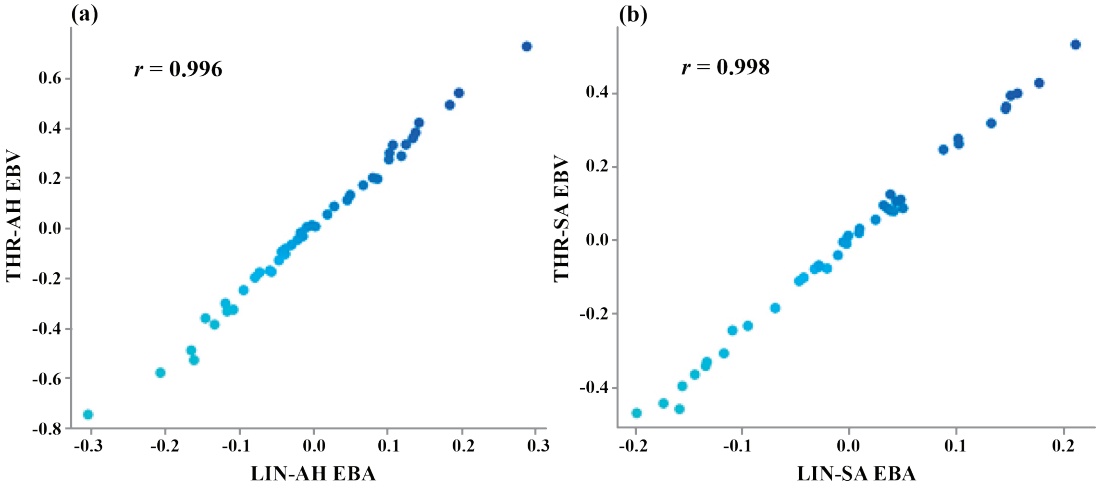

Figure 3. Spearman rank correlation of family EBVs for resistance to: *Aeromonas hydrophila* (a) and *Streptococcus agalactiae* (b) between the binary linear (LIN) and the threshold (THR) models.

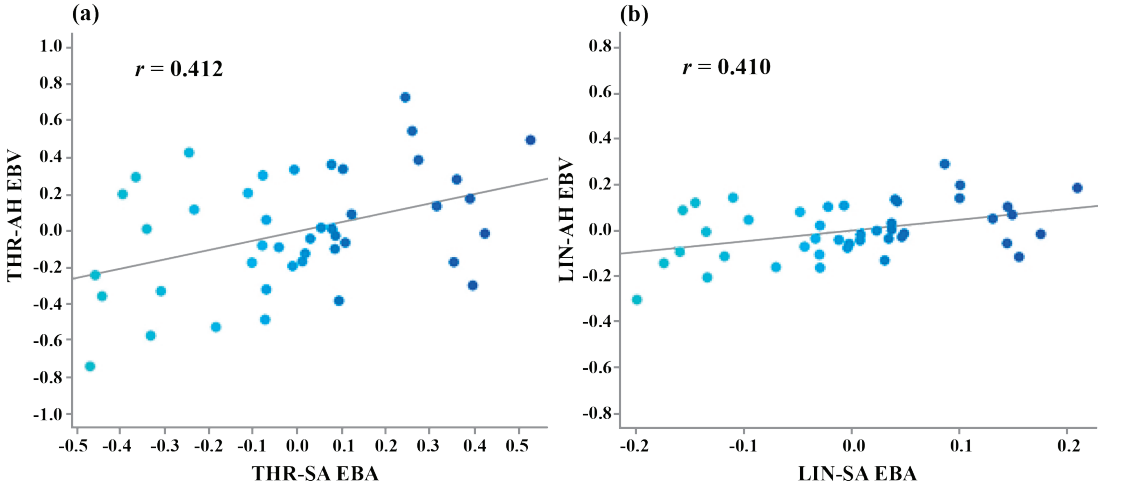

Figure 4. Genetic correlations between resistance to *Aeromonas hydrophila* and resistance to *Streptococcus agalactiae* for: the threshold (THR) model (a) and the linear (LIN) model (b).

DISCUSSION

An important first step to establish a selective breeding program is to evaluate the genetic variation of the trait, which measures genetic differences among animals within a population. For disease resistance, the variation of family survival after pathogen challenge can be used to represent genetic variation of the trait. Generally, the dose of pathogen used in challenge tests should be predetermined to allow genetic differences between resistant and susceptible individuals to be expressed (Fjalestad *et al*., 1993). The results of the challenge tests in our study revealed that the doses of pathogens used in the bath challenge were appropriate. We observed a sufficient amount of genetic variation to improve resistance to these diseases in this tilapia population. Survival after

a challenge of 43 families varied from 5 to 75 % and from 0 to 80 % for AH and SA, respectively. The estimates of the Kaplan-Meier survival function indicated similarity in survival over time between families for both challenge trials. Interestingly, the average survival patterns of tilapia fry may suggest that the progress of disease from infection to mortality was similar between AH and SA infections, suggesting that the genes responsible for the host immune functions may be shared between these traits.

We utilized two univariate statistical models to estimate variance components for the prediction of full-sib family EBVs. Heritability estimates for binary survival/death after bacterial challenge were moderate and slightly higher for AH (0.17 and 0.18 in the threshold and linear models, respectively) than those obtained for SA (0.15 in both models). We observed that the estimates for SA resistance in our study were lower than those reported for the Spring Genetics strain of Nile tilapia (0.38) (Shoemaker *et al*., 2017). Suebsong *et al*. (2019) using the same linear animal model to analyze a binary trait reported a much lower heritability (0.08) in a different tilapia population. In another study, Sukhavachana *et al*. (2019) using a binary threshold model reported a heritability of 0.13 for hybrid red tilapia survival following SA infection. It should be noted that differences in the heritability estimates for resistance to SA in different tilapia populations can be attributed to several factors, including background genetic composition, mating designs (i.e., nested design and partial factorial design), challenge methods (i.e., bath challenge and injection), life stage of the animals (i.e., fry and juvenile) used in the analyses as well as environmental conditions under challenge tests. Considering the accuracy of the models in predicting the family EBVs, the linear animal models (0.61 and 0.62) performed slightly better than the threshold models (0.57 and 0.58) for both traits. Model accuracy is defined as the correlation between true and estimated breeding values, which determines the accuracy of EBV as a predictor of breeding value (Mrode, 2014). The accuracy depends on the genetic variance component of the trait. The greater the additive genetic variance, the greater the accuracy will be for that trait. For a highly heritable trait ($h^2 \geq 0.5$), the accuracy of predicting breeding value from a phenotype of the animals would be 0.7 (Goddard, 2009).

When different models are used for genetic prediction of the same trait, it would be meaningful to evaluate the models in terms of rank-order correlations of the predicted family EBVs between models. In our study, the correlation between the threshold and the linear models was almost unity ($r \sim 1$), suggesting a near identical ranking of the families in these models. The results indicated that both models were appropriate for genetic evaluation and that either model can be used for selecting the best-performing families. Several studies also showed that the estimates of breeding values for disease resistance traits from linear and threshold models are highly correlated, e.g., furunculosis and infectious salmon anaemia in Atlantic salmon (Ødegård *et al*., 2006, 2007; Yáñez *et al*., 2013); viral nervous necrosis in Atlantic cod (Ødegård *et al*., 2010); white spot syndrome virus in Pacific white shrimp (Gitterle *et al*., 2006) and columnaris and streptococcosis in tilapia (Wonmongkol *et al*., 2018; Suebsong *et al*., 2019; Sukhavachana *et al*., 2019).

This study aimed to determine whether a genetic correlation exists between these disease resistance traits in Nile tilapia. It is important to understand that in a fish breeding program, the selection on one trait as a breeding goal can impact other traits that are not being considered due to correlation between traits (Gjedrem, 2005). These correlations can be either positive or negative, desirable or not desirable. Therefore, knowledge of correlations between two traits is needed to minimize the impact of undesirable genetic correlations that occurs in the program (Gjedrem, 2005). We found that the survival rates of families to AH and SA were positively and phenotypically correlated (r = 0.63). Additionally, we found a moderate positive genetic correlation between resistance to AH and SA (r_{EBVs} = 0.41) from both threshold and linear

models. This finding suggested that selection for improved resistance in one trait would result in a positive correlated response of the other trait. However, results of simultaneous selection for increased disease resistance depend upon the magnitude of genetic correlation (Evenhuis *et al*., 2015). For instance, if the breeding goal was to improve resistance to SA, our results suggest that approximately 40 % of the families selected for SA resistance would confer resistance to AH as well. The genetic correlations indicate pleiotropy between traits and suggest that these traits were controlled by similar groups of disease-resistance genes within the host genome. From a breeding perspective, this positive correlation is favorable for tilapia fry production, as resistance to one disease tends to increase resistance to the other disease. If a multi-trait selection is practiced, it is recommended that a direct selection should be made on a trait that is highly heritable and is easy to measure (Lindhé and Philipsson, 1998). In our study, a direct selection can be practiced on AH resistance because the heritability of this trait was slightly higher than that for SA resistance. More importantly, it should be noted that to properly utilize these traits in breeding programs, further investigations are needed to determine how results of experimental challenge correlate with those from a natural disease outbreak (Gjedrem and Gjøen, 1995; Ødegård *et al*., 2006). Genetic correlations among disease resistance traits also occur in farmed Atlantic salmon and rainbow trout. Previous studies by Gjedrem and Gjøen (1995) and by Gjøen *et al*. (1997) reported positive genetic correlations between resistance to bacterial diseases such as furunculosis, bacterial kidney disease and cold-water vibriosis in Atlantic salmon. Gjøen *et al*. (1997) also found a weak negative genetic correlation between resistance to viral infectious salmon anaemia (ISA) with bacterial diseases. In contrast, Ødegård *et al*. (2007) reported a positive genetic correlation between furunculosis and ISA. Henryon *et al*. (2005) and Kjøglum *et al*. (2008) reported weak genetic correlations between resistance to viral and bacterial diseases in rainbow trout. In another study, Evenhuis *et al*. (2015) found favorable genetic correlation between resistance to columnaris disease and bacterial cold water disease in rainbow trout.

CONCLUSION

This study demonstrated that resistance to AH and SA in Nile tilapia are heritable traits and that including both traits in a breeding objective would be advantageous. This favorable genetic correlation suggests that one resistance trait can be used as a genetic prediction of the other trait in selecting best families, thus a single experimental challenge would be sufficient for genetic evaluation in the following generations.

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