Novel insights into the genetic relationship between growth and disease resistance in Pacific salmon

Agustin. Barría[a], Andrea. B. Doeschl-Wilson[b], Jean P. Lhorente[c], Ross. D. Houston[b], José. M. Yáñez[a,c],

[a] *Facultad de Ciencias Veterinarias y Pecuarias, Universidad de Chile, Santa Rosa 11735, La Pintana, Santiago, Chile*

[b] *The Roslin Institute and Royal (Dick) School of Veterinary Studies, University of Edinburgh Easter Bush, EH25 9RG, Midlothian, United Kingdom*

[c] *Benchmark Genetics Chile S.A., Puerto Montt, Chile*

E-mail: jmayanez@uchile.cl

Abstract

Background

Breeding for disease resistance has become a highly desirable strategy for mitigating infectious disease problems in aquaculture. However, knowledge of the genetic relationship between resistance and other economically important traits, such as growth, is important to assess prior to including disease resistance into the breeding goal. Our study assessed the genetic correlations between growth and survival traits in a large bacterial infection challenge experiment. A population of 2,606 coho salmon individuals from 107 full-sibling families were challenged with the bacteria *Piscirickettsia salmonis*. Growth was measured as average daily gain prior (ADG0) and during (ADGi) the experimental infection and as harvest weight (HW). Resistance was measured as Survival time (ST) and binary survival (BS). Furthermore, individual measures of bacterial load (BL) were assessed as new resistance phenotypes and to provide an indication of genetic variation in tolerance in salmonid species.

Results

Significant moderate heritabilities were estimated for ADG0 (0.30 ± 0.05), HW (0.38 ± 0.03), and for the survival traits ST (0.16 ± 0.03) and BS (0.18 ± 0.03). In contrast, heritabilities for ADGi and log-transformed BL were low (0.07 ± 0.02 (significant) and 0.04 ± 0.03, respectively), although these increased to moderate significant levels (0.20 ± 0.09 and 0.12 ± 0.05, respectively) when traits were assessed in survivors only. Significant and favorable genetic correlations were found between ADG0 and the growth traits ADGi (0.40 ± 0.16) and HW (0.64 ± 0.09), as well as with resistance as ST (0.43 ± 0.18), indicating that fish with higher genetic growth rate early on and prior to infection not only tend to maintain their genetic growth advantage until harvest, but also tend to grow faster and survive longer during infection. Furthermore, no robust

unfavorable genetic correlations between ADG0 and any of the other traits considered in this study, in particular BL, was identified. Adding log BL as covariates into the models for growth under infection and survival provided an indication for genetic variation in tolerance.

Conclusions

These results suggest that selective breeding for early growth would be expected to simultaneously increase survival time and growth performance during an infection with *Piscirickettsia salmonis* after accounting for variation in bacterial load, and harvest weight in this coho salmon population, without negatively impacting on pathogen burden.

Keywords: Aquaculture; Bacterial Infection; Disease Resistance; Heritability; Genetic Correlation; Growth Rate

Background

Chile is the main producer of farmed coho salmon (*Oncorhynchus kisutch*) globally, with approximately 90 % of the total production [1]. In common with other intensive production systems, the health status of farmed coho salmon is a major concern for profitability and animal welfare. One of the main sanitary issues affecting the Chilean coho salmon industry is Salmon Rickettsial Syndrome (SRS), caused by *Piscirickettsia salmonis*, a facultative intracellular bacteria which was first isolated in Chile [2]. SRS is responsible for great economic losses, either directly through mortality, or indirectly through treatment costs or reduction on fish performance. During the first half of 2016, *P. salmonis* was responsible for 53 % of mortalities attributed to infectious disease in farmed coho salmon [3]. Current strategies to control

SRS, such as vaccines and antibiotics, have not been fully effective in tackling this disease under field conditions [4].

Selective breeding for improved resistance to infectious diseases is a feasible and potentially more sustainable strategy for the long-term control of disease outbreaks in both livestock and aquaculture species [5]. To date, salmonid breeding programs typically use disease challenge testing of relatives of the selection candidates to enable breeding values estimations and genetic improvement of disease resistance [6,7]. Accordingly, there is an increasing number of studies aimed at quantifying and dissecting the host genetic variation for disease resistance by measuring survival after exposure to diverse infectious pathogens [6,8–10]. Previous studies have demonstrated significant genetic variation for resistance to *Piscirickettsia salmonis* in Atlantic salmon (*Salmo salar*), rainbow trout (*Oncorhynchus mykiss*) and coho salmon using disease challenge data, with heritability estimates ranging from 0.11 to 0.62 [11–16].

From an economic perspective, growth, SRS resistance and flesh color are key traits to be included into the breeding goal of Chilean salmon [17]. Before including all these traits simultaneously into the breeding objective, knowledge of the genetic correlations between traits is needed. A positively correlated response to selection between growth at harvest and flesh color has been reported in a Chilean coho salmon breeding population [18]. Moreover, although [15] estimated a genetic correlation not significantly different from zero between SRS resistance (defined as day of death) and body weight in Atlantic salmon, the same authors reported a negative genetic correlation of -0.50 ± 0.13 between SRS resistance (defined as day of death) and harvest weight in coho salmon [12]. However, little is known about the relationship between growth prior to and during infection and SRS resistance.

In aquaculture, disease resistance is commonly defined using host survival data (measured as binary or day of death) after being exposed to an infection, either in an experimental challenge [6,12,14,19,20] or under field conditions [10]. However, this definition captures two different host response mechanisms to infections under potential genetic regulation, i.e. (i) the ability of the host to restrict pathogen invasion or replication (best described by within-host pathogen load) and (ii) the ability of an infected host (with a given pathogen load) to survive the infection [21]. Studies that include both types of mechanisms often refer to the first trait as 'resistance' and to the second trait as 'tolerance or endurance' [22–27]. Clearly, resistance and tolerance /endurance contribute both positively to an individual's ability to survive an infection. However, at the population level, tolerant individuals that tend to harbor and can cope with high pathogen load are undesirable, as these would be expected to shed more infectious material and thus to cause a higher disease threat to individuals in the same contact group [28]. Thus, in order to minimize disease prevalence and mortality due to disease in a population, a fuller understanding of the relationship between within-host pathogen load and mortality is required. However, measures of individual pathogen load are rarely available in large scale genetic studies, especially in aquaculture. In the present study we aimed to overcome this shortcoming by quantifying bacterial load as a measurement of disease resistance in coho salmon families with extremes survival rates after infection with *P. salmonis*. We then evaluated the phenotypic association and genetic correlation of this trait with SRS survival traits and growth rate.

The aim of the current study was to provide a better understanding of the genetic relationship between growth and SRS resistance traits in coho salmon. Specifically, the objectives were (i) to quantify the level of genetic variation for growth both prior to and during an infection with *P. salmonis*, and for harvest weight, in a coho salmon breeding

125 population, (ii) to assess the genetic correlations between these growth traits and
126 survival traits in a large SRS infection challenge experiment, and (iii) quantify the level
127 of genetic variation in individual bacterial loads as an alternative phenotype for disease
128 resistance, and their relationship with survival and growth traits.
129
130 **Methods**
131 **Breeding Population**
132 The study was performed on a coho salmon (*Oncorhynchus kisutch*) population
133 from the 2012 year-class, belonging to a genetic improvement program established in
134 1997. This breeding program is owned by Pesquera Antares and is managed by
135 Aquainnovo (Puerto Montt, Chile). The breeding population consists of two sub-
136 populations, depending on the spawning year. Both sub-populations have been selected
137 for eight generations for harvest weight (HW) using best linear unbiased prediction
138 (BLUP). Summary statistics for age at tagging (AT), weight at tagging (WT) and HW
139 for population with spawning at even years are described in supplementary material
140 (Table S1). More details about this breeding population are described in [12] and in
141 [18].
142
143 **Experimental Challenge**
144 The study comprised a total of 2606 individuals belonging to 107 maternal full-
145 sib families (60 half-sib families) from the 2012 spawning year from the breeding
146 nucleus described above. Prior to challenge, each fish was marked with a Passive
147 Integrated Transponder (PIT-tag), placed on the abdominal cavity for genealogy
148 traceability during challenge test. Body weight was measured for each fish prior to PIT-
149 tag placement. The average weight at tagging was 5.5 g (SD = 1.02 g) and the mean age

150 at tagging was 218 days (SD = 3). After tagging, fish were kept in communal tanks with
151 fresh water at 13°C and then transferred to salt water [31 ppt] with an initial density of
152 15Kg/m^3.

153 The strain of *P. salmonis* used in the current study was isolated in 2012 and
154 purchased from ADL Diagnostic Chile Ltda, (Puerto Montt, Chile). A lethal dose 50
155 (LD_{50}) was calculated from an independent assay prior to the main experimental
156 challenge. For this pre-challenge, a total of 80 fish were randomly selected from the
157 population. Four different dilutions (1/10, 1/100, 1/1000 and 1/10000) of the *P.*
158 *salmonis* inoculum were evaluated on twenty individuals per dilution. Fish were
159 intraperitoneally (IP) injected with a total volume of 0.2 ml / fish. Mortality was
160 recorded daily. This preliminary assay lasted 26 days. A LD_{50} of 1:680 was estimated as
161 described in [29] for use in the main challenge,

162 For the main challenge test, fish not used for the pre-challenge were distributed
163 amongst three tanks (7 m^3) with salt water concentration of 31 ppt. A mean of eight
164 individuals (ranging from 1 to 18) per family were allocated into each tank. Each
165 challenged family had on average 25 individuals (from 11 to 45), which were
166 distributed across all three tanks. After an acclimation period of 12 days, fish were
167 anesthetized using 30 ppm of benzocaine and body weight was measured for each
168 individual. The mean initial body weight (IW) at the inoculation procedure was 279 g
169 (SD = 138 g). The infection of each fish was then performed through an IP injection of
170 0.2 ml / fish of the LD_{50} inoculum. To ensure the absence of any other pathogens in the
171 population, a sample of 30 fish from the full-sib families were randomly tested.
172 Quantitative real-time PCR (qRT-PCR) was used to test for and exclude the presence of
173 Infectious Salmon Anaemia Virus (ISAV) and Infectious Pancreatic Necrosis Virus
174 (IPNV). Conventional PCR and culture was used to test for and exclude the presence of

175 *Flavobacterium psychrophilum*, and an immunoflouresence antibody test (IFAT) was
176 used to test for and exclude the presence of *Renibacterium salmoninarum.*

177 Mortalities returned to approximately baseline levels at day 47 which was
178 maintained for three days. Thus, the experimental challenge continued for 50 days post
179 injection. Mortalities were removed from each tank daily. At the end of the challenge
180 test, all surviving fish were euthanized. Head kidney samples were taken from all dead
181 and surviving fish and storage in RNALater at 4°C for 24 h and then transferred to -
182 80°C for longer term storage. Body weight at the day of death (FW) was measured for
183 each individual. The disease challenge and measurements were all performed on
184 Aquainnovo´s Research Station, in Lenca River, Xth Region, Chile.

185 A necropsy assay and qRT-PCR were performed on all dead fish, to confirm the
186 presence of *P. salmonis* as the likely cause of death. The presence of *Vibrio ordalli*,
187 *Renibacterium salmoninarum* and IPNV were discarded as mentioned above. Summary
188 statistics for age and weight at tagging (AT, WT) and initial and final weights (IW and
189 FW) for the challenged population is shown in Table S2.

190

191 **Growth and mortality phenotypes**

192 The survival time (ST), measured as the day of death after IP injection was
193 recorded for each fish. Values ranged from 1 to 49 depending on the time of the event.
194 Individuals that survived until the end of the challenge were assigned a ST value of 50.
195 Binary survival (BS) was defined as 1 if the fish survived until the end of the challenge
196 or 0 if the fish died during the experimental challenge.

197 Growth rate was measured prior to and during *P. salmonis* infection. Average
198 daily gain (g/day) before experimental challenge (ADG0) was measured as the
199 difference between body weight at the time of IP injection and body weight at the time

of tagging divided by the number of days (ranging from 239 to 251 days, depending on the family) between both procedures. Average daily gain during infection (ADGi) was calculated by the difference of weight at the day of death (or termination of challenge in the case of survivors) and weight at IP injection divided by the number of days between both timepoints. In addition to the records from the challenged individuals, harvest weight (HW) records from 41,597 fish with known relatedness to the challenge individuals (established through pedigree records) were available and included in the genetic analyses.

Quantification of bacterial load

A subset of 740 individuals from 33 full-sib families were selected from the population for measurement of bacterial load. Using data from the experimental challenge, these families were selected based on their estimated breeding values for ST using *best linear unbiased prediction* (BLUP). More specifically, the 16 and 17 families with the highest and lowest estimated breeding values, respectively, were chosen and are hereafter referred to as the most and least resistant families, respectively. All 33 families were equally represented in each tank. Bacterial load (BL) from these individuals was quantified through amplification of the 16S gene by qRT-PCR. The gene copy number was log-transformed and corrected by the six copies of 16S in *P. salmonis* [30]. The log-transformed BL (LogBL) was then used as a measure of host resistance to *P. salmonis* infection [25,31].

Statistical Analysis

Bivariate linear animal models were used to estimate the variance and covariance components among the traits. Bivariate models were defined as follows:

225 $$\begin{bmatrix} \boldsymbol{y}_1 \\ \boldsymbol{y}_2 \end{bmatrix} = \begin{bmatrix} \boldsymbol{X}_1 & 0 \\ 0 & \boldsymbol{X}_2 \end{bmatrix} \begin{bmatrix} \boldsymbol{b}_1 \\ \boldsymbol{b}_2 \end{bmatrix} + \begin{bmatrix} \boldsymbol{Z}_1 & 0 \\ 0 & \boldsymbol{Z}_2 \end{bmatrix} \begin{bmatrix} \boldsymbol{u}_1 \\ \boldsymbol{u}_2 \end{bmatrix} + \begin{bmatrix} 0 & 0 \\ 0 & \boldsymbol{W}_2 \end{bmatrix} \begin{bmatrix} 0 \\ \boldsymbol{c}_2 \end{bmatrix} + \begin{bmatrix} \boldsymbol{e}_1 \\ \boldsymbol{e}_2 \end{bmatrix}$$

226 Where, $\mathbf{y_1}$ and $\mathbf{y_2}$ are vectors of phenotypic records measures in animals for either ST,
227 BS, LogBL, ADG0, ADGi and HW; $\mathbf{b_i}$ are vectors of fixed effects, for HW the
228 contemporary group of sex:cage:year was included as factor, and harvest age, with
229 marking age (MA) and marking weight (MW) fitted as covariates. For all remaining
230 traits, sex and tank were included as fixed effects, and MW and MA were fitted as
231 covariates. To account for different recording times for body weight and bacterial load
232 in survivors and non-survivors, binary survivor / non-survivor status at the end of the
233 challenge was included as fixed effect for ST, ADGi and LogBL. The variable ADG0
234 was included as covariate in the bivariate models between ADGi, logBL, ST and BS
235 that did not also include ADG0 as response variable. Similarly, the effect of LogBL was
236 included for ADGi, ST and BS that did not include LogBL as response variable; $\mathbf{u_i}$ and
237 $\mathbf{e_i}$ are vectors of random animal genetic and residual effects, respectively, $\mathbf{c_2}$ is the
238 vector of random environmental effect associated with common rearing of full-sib
239 families for HW prior to tagging; $\mathbf{X_i}$ and $\mathbf{Z_i}$ are the design matrices for the
240 corresponding fixed and random effects for both traits, and $\mathbf{W_2}$ is the design matrix for
241 HW.

242 The random effects associated to each animal and residual effects, in
243 conjunction with common environment effect for HW, were assumed to be normally
244 distributed according to:

$$u = [u_1' u_2']' \sim N(0, \boldsymbol{G}_0 \otimes \boldsymbol{A})$$

$$c = [c_2']' \sim N(0, \boldsymbol{C}_0 \otimes \boldsymbol{I}_c)$$

$$e = [e_1' e_2']' \sim N(0, \boldsymbol{R}_0 \otimes \boldsymbol{I}_N)$$

245 Where, $\mathbf{A}$ is the matrix of additive genetic kinship among all the fish included in
246 the pedigree; $\mathbf{I}_C$ and $\mathbf{I}_N$ are the identity matrix of dimension $\mathbf{C}$ and $\mathbf{N}$; $\otimes$ indicates the

direct operator of the products; the matrices $\mathbf{G_0}$ and $\mathbf{R_0}$ denote the variances and co-variances of 2 x 2 additive genetic and residual effects, respectively. Common environment effect was evaluated for each trait using a single-trait likelihood ratio test [32]. This effect was significant only for HW ($P < 0.05$), and therefore included in the bivariate models when HW was analyzed. Thus, $\mathbf{C_0}$ represents a 1 x 1 scalar of common environment effect for HW. Given that HW was recorded on a different population of individuals to the challenge population, environmental covariance was set to zero in the $\mathbf{R_0}$ matrix. The parameters in the bivariate mixed linear models were estimated using the restricted maximum likelihood method (REML) implemented in ASREML version 3.0 [33].

To assess the influence of different recording times for body weight and bacterial load between survivors and non-survivors on (co-)variance estimates, bivariate analyses for logBL, ADG0, ADGi, and HW were repeated for subsets of data containing either survivors or non-survivors only. Similarly, bivariate analyses for ST were also performed exclusively for non-survivors.

Heritability and genetic correlations

The following formula was used to estimate heritability values for the different traits:

$$h_i^2 = \frac{\sigma_{Ai}^2}{\sigma_{Ai}^2 + \sigma_{Ci}^2 + \sigma_{Ei}^2}$$

Where, i is either ST, BS LogBL, ADG0, ADGi or HW, σ_{Ai}^2 are the additive genetic variance of matrix $\mathbf{G_0}$, σ_{Ei}^2 are the residual variances from the matrix $\mathbf{R_0}$ and σ_{Ci}^2 is the common environmental effect associated with the full-sib families (only for HW).

The genetic correlations (r_{xy}) among traits were calculated as follows, according to [34]:

$$r_{i,j} = \frac{\sigma_{Ai,Aj}}{\sqrt{\sigma_{Ai}^2 + \sigma_{Aj}^2}}$$

where, $\sigma_{Ai,Aj}$ corresponds to the additive genetic variance between the traits evaluated in the bivariate model, σ_{Ai}^2 corresponds to the additive genetic variance of trait *i* and σ_{Ajj}^2 corresponds to the additive genetic variance of trait *j*.

Results

SRS experimental challenge

Typical clinical signs and pathological lesions associated with a *P. salmonis* infection were observed after IP injection. These signs included inappetence, lethargy and pale gills [4]. Mortality began on day 10 post IP injection. Dead individuals showed a swollen kidney, splenomegaly and yellowish liver tone (typical symptoms of SRS infection; [4]). During the 50 days of challenge, the three replicate tanks reached a cumulative mortality of 35.6, 42.5 and 37.7%, respectively.

Figure 1A shows the observed mortality from all 107 challenged families, ranging from 5.0 to 81.8 %, with an average mortality of 38.5 %. The most susceptible / resistant families selected for bacterial quantification are highlighted, with a mean mortality of 63 and 17%, respectively. The proportion of survivors and non-survivors among these 33 extreme families are shown in Figure 1B. Except for one family, all families contained both survivors and non-survivors, although the percentage of survivors was considerably higher in the most resistant families (ranging from 67 to 100 % compared to 19 to 48 % in the most susceptible families).

Phenotypic variation for resistance and growth traits

Table 1 shows summary statistics of the phenotypic variation observed for the different measured traits. Prior to the challenge test, individuals gained on average 1.11 g/day (SD = 0.56) in body weight, ranging between 0.34 and 2.62 g/day. However, this average daily growth rate was reduced by almost half (0.69 g/day ± 1.65), and had far higher phenotypic variation during the infection process. Some individuals continued to grow (maximal gain of 6.36 g/day), whereas others experienced a weight loss (maximal weight loss of 5.85 g/day). The distribution for ST was right skewed, with 61% of fish having a ST value of 50 (Figure S1), i.e. they survived the experimental challenge. Amongst non-survivors, fish survived on average 41 days (SD=10) after IP injection, with a minimum value of 10 days and maximum value of 49 days.

Bacterial load quantification of 740 fish from 33 families showed that 6.5 % (n = 48) of individuals had a *P. salmonis* load below the qRT-PCR detection threshold; these fish were considered as bacterial-free. All these individuals survived the experimental challenge and belonged to the resistant families. The bacterial load measured on the $\log_{10}$ scale in the other 692 animals ranged from 0.81 to 2.36 with an average load of 1.53 log units (SD = 0.33). From these 692 individuals, 55 % were survivors, while the rest of the animals died during the experimental challenge. Harvest weight,obtained from 41,597 commercial fish with linked pedigree to the challenged population, had a mean of 6.36 kg (ranging from 0.05 to 7.5 kg).

Comparison of traits measured in survivors and non-survivors

Binary survival (BS), added as fixed effect in the statistical models, had a significant effect on ADGi and logBL ($p < 0.001$) (Table 2). Survivors grew on average by 2.09 ± 0.56 g/day faster than non-survivors during the experimental challenge and also experienced on average a 0.64 ± 0.03 times lower bacterial load (in log units) (data

not shown). Furthermore, genetic correlations between the traits ADGi, and LogBL measured in survivors and non-survivors, respectively, were low (0.026 ± 0.64 for ADGi and 0.001 ± 0.39 for logBL), indicating that these traits may be considered as genetically different traits in survivors and non-survivors. Interestingly, the same was true for growth prior to infection, where the genetic correlation between ADG0 in survivors and non-survivors was 0.032 ± 0.21 (Table S3).

Effect of early growth and bacterial load on growth and survival traits under infection

As shown in table 2, ADG0 had a significantly positive effect ($p < 0.001$) on the traits ADGi, LogBL, ST and BS, implying that fast growth prior to infection also corresponded on average to faster growth and higher chance for survival during the infection process. This significance was also found in survivors (for ADGi, $p < 0.05$) and non-survivors (for ADGi and ST, $p < 0.001$) seperately. LogBL, in contrast, was found to have a significant negative effect on both survival traits BS and ST, and a negative, though not significant ($p = 0.09$) effect on ADGi (Table 2). The latter suggests that differences in growth during infection occur due to other factors than differences in bacterial load.

Heritabilities and genetic correlations

Estimated heritabilities and genetic correlations obtained by including both survivors and non-survivors in the models, and by analyzing both categories separately, are presented in Table 3. A significant and moderate heritability was estimated for growth rate prior to the experimental challenge ($h^2 = 0.30 \pm 0.05$ in pooled dataset, and slightly lower values when survivors and non-survivors were analyzed separately (Table

343 3)). This estimate decreased considerably during the experimental challenge test (e.g. h^2
344 = of 0.07 ± 0.02 in pooled dataset), which could be explained by a substantial increase
345 in the phenotypic variance of ADGi compared to ADG0 (Table 3). Higher heritability
346 estimates were obtained for HW of related individuals (0.38 ± 0.03 in pooled dataset).
347 The survival traits ST and BS were found to be moderately heritable (0.16 ± 0.04 and
348 0.18 ± 0.03, for ST and BS respectively, in the full dataset, although heritability of ST
349 dropped to 0.08 ± 0.04 when survivors were removed), when differences in ADG0 and
350 LogBL were accounted for in the models. The estimate of heritability for LogBL was
351 low and not significantly different from zero (0.04 ± 0.03) in the pooled dataset, but
352 increased to 0.12 ± 0.05 and 0.11 ± 0.06, respectively, when survivors and non-
353 survivors were analyzed separately.

354 A significant and positive genetic correlation was estimated between ADG0 and
355 ADGi in the full dataset (0.40 ± 0.16) and for survivors only (0.36 ± 0.16), whereas
356 genetic correlations between these traits were not found significant for non-survivors.
357 Estimates of genetic correlations between ADG0 and HW were favorable (0.64 ± 0.09
358 in pooled dataset) and robust across the datasets (Table 3). Growth prior to infection and
359 ST also showed a significant and positive genetic correlation (0.43 ± 0.18 and 0.64 ±
360 0.17 in full dataset and non-survivors, respectively), indicating that fish with higher
361 growth rates prior to infection are more likely to survive the infection. However, genetic
362 correlations between ADG0 and BS were not found significantly different from zero
363 (0.05 ± 0.19). Lastly, no significant genetic correlation was found between ADG0 and
364 LogBL in either dataset.

365 Binary survival was strongly and favorably correlated with ST (0.85 ± 0.09),
366 ADGi (0.84 ± 0.07) and LogBL (-0.97 ± 0.10), whilst no significant correlation with
367 HW was found. Surprisingly, a significant unfavorable correlation was found between

ST and HW (-0.50 ± 0.13), although the association became weaker and non-significant once the censored ST values of survivors were removed from the analyses (Table 3). Similarly, the statistically significant undesirable positive correlation between HW and LogBL estimated with the pooled dataset was no longer observed when the analysis was stratified into survivors and non-survivors (Table 3). Lastly, genetic correlations between ADGi and LogBL tended to be favorable, but were not found statistically significant in either of the datasets.

Discussion

In order to include *P. salmonis* resistance into the breeding goal it is necessary to determine if the trait is heritable and its potential association with other economically important traits, such as growth. The current dataset comprises animals that were exposed to *P. salmonis* using an experimental challenge, and previously analyzed by Yáñez *et al.*, [12]. However, these authors only focused on the genetic association between harvest weight and day of death as a measure of resistance.

The current work provides novel insights into the genetic (co)variation between growth and *P. salmonis* resistance. By defining growth as average daily gain prior and during an infection with *P. salmonis*, we estimated heritabilities and its genetic correlation with resistance defined as survival time and binary survival, and the less commonly measured but epidemiologically important bacterial load. Moreover, estimates of the genetic correlation of all these traits with harvest weight was also determined using a large cohort from a coho salmon breeding population.

We found a moderate significant genetic variation for early growth rate (0.30 ± 0.05). Similar heritability values have been reported for growth rate in others salmonid species, ranging from 0.32 to 0.35 [35,36].

When growth rate was measured during infection with *P. salmonis*, heritability was up to six fold lower than the value for growth prior to infection. A similar drop in heritability for average daily gain during infection, compared growth rate prior infection have been observed in pigs [37] and chickens [38]. In our study, this drop in heritability could be explained by a relatively stronger increase in the phenotypic variance (with some fish losing rather than gaining weight due to infection), than in the genetic variance (Table 3). The results suggest that differences in growth under infection are primarily controlled by environmental rather than genetic factors, once individual differences in early growth or in disease resistance (represented by log-transformed bacterial load included as fixed covariate) are accounted for. Nevertheless, heritability estimates for growth under infection were still significantly different from zero, which is indicative for genetic variation in tolerance, in addition to resistance [25,31].

A moderate and positive genetic correlation was found between growth prior to and under infection. This favorable and significant genetic correlation was also estimated between growth prior to infection and harvest weight. The results indicate not only that fish with greater genetic growth potential at early stage in a pathogen-free environment in fresh water also tend to have greater growth potential during infection with *P. salmonis*, but also during the sea-rearing period, reaching higher body mass at harvest.

Significant additive genetic variation was estimated for ST and BS. These estimates are in agreement with previous estimates for the same and other types of pathogens for salmonid species (for a detailed review see [9]). Furthermore, a moderate and favorable genetic correlation between early growth and ST was found. These results corroborate findings indicating that fish with faster growth prior to and during infection are more likely to survive after an experimental challenge with a bacterial agent [39,40].

418 Hence, together the results of this study suggest that selection for early growth is
419 expected to have a positive effect on growth under *P. salmonis* infection and harvest
420 weight, without negatively impacting on survival.

421 One of the novelties of the present studies is the inclusion of bacterial load as
422 additional measures of host resistance to infection. Even though pathogen load is
423 commonly used as measure of disease resistance in domestic livestock [41–43], it is
424 rarely used in aquaculture for practical reasons [44]. Measurements of individual
425 pathogen load not only provide novel insights into different genetic response
426 mechanisms to infection, such as resistance and tolerance or endurance [31,45,46] and
427 their impact on survival [21], but may also help to predict potential epidemiological
428 effects of selection, as individuals with high pathogen load may be more infectious.

429 In our study, the regression coefficient for logBL, when fitted into the statistical
430 models for ST and BS, was significantly different from zero and negative, indicating
431 that individuals with higher bacterial load were more likely to die and tended to die
432 faster when infected with *P. salmonis*. Although the sample size for bacterial load in our
433 study was too small to obtain accurate genetic parameter estimates, we found significant
434 genetic variation for bacterial load in surviving animals (0.12 ± 0.05) and a similar
435 borderline significant genetic variation in non-survivors (0.11 ± 0.06). Furthermore, a
436 strong favorable genetic correlation was found between log-transformed bacterial load
437 and binary survival, and genetic correlations between LogBL and ST or growth traits
438 tended to be negative, suggesting that selection for growth or survival post *P. salmonis*
439 infection will not simultaneously increase pathogen load.

440 In our study, final body weight used to calculate ADGi, and BL were measured
441 at time of death for non-survivors and at the end of the trial for survivors. This implies
442 that the trait measurements may relate to different stages of infection in survivors and

443 non-survivors. The low genetic and phenotypic correlations for these traits measured in
444 survivors and non-survivors indicate that these traits should be considered as
445 biologically different in both groups of individuals. Indeed, survivors may have already
446 fully or partially recovered from infection at the time of recording and may thus have
447 had reduced bacterial load in contrast to non-survivors whose bacterial load may have
448 peaked at the time of death. Similarly, in the case of ADGi, non-survivors fish may
449 have died when body weight reached a minimum, whereas survivors may have
450 experienced compensatory growth at the later stages of the experiment. For these
451 reasons, the analyses were carried out with data from survivors and non-survivors
452 pooled (with BS fitted as fixed effect to partly account for these differences) in order to
453 maximize statistical power, and for survivors and non-survivors separately to
454 disentangle the effects of confounding with recording times. Furthermore, genetic
455 parameter estimates may be slightly upward biased due to the fact that bacterial load
456 was only measured in families from the extreme ends of the survival time breeding
457 value distributions.

458 Nevertheless, results of the genetic estimates within survivors and non-survivors
459 analyzed separately were overall consistent with those obtained with pooled animals,
460 although standard errors were higher. In particular, growth prior to infection showed a
461 generally favorable correlation with growth and survival during *P. salmonis* infection,
462 and harvest weight, and no robust antagonistic genetic relationship between growth,
463 survival and bacterial load was identified in this study.

464 From a resource allocation theory point of view, a negative correlation between
465 resistance and growth would be expected, given that these are two competing resource-
466 demanding mechanisms [47]. Indeed, previous studies found a negative genetic
467 correlation between body weight and resistance (as day of death) to SRS and *viral*

468 *haemorrhagic septicaemia* (VHS) in salmonid species [12,15,48]. Our current results do
469 not support this trade-off, as neither ADG0 or ADGi were antagonistically related to
470 survival. Instead, the estimated positive and favorable genetic correlations in pooled and
471 non-survivors individuals, suggest that fish with higher genetic growth rate measured in
472 freshwater at early stage are also genetically more resistant to *P. salmonis*. Similar
473 results have been obtained in Atlantic salmon and rainbow trout [39,49]. This trade-off
474 was only observed due to the unfavorable genetic correlation between ST and HW when
475 the former was measured in pooled animals. However, the genetic correlation between
476 ST and HW was not significantly different from zero when only non-survivors animals
477 were used, suggesting a less robust estimation compared to ST and ADG0, which was
478 positive and significantly different from zero when using only susceptible animals.
479 Furthermore, we found a favorable genetic correlation for ADG0 with respect to ST and
480 HW, which indicate a positive relationship between early growth in fresh water
481 (ADG0), late growth in seawater (HW) and survival time (ST).

482 Differences at the development of the immune system at early life stages, given
483 by body size at time of infection may explain the lack of trade-off [39]. Furthermore,
484 the role of insulin-like growth factor (IGF) could play a key role as has been associated
485 with increased survival and detected in higher levels in faster growing fish [50–52].

486 Previously, an up-regulation of pro-inflammatory genes has been detected in
487 Atlantic salmon families with early mortality following a *P. salmonis* infection
488 [16,30,53]. Moreover, using genome-wide association studies, candidate genes related
489 with pro-inflammatory response proximate to markers associated with *P. salmonis*
490 survival were identified in Atlantic [16] and Coho salmon [13]. In our work, fish from
491 the 17 more susceptible families experienced a higher weight loss than those from the
492 16 most resistant families, ($p < 0.0001$, data not shown). We propose that an

493 exacerbated, ineffective inflammatory response may have led to tissue damage and the
494 subsequent weight reduction in these individuals, with subsequent mortality. However,
495 further studies are necessary to test these relationships between immune response and
496 weight lost in coho salmon. The availability of a coho salmon reference genome
497 (assembly accession = GCA_002021735.1) and the international initiative on
498 Functional Annotation of All Salmonid Genomes (FAASG), will facilitated further
499 functional studies in salmonid species [54].

500 One potential limitation of the current study refers to the censored data. The
501 current censored distribution for mortality violates the normality assumption for the
502 linear mixed models. Moreover, ignoring the censoring could cause slight bias in the
503 estimates. Repeating the analyses for uncensored non-survivors only could partly
504 overcome this problem, but at the loss of statistical power. Alternatively, this situation
505 can be partly overcome with using survival analysis (e.g. proportional hazard frailty
506 models) [6]. However, bivariate analyses with such models present some difficulties in
507 terms of fitting and interpretation and therefore linear mixed models are often
508 considered more robust in this case. From the genetic improvement perspective,
509 predictive ability can be considered more relevant than goodness of fit for a given
510 model. In this regard, it has been found that when comparing proportional hazard frailty
511 models with linear mixed models, the increase in accuracy of selection is marginal in
512 the case of *P. salmonis* resistance in Atlantic salmon [14].

513 Finally, although survival to infection is generally considered as desirable
514 breeding goal in aquaculture, from an epidemiological point of view, fish that survive
515 an infection, but that harbor and shed a large amount of infectious pathogens may be
516 highly undesirable as they are more likely to infect others. The results of this study
517 would suggest that selection for survival to *P. salmonis* infection will not

simultaneously increase bacterial load. However, recent infection studies in Turbot demonstrated that survival is a composite genetic trait influenced by genetic variation in host resistance, tolerance and infectivity [27,55]. Future studies that provide a deeper understanding of the underlying mechanisms and their genetic regulation affecting survival of coho salmon to *P. salmonis* infection, are therefore warranted.

Conclusion

The current study showed the presence of significant genetic variation for average daily gain in an early stage of a coho salmon life cycle. This genetic variation decreased during infection by the facultative intracellular bacteria *Piscirickettsia salmonis*, and a moderate positive genetic correlation between growth prior and during infection was observed. We identified that early growth is positive genetically correlated with *P. salmonis* resistance measured as day of death and with harvest weight. Furthermore, we found no robust antagonistic genetic relationship between growth, survival and bacterial load.These results suggest that selective breeding for early growth, can indirectly improve harvest weight and resistance to *P. salmonis* in the current population. To our knowledge this is the first study elucidating significant genetic variation for pathogen load in salmonid species as a measurement of resistance, and its genetic correlation with commercially important traits.

Declarations

Ethics approval and consent to participate

Experimental challenge and sample procedures were approved by the Comité de Bioética Animal from the Facultad de Ciencias Veterinarias y Pecuarias, Universidad de Chile (Certificate N08-2015).

Consent for publication

Not applicable

Availability of data and materials

The dataset used during the current study is commercially sensitive and could be available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

This work has been conceived on the frame of the grant FONDEF NEWTON-PICARTE, funded by CONICYT (Government of Chile) and the Newton fund The British Council (Government of United Kingdom). ADW's and RH's contributions were funded by RCUK-CONICYT grant (BB/N024044/1) and Institute Strategic Funding Grants to The Roslin Institute (BBS/E/D/20002172, BBS/E/D/30002275 and BBS/E/D/10002070).

Author's contribution

563 JY and JL conceived the experiment and provided data for analysis. AB performed the
564 analysis. AW and RH helped to optimize the analysis. AB, AW, RH, and JY interpreted
565 the results. AB and AW drafted the manuscript. All authors improved the writing, read
566 and approved the final manuscript.

567

568 **Acknowledgements**

569 AB want to acknowledge to the National Commission of Scientific and Technologic
570 Research (CONICYT) for the funding through the National PhD funding program.

571

572 **References**

573 1. FAO. Fisheries and aquaculture information and statistical branch. 2016.
574 2. Cvitanich J, Garate O, Smith CE. The isolation of a rickettsia-like organism causing
575 disease and mortality in Chilean salmonids and its confirmation by Koch's postulate. J.
576 Fish Dis. 1991;14:121–46.
577 3. Sernapesca. Informe sanitario de salmonicultura en centros marinos 2016. Servicio
578 Nacional de Pesca y Acuicultura. 2016;
579 4. Rozas M, Enríquez R. Piscirickettsiosis and Piscirickettsia salmonis in fish: a review.
580 J. Fish Dis. 2014;37:163–88.
581 5. Bishop SC, Woolliams JA. Genomics and disease resistance studies in livestock.
582 Livest. Sci. Elsevier; 2014;166:190–8.
583 6. Ødegård J, Baranski M, Gjerde B, Gjedrem T. Methodology for genetic evaluation of
584 disease resistance in aquaculture species: challenges and future prospects. Aquac. Res.
585 2011;42:103–14.
586 7. Gjedrem T. Genetic improvement for the development of efficient global
587 aquaculture: a personal opinion review. Aquaculture [Internet]. Elsevier B.V.;

588 2012;344–349:12–22. Available from:

589 http://dx.doi.org/10.1016/j.aquaculture.2012.03.003

590 8. Yáñez JM, Martinez V. Genetic factors involved in resistance to infectious diseases

591 in salmonids and their application in breeding programmes. Arch. Med. Vet. 2010;42:1–

592 13.

593 9. Yáñez JM, Houston RD, Newman S. Genetics and genomics of disease resistance in

594 salmonid species. Front. Genet. 2014;5:1–13.

595 10. Houston RD, Haley CS, Hamilton A, Guy DR, Tinch AE, Taggart JB, et al. Major

596 quantitative trait loci affect resistance to infectious pancreatic necrosis in Atlantic

597 salmon (Salmo salar). Genetics. 2008;178:1109–15.

598 11. Yoshida G, Bangera R, Carvalheiro R, Correa K, Figueroa R, Lhorente JP, et al.

599 Genomic prediction accuracy for resistance against Piscirickettsia salmonis in farmed

600 rainbow trout. Genes\Genomes\Genetics. 2017;

601 12. Yáñez JM, Bangera R, Lhorente JP, Barría A, Oyarzún M, Neira R, et al. Negative

602 genetic correlation between resistance against Piscirickettsia salmonis and harvest

603 weight in coho salmon (Oncorhynchus kisutch). Aquaculture. Elsevier B.V.;

604 2016;459:8–13.

605 13. Barría A, Christensen KA, Yoshida GM, Correa K, Jedlicki A, Lhorente JP, et al.

606 Genomic predictions and genome-wide association study of resistance against

607 Piscirickettsia salmonis in coho salmon (Oncorhynchus kisutch) using ddRAD

608 sequencing. G3 Genes Genomes Genet. [Internet]. 2018;4231:g3.200053.2018.

609 Available from: http://g3journal.org/lookup/doi/10.1534/g3.118.200053

610 14. Yáñez JM, Bangera R, Lhorente JP, Oyarzún M, Neira R. Quantitative genetic

611 variation of resistance against Piscirickettsia salmonis in Atlantic salmon (Salmo salar).

612 Aquaculture. Elsevier B.V.; 2013;414–415:155–9.

613 15. Yáñez JM, Lhorente JP, Bassini LN, Oyarzun M, Neira R, Newman S. Genetic co-
614 variation between resistance against both Caligus rogercresseyi and Piscirickettsia
615 salmonis, and body weight in Atlantic salmon (Salmo salar). Aquaculture.
616 2014;433:295–8.
617 16. Correa K, Lhorente JP, López ME, Bassini L, Naswa S, Deeb N, et al. Genome-
618 wide association analysis reveals loci associated with resistance against Piscirickettsia
619 salmonis in two Atlantic salmon (Salmo salar L.) chromosomes. BMC Genomics. BMC
620 Genomics; 2015;16:854.
621 17. Neira R, Lhorente JP, Newman S, Yáñez JM, Araneda M, Flip M. Evolution of
622 coho salmon (Oncorhynchus kisutch) breeding programs. Proceedings, 10th World
623 Congr. Genet. Appl. to Livest. Prod. 2014;
624 18. Dufflocq P, Lhorente JP, Bangera R, Neira R, Newman S, Yáñez JM. Correlated
625 response of flesh color to selection for harvest weight in coho salmon (Oncorhynchus
626 kisutch). Aquaculture. 2016;6–11.
627 19. Vallejo RL, Leeds TD, Fragomeni BO, Gao G, Hernandez AG, Misztal I, et al.
628 Evaluation of genome-enabled selection for bacterial cold water disease resistance using
629 progeny performance data in rainbow trout: Insights on genotyping methods and
630 genomic prediction models. Front. Genet. 2016;7:1–13.
631 20. Houston RD, Haley CS, Hamilton A, Guy DR, Mota-Velasco JC, Gheyas a a, et al.
632 The susceptibility of Atlantic salmon fry to freshwater infectious pancreatic necrosis is
633 largely explained by a major QTL. Heredity (Edinb). Nature Publishing Group;
634 2010;105:318–27.
635 21. Lough G, Kyriazakis I, Bergmann S, Lengeling A, Doeschl-Wilson AB. Health
636 trajectories reveal the dynamic contributions of host genetic resistance and tolerance to
637 infection outcome. Proc. R. Soc. B Biol. Sci. 2015;282:20152151.

638 22. Roy BA, Kirchner JW. Evolutionary dynamics of pathogen resistance and tolerance.
639 Evolution (N. Y). 2000;54:51–63.
640 23. Ødegård J, Gitterle T, Madsen P, Meuwissen THE, Yazdi MH, Gjerde B, et al.
641 Quantitative genetics of Taura syndrome resistance in Pacific white shrimp (Penaeus
642 vannamei): a cure model approach. Genet. Sel. Evol. BioMed Central Ltd; 2011;43:14.
643 24. Doeschl-Wilson AB, Kyriazakis I. Should we aim for genetic improvement in host
644 resistance or tolerance to infectious pathogens? Front. Genet. 2012;3:2–4.
645 25. Mazé-guilmo E, Loot G, Páez DJ, Lefèvre T, Blanchet S. Heritable variation in host
646 tolerance and resistance inferred from a wild host − parasite system heritable. Proc. R.
647 Soc. B. 2014;281:20132567.
648 26. Restif O, Koella JC. Concurrent evolution of resistance and tolerance to pathogens.
649 Am. Nat. 2004;164:E90–102.
650 27. Saura M, Fernandez A, Maroso F, Hermida M, Martinez P, Cabaleiro S, et al.
651 Disentangling genetic variation for resistance and tolerance to scuticociliatosis in turbot
652 using pedigree and genomic information. Front. Genet. 2018;Accepted.
653 28. Lipschutz-Powell D, Woolliams JA, Bijma P, Doeschl-Wilson AB. Indirect genetic
654 effects and the spread of infectious disease: Are we capturing the full heritable variation
655 underlying disease prevalence? PLoS One. 2012;7.
656 29. Reed LJ, Muench H. A simple method of estimating fifty per cent endpoints. Am. J.
657 Hyg. 1938;27:493–7.
658 30. Pulgar R, Hödar C, Travisany D, Zuñiga A, Domínguez C, Maass A, et al.
659 Transcriptional response of Atlantic salmon families to Piscirickettsia salmonis
660 infection highlights the relevance of the iron-deprivation defence system. BMC
661 Genomics. BMC Genomics; 2015;16:1–21.
662 31. Lough G, Rashidi H, Kyriazakis I, Dekkers JCM, Hess A, Hess M, et al. Use of

663 multi-trait and random regression models to identify genetic variation in tolerance to
664 porcine reproductive and respiratory syndrome virus. Genet. Sel. Evol. 2017;49:37.
665 32. Lynch M, Walsh B. Genetics and analysis of quantitative traits. 1998.
666 33. Gilmour AR, Gogel BJ, Cullis BR, Thompson R. ASReml User. Guid. release 3.0.
667 372 p. VSN Int. Ltd, Hemel Hempstead, UK. 2009;372.
668 34. Falconer DS, Mackay TFC. Quantitative Genetics. 1996.
669 35. Silverstein JT, Vallejo RL, Palti Y, Leeds TD, Rexroad CE, Welch TJ, et al.
670 Rainbow trout resistance to bacterial cold-water disease is moderately heritable and is
671 not adversely correlated with growth. J. Anim. Sci. 2009;87:860–7.
672 36. Lillehammer M, Odegård J, Madsen P, Gjerde B, Refstie T, Rye M. Survival,
673 growth and sexual maturation in Atlantic salmon exposed to infectious pancreatic
674 necrosis: a multi-variate mixture model approach. Genet. Sel. Evol. [Internet].
675 2013;45:8. Available from:
676 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3652765&tool=pmcentrez&
677 rendertype=abstract
678 37. Clapperton M, Diack AB, Matika O, Glass EJ, Gladney CD, Mellencamp MA, et al.
679 Traits associated with innate and adaptive immunity in pigs: heritability and
680 associations with performance under different health status conditions. Genet. Sel. Evol.
681 2009;41:1–11.
682 38. Rowland K, Wolc A, Gallardo RA, Kelly T, Zhou H, Dekkers JCM, et al. Genetic
683 analysis of a commercial egg laying line challenged with Newcastle disease virus.
684 Front. Genet. 2018;9:1–12.
685 39. Overturf K, LaPatra S, Towner R, Campbell N, Narum S. Relationships between
686 growth and disease resistance in rainbow trout, Oncorhynchus mykiss (Walbaum). J.
687 Fish Dis. 2010;33:321–9.

688 40. Imsland AK, Jonassen TM, Langston A, Hoare R, Wergeland H, Fitzgerald R, et al.
689 The interrelation of growth and disease resistance of different populations of juvenile
690 Atlantic halibut (Hippoglossus hippoglossus L.). Aquaculture. 2002;204:167–77.
691 41. Psifidi A, Fife M, Howell J, Matika O, van Diemen PM, Kuo R, et al. The genomic
692 architecture of resistance to Campylobacter jejuni intestinal colonisation in chickens.
693 BMC Genomics. BMC Genomics; 2016;17:1–18.
694 42. Bishop SC, Jackson F, Coop RL, Stear MJ. Genetic parameters for resistance to
695 nematode infections in Texel lambs and their utility in breeding programmes. Anim.
696 Sci. 2004;78:185–94.
697 43. Boddicker NJ, Bjorkquist A, Rowland RRR, Lunney JK, Reecy JM, Dekkers JCM.
698 Genome-wide association and genomic prediction for host response to porcine
699 reproductive and respiratory syndrome virus infection. Genet. Sel. Evol. 2014;46:18.
700 44. Cunnington AJ. The importance of pathogen load. PLoS Pathog. 2015;11:1–2.
701 45. Kause A, Ødegård J. The genetic analysis of tolerance to infections: A review.
702 Front. Genet. 2012;3:1–9.
703 46. Raberg L, Graham AL, Read AF. Decomposing health: tolerance and resistance to
704 parasites in animals. Philos. Trans. R. Soc. B Biol. Sci. 2009;364:37–49.
705 47. Rauw WM, Kanis E, Noordhuizen Stassen EN, Grommers FJ. Undesirable side
706 effects of selection for high production efficiency in farm animals: a review. Livest.
707 Prod. Sci. 1998;56:15.
708 48. Henryon M, Jokumsen A, Berg P, Lund I, Pedersen PB, Olesen NJ, et al. Genetic
709 variation for growth rate, feed conversion efficiency, and disease resistance exists
710 within a farmed population of rainbow trout. Aquaculture. 2002;216:389–90.
711 49. Gjedrem T, Salte R, Gjsen HM. Genetic variation in susceptibility of Atlantic
712 salmon to furunculosis. Aquaculture. 1991;97:1–6.

713 50. Bilodeau-Bourgeois L, Bosworth BG, Peterson BC. Differences in mortality,
714 growth, lysozyme, and Toll-like receptor gene expression among genetic groups of
715 catfish exposed to virulent Edwardsiella ictaluri. Fish Shellfish Immunol. 2008;24:82–9.
716 51. Perez-Sanches J. The involvement of growth hormone in growth regulation, energy
717 homeostais and immune function in the gilthead sea bream (Sparus aurata): a short
718 review. J. Fish Physiol. Biochem. 2000;22:135.
719 52. Dyer AR, Barlow CG, Bransden MP, Carter CG, Glencross BD, Richardson N, et
720 al. Correlation of plasma IGF-I concentrations and growth rate in aquacultured finfish:
721 A tool for assessing the potential of new diets. Aquaculture. 2004;236:583–92.
722 53. Dettleff P, Bravo C, Patel A, Martinez V. Patterns of Piscirickettsia salmonis load in
723 susceptible and resistant families of Salmo salar. Fish Shellfish Immunol. [Internet].
724 Elsevier Ltd; 2015;45:67–71. Available from:
725 http://dx.doi.org/10.1016/j.fsi.2015.03.039
726 54. Macqueen DJ, Primmer CR, Houston RD, Nowak BF, Bernatchez L, Bergseth S, et
727 al. Functional Annotation of All Salmonid Genomes (FAASG): an international
728 initiative supporting future salmonid research , conservation and aquaculture. BMC
729 Genomics. BMC Genomics; 2017;18:1–9.
730 55. Anacleto O, Cabaleiro S, Villanueva B, Saura M, Houston R, Woolliams JA, et al.
731 Genetic differences in host infectivity affect disease spread and survival in epidemics.
732 Nat. Sci. Reports. 2018;
733
734
735
736
737

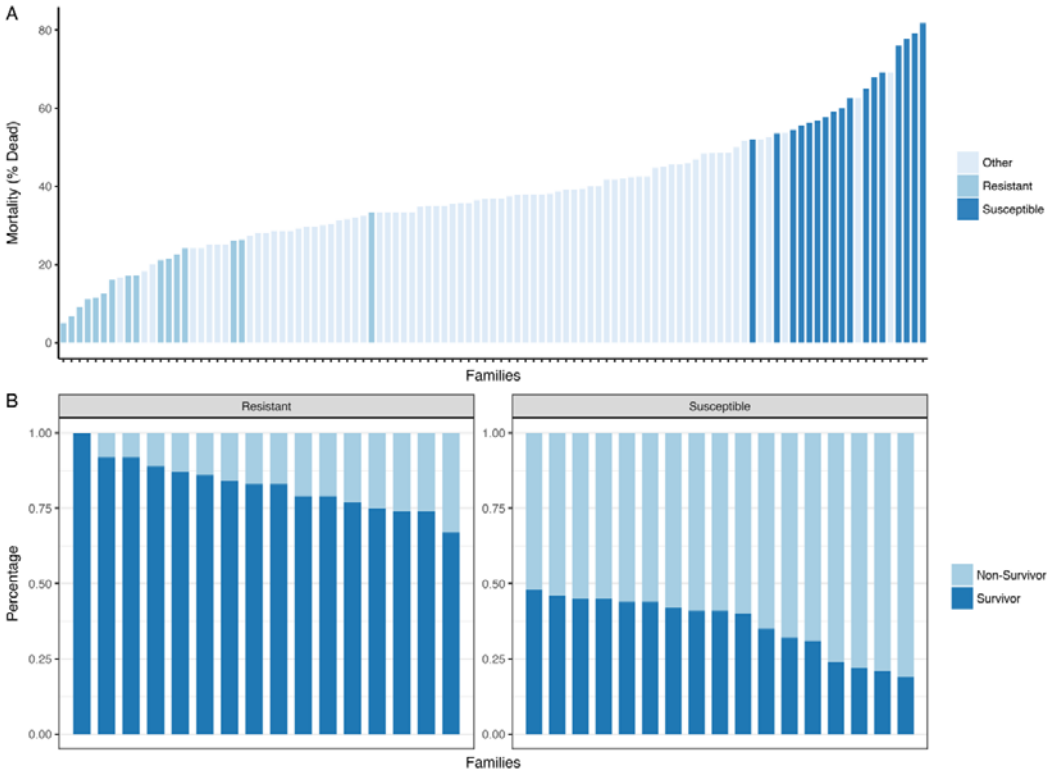

Fig. 1. Observed mortalities for all the 107 coho salmon families challenged with *P. salmonis*. The 16 most resistant and 17 most susceptible families for which bacterial load was quantified are highlighted in light and dark grey, respectively (Fig 1A). Percentage of survivors and non-survivors for each of the 16 most resistant and 17 most susceptible families selected after experimental challenge against *P. salmonis* (Fig. 1B).

Table 1. Summary statistics for average daily gain prior P. salmonis challenge (ADG0), during challenge test (ADGi), harvest weight (HW), log10 of bacterial load (LogBL), day of death (ST) and binary survival (BS) in the coho salmon (Oncorhynchus kisutch) breeding population used in the present study.

Trait	Mean	SD[a]	CV[b] (%)	Min[c]	Max[d]	Number of records
ADG0 (g/day)	1.11	0.56	50.29	0.34	2.62	2605
ADGi (g/day)	0.69	1.65	239.13	-5.85	6.36	2597
HW (Kg)	6.37	1.32	20.72	0.05	7.5	41597
LogBL	1.44	0.51	35.42	0.0	2.36	740
ST	41.56	10.01	24.09	10	50	2606
BS	0.61	0.49	80.33	0.0	1.0	2606

[a] Standard deviation

[b] Coefficient of variation

[c] Minimum

[d] Maximum

Table 2. Summary of the variables used for each mixed models and the significance effect

Trait	Pooled Animals								
	Sex	**Tank**	**MA[a]**	**MW[b]**	**ADG0[c]**	**LogBL[d]**	**BS[e]**	**CG[f]**	**HA[g]**
ADG0	**	NS[k]	-2.2E-02(5.5E-03)**	1.4E-01(1.1E-02)**	NA[l]	NA	NA	NA	NA
ADGi[h]	**	**	3.4E-03(1.0E-02)NS	-2.9E-02(2.8E-02)*	8.8E-02(5.1E-02)**	-7.7E-02(4.5E-02)NS	2.1(5.5E-02)**	NA	NA
HW[i]	NA	NA	-2.1E-02(4.1E-03)**	92.8(7.4)NS	NA	NA	NA	**	1.4E-02(2.8E-03)**
LogBL	**	**	-7.3E-04(5.3E-03)NS	2.1E-02(1.5E-02)*	-3.8E-02(2.7E-02)**	NA	-6.4E-01(3.0E-02)**	NA	NA
ST[j]	**	**	-1.8E-02(4.3E-02)*	NS	2.4(0.2)**	-3.1E-01(1.8E-01)**	15.7(0.2)**	NA	NA
BS	**	*	NS	NS	4.1E-01(5.5E-02)**	-4.4E-01(5.3E-02)**	NA	NA	NA
Trait	**Survivors**								
	Sex	**Tank**	**MA**	**MW**	**ADG0**	**LogBL**	**BS**	**CG**	**HA**
ADG0	**	**	-2.1E-05(6.1E-06)**	1.4E-04(1.3E-05)**	NA[l]	NA	NA	NA	NA
ADGi	**	**	-1.8E-05(2.5E-05)NS	-3.7E-05(6.4E-05)NS	2.2E-01(1.1E-01)*	-3.0E-04(1.3E-04)*	NA	NA	NA
LogBL	NS	**	1.5E-03(7.8E-03)NS	2.6E-02(2.3E-02)NS	-3.2(4.5)NS	NA	NA	NA	NA
Trait	**Non-Survivors**								
	Sex	**Tank**	**MA**	**MW**	**ADG0**	**LogBL**	**BS**	**CG**	**HA**
ADG0	NS	*	-2.6E-05(7.3E-06)**	1.4E-04(1.8E-05)**	NA	NA	NA	NA	NA
ADGi	NS	NS	7.1E-06(1.3E-05)NS	-9.7E-05(4.0E-5)**	-4.4E-01(7.5E-02)**	1.2E-07(9.0E-08)NS	NA	NA	NA
LogBL	NS	NS	-3.4E-03(4.8E-03)NS	1.4E-02(1.3E-02)NS	-5.0(2.7)NS	NA	NA	NA	NA
ST	**	*	-1.5E-02(1.0E-01)NS	-7.9E-01(2.8E-01)NS	5.6(0.5)**	-3.4E-01(3.9E-01)NS	NA	NA	NA

∓ LogBL, ADG0, ADGi, ST and BS were not included into the models for HW as HW was recorded on relatives

[a] Marking age

[b] Marking weight

[c] Average daily gain prior infection

[d] Logarithm of bacterial load

[e] Binary survival

[f] Contemporary group

[g] Harvest age

[h] Average daily gain during infection

[i] Harvest weight

[j] Survival time

[k] Not significant

[l] Not assessed

* $p < 0.05$

** $p < 0.001$

Table 3. Genetic parameters and estimated heritabilities (SE), genetic and phenotypic correlations (below and above diagonal, respectively) for average daily gain prior infection (ADG0), during infection (ADGi), harvest weight (HW), bacterial load (logBL), day of death (ST) and binary survival (BS) for pooled, survivors and non-survivors animals

Trait	Pooled animals								
	GenVar[b]	PhenVar[c]	ResVar[d]	ADG0	ADGi	HW	Log BL	ST	BS
ADG0	0.08 ± 0.02	0.28 ± 0.01	0.20 ± 0.01	**0.30(0.05)***	0.05(0.02)*	0	-0.05(0.04)	0.22(0.02)*	0.10(0.02)*
ADGi	0.11 ± 0.04	1.69 ± 0.05	1.58 ± 0.05	0.40(0.16)*	**0.07(0.02)***	0	-0.11(0.04)*	0.12(0.02)*	0.53(0.01)*
HW	0.23 ± 0.02	0.59 ± 0.01	0.36 ± 0.01	0.64(0.09)*	-0.14(0.20)	**0.38(0.03)***	0	0	0
LogBL	5.19E-03 ± 4.8E-03	0.14 ± 7.32E-03	0.13 ± 7.8E-03	0.09(0.43)	-0.23(0.50)	0.63(0.28)*	**0.04(0.03)**	-0.07(0.04)	-0.50(0.03)*
ST	14.3 ± 3.68	89.2 ± 2.89	74.9 ± 3.01	0.43(0.18)*	0.15(0.28)	-0.50(0.13)*	-0.03(0.57)	**0.16(0.04)***	0.70(0.01)*
BS	0.22 ± 0.51E-01	1.23 ± 0.51E-01	1.00 ± 0.01	0.05(0.19)	0.84(0.07)*	0.23(0.16)	-0.97(0.10)*	0.85(0.09)*	**0.18(0.03)***
Trait	**Survivors**								
	GenVar	PhenVar	ResVar	ADG0	ADGi	HW	LogBL	ST	BS
ADG0	6.91E-08 ± 1.37E-08	2.57E-07 ± 1.31E-08	1.87E-07 ± 1.41E-08	**0.27(0.05)***	0.14(0.03)*	0	-0.01(0.05)	NA[a]	NA
ADGi	2.72E-07 ± 1.38E-07	1.36E-06 ± 1.11E-07	1.10E-06 ± 1.15E-07	0.36(0.16)*	**0.20(0.09)***	0	-0.12(0.05)*	NA	NA
HW	0.35 ± 2.05E-02	0.68 ± 0.11E-02	0.33 ± 0.11E-02	0.63(0.09)*	-0.16(0.19)	**0.52(0.02)***	0	NA	NA
LogBL	1.24E-02 ± 5.75E-03	0.11 ± 4.27E-03	9.41E-02 ± 4.55E-03	0.39(0.60)	0.11(0.77)	0.25(0.32)	**0.12(0.05)***	NA	NA
ST	NA	NA	NA	NA	NA	NA	NA	**NA**	NA
BS	NA	NA	NA	NA	NA	NA	NA	NA	**NA**
Trait	**Non-Survivors**								
	GenVar	PhenVar	ResVar	ADG0	ADGi	HW	LogBL	ST	BS
ADG0	5.82E-08 ± 1.97E-08	2.77E-07 ± 1.63E-08	2.19E-07 ± 1.80E-08	**0.21(0.07)***	-0.27(0.03)*	0	-0.19(0.07)*	0.33(0.03)*	NA
ADGi	2.13E-08 ± 3.62E-08	1.46E-06 ± 6.58E-08	1.44E-06 ± 7.17E-08	-0.50(0.57)	**0.02(0.03)**	0	-0.05(0.07)	0.28(0.03)*	NA
HW	0.35 ± 2.05E-02	0.68 ± 0.11E-02	0.33 ± 0.11E-02	0.58(0.13)*	-0.28(0.37)	**0.52(0.02)***	0	0	NA
LogBL	3.39E-03 ± 2.04E-03	3.11E-02 ± 1.44E-03	2.77E-02 ± 1.59E-03	0.11(0.44)	-0.89(0.56)	-0.36(0.27)	**0.11(0.06)**	-0.11(0.06)	NA
ST	5.98 ± 3.25	70.47 ± 3.27	64.48 ± 3.75	0.64(0.17)*	0.54(0.54)	-0.35(0.20)	-0.09(0.41)	**0.08(0.04)**	NA
BS	NA	NA	NA	NA	NA	NA	NA	NA	**NA**

* $p < 0.05$

[a] Not assessed

[b] Genetic variance

[c] Phenotipic variance

[d] Residual variance