

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

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26 **Abstract**

27 **Background**

28 Breeding for disease resistance has become a highly desirable strategy for mitigating  
29 infectious disease problems in aquaculture. However, knowledge of the genetic  
30 relationship between resistance and other economically important traits, such as growth,  
31 is important to assess prior to including disease resistance into the breeding goal. Our  
32 study assessed the genetic correlations between growth and survival traits in a large  
33 bacterial infection challenge experiment. A population of 2,606 coho salmon  
34 individuals from 107 full-sibling families were challenged with the bacteria  
35 *Piscirickettsia salmonis*. Growth was measured as average daily gain prior (ADG<sub>0</sub>) and  
36 during (ADG<sub>i</sub>) the experimental infection and as harvest weight (HW). Resistance was  
37 measured as Survival time (ST) and binary survival (BS). Furthermore, individual  
38 measures of bacterial load (BL) were assessed as new resistance phenotypes and to  
39 provide an indication of genetic variation in tolerance in salmonid species.

40 **Results**

41 Significant moderate heritabilities were estimated for ADG<sub>0</sub> ( $0.30 \pm 0.05$ ), HW ( $0.38 \pm$   
42  $0.03$ ), and for the survival traits ST ( $0.16 \pm 0.03$ ) and BS ( $0.18 \pm 0.03$ ). In contrast,  
43 heritabilities for ADG<sub>i</sub> and log-transformed BL were low ( $0.07 \pm 0.02$  (significant) and  
44  $0.04 \pm 0.03$ , respectively), although these increased to moderate significant levels ( $0.20$   
45  $\pm 0.09$  and  $0.12 \pm 0.05$ , respectively) when traits were assessed in survivors only.  
46 Significant and favorable genetic correlations were found between ADG<sub>0</sub> and the  
47 growth traits ADG<sub>i</sub> ( $0.40 \pm 0.16$ ) and HW ( $0.64 \pm 0.09$ ), as well as with resistance as ST  
48 ( $0.43 \pm 0.18$ ), indicating that fish with higher genetic growth rate early on and prior to  
49 infection not only tend to maintain their genetic growth advantage until harvest, but also  
50 tend to grow faster and survive longer during infection. Furthermore, no robust

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

## 55 **Conclusions**

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

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

64

## 65 **Background**

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

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

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

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

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

121           The aim of the current study was to provide a better understanding of the genetic  
122 relationship between growth and SRS resistance traits in coho salmon. Specifically, the  
123 objectives were (i) to quantify the level of genetic variation for growth both prior to and  
124 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<sup>3</sup>.

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<sub>50</sub>) 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<sub>50</sub> 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<sup>3</sup>) 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<sub>50</sub> 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 immunofluorescence 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 stored 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



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

208

### 209 **Quantification of bacterial load**

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

221

### 222 **Statistical Analysis**

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

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

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:

$$u = [u'_1 u'_2]' \sim N(0, \mathbf{G}_0 \otimes \mathbf{A})$$

$$c = [c'_2]' \sim N(0, \mathbf{C}_0 \otimes \mathbf{I}_c)$$

$$e = [e'_1 e'_2]' \sim N(0, \mathbf{R}_0 \otimes \mathbf{I}_N)$$

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  $C$  and  $N$ ;  $\otimes$  indicates the

247 direct operator of the products; the matrices  $\mathbf{G}_0$  and  $\mathbf{R}_0$  denote the variances and co-  
248 variances of 2 x 2 additive genetic and residual effects, respectively. Common  
249 environment effect was evaluated for each trait using a single-trait likelihood ratio test  
250 [32]. This effect was significant only for HW ( $P < 0.05$ ), and therefore included in the  
251 bivariate models when HW was analyzed. Thus,  $\mathbf{C}_0$  represents a 1 x 1 scalar of common  
252 environment effect for HW. Given that HW was recorded on a different population of  
253 individuals to the challenge population, environmental covariance was set to zero in the  
254  $\mathbf{R}_0$  matrix. The parameters in the bivariate mixed linear models were estimated using the  
255 restricted maximum likelihood method (REML) implemented in ASREML version 3.0  
256 [33].

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

262

### 263 **Heritability and genetic correlations**

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

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

266 Where, i is either ST, BS LogBL, ADG0, ADGi or HW,  $\sigma_{Ai}^2$  are the additive genetic  
267 variance of matrix  $\mathbf{G}_0$ ,  $\sigma_{Ei}^2$  are the residual variances from the matrix  $\mathbf{R}_0$  and  $\sigma_{Ci}^2$  is the  
268 common environmental effect associated with the full-sib families (only for HW).

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

$$r_{i,j} = \frac{\sigma_{A_i,A_j}}{\sqrt{\sigma_{A_i}^2 + \sigma_{A_j}^2}}$$

271 where,  $\sigma_{A_i,A_j}$  corresponds to the additive genetic variance between the traits evaluated in  
272 the bivariate model,  $\sigma_{A_i}^2$  corresponds to the additive genetic variance of trait  $i$  and  $\sigma_{A_j}^2$   
273 corresponds to the additive genetic variance of trait  $j$ .

274

## 275 **Results**

### 276 **SRS experimental challenge**

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

283 Figure 1A shows the observed mortality from all 107 challenged families,  
284 ranging from 5.0 to 81.8 %, with an average mortality of 38.5 %. The most susceptible /  
285 resistant families selected for bacterial quantification are highlighted, with a mean  
286 mortality of 63 and 17%, respectively. The proportion of survivors and non-survivors  
287 among these 33 extreme families are shown in Figure 1B. Except for one family, all  
288 families contained both survivors and non-survivors, although the percentage of  
289 survivors was considerably higher in the most resistant families (ranging from 67 to 100  
290 % compared to 19 to 48 % in the most susceptible families).

291

### 292 **Phenotypic variation for resistance and growth traits**

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

303 Bacterial load quantification of 740 fish from 33 families showed that 6.5 % (n =  
304 48) of individuals had a *P. salmonis* load below the qRT-PCR detection threshold; these  
305 fish were considered as bacterial-free. All these individuals survived the experimental  
306 challenge and belonged to the resistant families. The bacterial load measured on the  
307 log<sub>10</sub> scale in the other 692 animals ranged from 0.81 to 2.36 with an average load of  
308 1.53 log units (SD = 0.33). From these 692 individuals, 55 % were survivors, while the  
309 rest of the animals died during the experimental challenge. Harvest weight, obtained  
310 from 41,597 commercial fish with linked pedigree to the challenged population, had a  
311 mean of 6.36 kg (ranging from 0.05 to 7.5 kg).

312

### 313 **Comparison of traits measured in survivors and non-survivors**

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

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

324

### 325 **Effect of early growth and bacterial load on growth and survival traits under** 326 **infection**

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

336

### 337 **Heritabilities and genetic correlations**

338 Estimated heritabilities and genetic correlations obtained by including both  
339 survivors and non-survivors in the models, and by analyzing both categories separately,  
340 are presented in Table 3. A significant and moderate heritability was estimated for  
341 growth rate prior to the experimental challenge ( $h^2 = 0.30 \pm 0.05$  in pooled dataset, and  
342 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  $0.07 \pm 0.02$  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 ( $0.38 \pm 0.03$  in pooled dataset).  
347 The survival traits ST and BS were found to be moderately heritable ( $0.16 \pm 0.04$  and  
348  $0.18 \pm 0.03$ , for ST and BS respectively, in the full dataset, although heritability of ST  
349 dropped to  $0.08 \pm 0.04$  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 ( $0.04 \pm 0.03$ ) in the pooled dataset, but  
352 increased to  $0.12 \pm 0.05$  and  $0.11 \pm 0.06$ , 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 ( $0.40 \pm 0.16$ ) and for survivors only ( $0.36 \pm 0.16$ ), 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 ( $0.64 \pm 0.09$   
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 ( $0.43 \pm 0.18$  and  $0.64 \pm$   
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 ( $0.05 \pm 0.19$ ). 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 ( $0.85 \pm 0.09$ ),  
366 ADGi ( $0.84 \pm 0.07$ ) and LogBL ( $-0.97 \pm 0.10$ ), whilst no significant correlation with  
367 HW was found. Surprisingly, a significant unfavorable correlation was found between

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

375

## 376 **Discussion**

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

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

390 We found a moderate significant genetic variation for early growth rate ( $0.30 \pm$   
391  $0.05$ ). Similar heritability values have been reported for growth rate in others salmonid  
392 species, ranging from 0.32 to 0.35 [35,36].



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

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

412           Significant additive genetic variation was estimated for ST and BS. These  
413 estimates are in agreement with previous estimates for the same and other types of  
414 pathogens for salmonid species (for a detailed review see [9]). Furthermore, a moderate  
415 and favorable genetic correlation between early growth and ST was found. These results  
416 corroborate findings indicating that fish with faster growth prior to and during infection  
417 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 ( $0.12 \pm 0.05$ ) and a similar  
435 borderline significant genetic variation in non-survivors ( $0.11 \pm 0.06$ ). 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 ADG<sub>0</sub> or ADG<sub>i</sub> 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 ADG<sub>0</sub>, which was  
478 positive and significantly different from zero when using only susceptible animals.  
479 Furthermore, we found a favorable genetic correlation for ADG<sub>0</sub> with respect to ST and  
480 HW, which indicate a positive relationship between early growth in fresh water  
481 (ADG<sub>0</sub>), 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

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

523

## 524 **Conclusion**

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

537

## 538 **Declarations**

## 539 **Ethics approval and consent to participate**

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

543

544 **Consent for publication**

545 Not applicable

546

547 **Availability of data and materials**

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

550

551 **Competing interests**

552 The authors declare that they have no competing interests

553

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561

562 **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

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571

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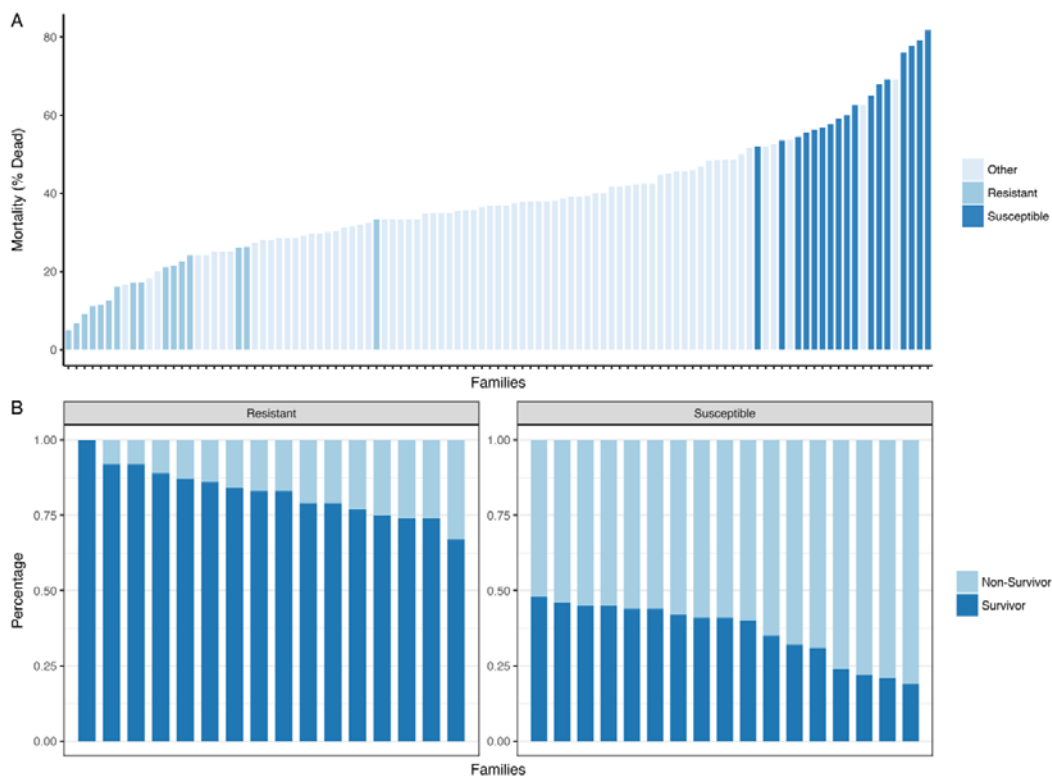
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745 **Fig. 1.** Observed mortalities for all the 107 coho salmon families challenged with *P.*  
746 *salmonis*. The 16 most resistant and 17 most susceptible families for which bacterial  
747 load was quantified are highlighted in light and dark grey, respectively (Fig 1A).  
748 Percentage of survivors and non-survivors for each of the 16 most resistant and 17 most  
749 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 <sup>a</sup>	CV <sup>b</sup> (%)	Min <sup>c</sup>	Max <sup>d</sup>	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

<sup>a</sup> Standard deviation

<sup>b</sup> Coefficient of variation

<sup>c</sup> Minimum

<sup>d</sup> Maximum



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

Trait	Pooled Animals								
	Sex	Tank	MA <sup>a</sup>	MW <sup>b</sup>	ADG0 <sup>c</sup>	LogBL <sup>d</sup>	BS <sup>e</sup>	CG <sup>f</sup>	HA <sup>g</sup>
ADG0	**	NS <sup>k</sup>	-2.2E-02(5.5E-03)**	1.4E-01(1.1E-02)**	NA <sup>l</sup>	NA	NA	NA	NA
ADGi <sup>h</sup>	**	**	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 <sup>i</sup>	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 <sup>j</sup>	**	**	-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 <sup>l</sup>	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

<sup>a</sup> Marking age

<sup>b</sup> Marking weight

<sup>c</sup> Average daily gain prior infection

<sup>d</sup> Logarithm of bacterial load

<sup>e</sup> Binary survival

<sup>f</sup> Contemporary group

<sup>g</sup> Harvest age

<sup>h</sup> Average daily gain during infection

<sup>i</sup> Harvest weight

<sup>j</sup> Survival time

<sup>k</sup> Not significant

<sup>l</sup> 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 <sup>b</sup>	PhenVar <sup>c</sup>	ResVar <sup>d</sup>	ADG0	ADGi	HW	Log BL	ST	BS
ADG0	0.08 ± 0.02	0.28 ± 0.01	0.20 ± 0.01	<b>0.30(0.05)*</b>	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)*	<b>0.07(0.02)*</b>	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)	<b>0.38(0.03)*</b>	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)*	<b>0.04(0.03)</b>	-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)	<b>0.16(0.04)*</b>	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)*	<b>0.18(0.03)*</b>
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	<b>0.27(0.05)*</b>	0.14(0.03)*	0	-0.01(0.05)	NA <sup>a</sup>	NA
ADGi	2.72E-07 ± 1.38E-07	1.36E-06 ± 1.11E-07	1.10E-06 ± 1.15E-07	0.36(0.16)*	<b>0.20(0.09)*</b>	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)	<b>0.52(0.02)*</b>	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)	<b>0.12(0.05)*</b>	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	<b>0.21(0.07)*</b>	-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)	<b>0.02(0.03)</b>	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)	<b>0.52(0.02)*</b>	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)	<b>0.11(0.06)</b>	-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)	<b>0.08(0.04)</b>	NA
BS	NA	NA	NA	NA	NA	NA	NA	NA	NA

\* p < 0.05

<sup>a</sup> Not assessed

<sup>b</sup> Genetic variance

<sup>c</sup> Phenotypic variance

<sup>d</sup> Residual variance