Early survival in Atlantic salmon is associated with parental genotypes at loci linked to timing of maturation

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Abstract

Large effects loci often contain genes with critical developmental functions with potentially broad effects across life-stages. However, the life-stage-specific fitness consequences are rarely explored. In Atlantic salmon, variation in two large-effect loci, *six6* and *vgll3*, is linked to age at maturity, and several physiological and behavioural traits in early life. By genotyping the progeny of wild Atlantic salmon that were planted into natural streams with nutrient manipulations, we tested if genetic variation in these loci is associated with survival in early life. We found that higher early life survival was linked to the genotype associated with late maturation in the *vgll3*, but with early maturation in the *six6* locus. These effects were significant in high-nutrient, but not in in low-nutrient streams. The differences in early survival were not explained by additive genetic effects in the offspring generation, but by maternal genotypes in the *six6* locus, and by both parents' genotypes in the *vgll3* locus. Our results suggest that indirect genetic effects by large-effect loci can be significant determinants of

offspring fitness. This study demonstrates an intriguing case of how large-effect loci can exhibit complex fitness associations across life stages in the wild and indicates that predicting evolutionary dynamics is difficult.

Keywords: age at maturity, indirect genetic effects, parental fitness effect, *vgll3*, *six6*, Atlantic salmon

Introduction

Adaptation in the wild is a complex process, composed of interactions between many mechanisms, such as context-dependency of fitness across time and space. Understanding the genetic architecture of fitness has been one of the key aims of evolutionary quantitative genetics. Classical theory suggests that mutations with large adaptive effects may hinder fine scale adaptation (Orr 2000, 2005). Yet, several quantitative trait loci (QTLs) have been identified to be associated with fitness in natural systems (Bradshaw and Schemske 2003; Colosimo et al. 2005; Johnston et al. 2013; Tishkoff et al. 2007), indicating that adaptive genetic variation via large effect loci can persist. Orr (2000), on the other hand, suggests that genetic correlations between fitness components should be selected against. However, Yeaman and Whitlock (2011) predict that under certain migration-selection scenarios, adaptive loci will be selected for to cluster tightly within a genomic region. As such, adaptive genomic regions with large phenotypic effects may contain multiple loci associated with different fitness components, resulting in high genetic correlations among them. How such genetic architecture is tied to physiological processes remains poorly understood. For example, a genomic region with a large phenotypic effect may be centrally located within cellular and developmental networks, and the genetic variation may in turn be linked to broad changes in body plan and/or physiology (Chan et al. 2010; Colosimo et al. 2005; Jimenez-Gomez et al. 2010; Snoek et al. 2012; Weith et al. 2023). Such broad expression of phenotypes is likely to alter fitness via different pathways, perhaps across different tissues or life stages. Yet, little is known of the fitness landscapes of large effect loci across life stages in the wild. Determining the direction of genetic correlations between fitness components and their potential costs across different environmental conditions is crucial to a better understanding of how genetic variation is maintained in populations, and of evolutionary responses to environmental change.

The Atlantic salmon has been emerging as a promising wild model to explore the multitude of fitness effects associated with large effect loci. Wild salmon populations are adapted to their local environments, so that even those in close proximity and lacking barriers to migration can exhibit genetic and phenotypic differences

(Taylor 1991; Garcia de Leaniz et al. 2007). At the genetic level, two genomic regions, so-called *vgll3* and *six6* (named after the most predominant genes within the loci, *vestigial-like family member 3* and *SIX homeobox 6*, respectively) exhibit substantial signatures of adaptation within and among populations (Barson et al. 2015; Pritchard et al. 2018). These genomic regions harbour genes encoding transcription (co)factors, and are expressed as early as embryonic development (Halperin et al. 2013; Kurko et al. 2020; Lee et al. 2012; Moustakas-Verho et al. 2020). Genetic variation in the *vgll3* underpins key life-history traits in Atlantic salmon, such as the age at maturity in wild individuals (Ayllon et al. 2015; Barson et al. 2015) and in captivity (Asheim et al. 2023), the probability of males becoming precociously mature prior to sea migration (Debes et al. 2021), and iteroparity (Aykanat et al. 2019). *Vgll3* is also associated with physiological and behavioural traits in juvenile fish, such as lipid profiles (House et al. 2021), aggression (Bangura et al. 2022), and (sex-specific) smolt migration (Niemela et al. 2022), suggesting that this single QTL can have broad effects across multiple life stages. In addition, the genetic variation in these loci is associated with metabolic phenotypes, whereby juvenile salmon with the *vgll3* early genotype exhibit a higher maximum metabolic rate and aerobic scope, with the former trait also affected by *six6* loci via epistasis (Prokkola et al. 2022). These genomic regions also show physiological epistasis via the maximal activities of mitochondrial and anaerobic metabolic enzymes in the heart and intestine (Prokkola et al. 2024). Variation in *six6*, in turn, has been associated with stomach content volume during ocean feeding (Aykanat et al. 2020). Similar to *vgll3,* the allele frequencies of the *six6* region are highly correlated with the average age at maturity in wild populations (Barson et al. 2015), and explain variation in age-at-maturity of a domesticated aquaculture strain of Atlantic salmon (Sinclair-Waters et al. 2020), as well as in Pacific salmonids (Waters et al. 2021). Taken together, these studies suggest that genetic variation in these two loci may be linked to differences in resource acquisition and allocation in juvenile salmon, with cascading effects on life-history strategies.

The early life stages of Atlantic salmon are characterized by high rates of mortality, in large part due to intense density-dependent resource competition (Einum et al. 2006; Grossman and Simon 2019). The availability of resources such as food and territorial refuge may strengthen or weaken this competition. The likelihood of an individual surviving to maturation may depend on what resources are available and how capable that individual is at competing for such resources. Considering the associations of *vgll3* and *six6* with resource acquisition and allocation, we predict that these loci interact with variation in stream nutrient levels to predict survival rates of juvenile salmon. However, directional predictions on how freshwater conditions (i.e., nutrient availability) should lead to adaptive differences in the maturation age of Atlantic salmon (i.e., the orientation and strength of selection) are challenging to formulate. For example, favourable growth opportunities and increased freshwater growth could induce early maturation (Salminen 1997), but also reduce the age when salmon

89 juveniles migrate to sea, which imposes an opposite effect on maturation timing (Marschall et al. 1998). Such
90 physiological complexities, coupled with context-dependent adaptive responses, make it difficult to formulate
91 *a priori* predictions on the gene-phenotype relationship in relation to the adaptive significance of maturation
92 timing (Barrett et al. 2009; Reznick 2016).

93 In this study we test whether the *vgll3* and *six6* loci are linked to early life survival in Atlantic salmon. We used
94 data from a field experiment in which fertilized eggs from the same wild-origin families were divided among 10
95 experimental streams, all of which had become increasingly oligotrophic in recent years as a result of land
96 management practices and anthropogenic barriers to the migration of anadromous fish (e.g., Bernthal et al.
97 2022). Five of these streams were given an experimental supplement to restore nutrient that imitates
98 conditions of natural spawning levels prior to the river became inaccessible to migrating salmon (Auer et al.
99 2018). A previous study using the same field system showed that family-level juvenile survival was influenced
100 by this manipulation of stream nutrient availability in addition to family-level maximum metabolic rate and egg
101 mass (Auer et al. 2018). In this current study, we test for associations between juvenile survival and genetic
102 variation in the two life-history loci, *vgll3* and *six6*. More specifically, we first tested whether differences in
103 survival are due to family-wise genetic effects, i.e., associated with family-level allele frequencies of *vgll3* and
104 *six6*, and second, we tested for direct additive effects of the loci, and parental effects, as occurs when the
105 outcome on offspring survival depends on which parent passed on the allele.

106

107 Materials and Methods

108 The full field protocol is described by Auer et al. (2018). In brief, wild adult Atlantic salmon were trapped on
109 their upstream spawning migration as part of fishery management operations in the River Conon catchment in
110 northern Scotland in late autumn 2015 and used to generate 30 full-sib crosses (different parental fish were
111 used for each full-family) by using *in vitro* fertilization. Genotype data were lost for one family, and so 29
112 families were used in all analyses in the present study. All parental fish were selected to be fish that had spent
113 one winter at sea (the most common marine life history phenotype in this catchment, subsequently confirmed
114 by scale reading) to avoid major differences in egg (and hence initial offspring) size, which could affect among-
115 family differences in early life survival. Egg mass was estimated for all families using a subset of eggs. Parents
116 were weighed (to nearest 10 g) and measured for fork length (to nearest 5 mm), and a fin clip was taken for
117 DNA analyses, i.e., for the parental assignment of each of the recaptured offspring (see below). Condition
118 factor was calculated using a modified version of Fulton's condition factor, $CF = 100 \times Weight/(Length)^m$, where

m is the slope coefficient of the linear regression between log(weight) (response variable) and log(length), as the covariate (Bolger and Connolly 1989). This formula corrects for the residual relationship between length (or weight) and condition factor, hence condition factor can be modelled independently from the length of individuals.

Eggs were initially reared as family-specific groups and were overwintered in a local hatchery until the eyed stage of development, when a subsample of eggs from each of the full-sib families were transferred to the aquarium facilities at the University of Glasgow to be reared under standardized conditions. Hatchery mortality of eggs and subsequently of fry in the aquarium was negligible (<5%). Meanwhile, another subsample of 100 eggs from each of the same families were planted at the same density in each of 10 streams (in the same River Conon catchment in which the parent fish had been caught) in February/early March 2016, thus equalling 3,000 eggs per stream. There was no natural spawning of Atlantic salmon in these streams due to the presence of downstream dams that prevented the upstream migration of spawning fish. All ten streams were oligotrophic at the start of the experiment. Half of these streams were then experimentally supplemented with nutrient pellets at the time of egg planting, thereby simulating the decay of parental carcasses (referred to as the high nutrient streams, Auer et al. 2018), whereas nutrient levels in the other five streams were unaltered (referred to as the low nutrient streams). Previous ecological analyses of data from this experiment have shown that these nutrient additions led to significant increases in macroinvertebrate densities, and consequently faster growth of the young salmon (details in Auer et al. 2018; McLennan et al. 2019).

The maximum metabolic rate (MMR) and standard metabolic rate (SMR) of 10 individuals from each family were measured using continuous flow-through respirometry in late June 2016, using the offspring that had been reared under common garden conditions (Auer et al. 2018) following protocols from (Auer et al. 2015). Standardized triple-pass electrofishing surveys were conducted in each of the experimental streams in July 2016, when the fish were approximately three months post-first-feeding (Auer et al. 2018), to calculate-family level rates of growth and survival. A small sample of adipose fin tissue was taken from the recaptured individuals to allow parental (and thus family) assignment (Auer et al. 2018). In the present study, we used these same DNA samples of the parental fish and of the offspring that survived in the streams to genotype individuals at the *vgll3* and *six6* loci, using kompetitive allele specific PCR (KASP) method, as described in Prokkola et al. (2022). Throughout the paper, we refer to the alleles associated with early and late maturation as E and L, respectively. Consequently, EE and LL will be used for fish that are homozygous for E and L alleles and EL for heterozygotes, respectively, for both loci (so that the possible genotypes are $vgll3^{EE}$, $vgll3^{LL}$, $vgll3^{EL}$, and $six6^{EE}$, $six6^{EL}$, $six6^{LL}$). Out of 1246 juveniles that were collected and genotyped, the genotyping success was

150 96.3% and 97.5% for *six6* and *vgll3* genotypes, respectively. Three individuals were scored with improbable
151 genotypes (one for *six6*, and two for *vgll3* loci) which did not conform to the Mendelian expectations based on
152 parental genotypes. The genotype of one of these individuals, which could not be inferred, was excluded, while
153 the genotypes of two individuals were corrected to the genotype value that was invariable within the full-sib
154 family. Across the 58 parents that were used to generate the 29 families, the gene frequencies were
155 unbalanced towards the early genotypes (0.85 and 0.63 for $vgll3^{E}$ and $six6^{E}$, respectively, see Supplementary
156 Table 1), likely due to selecting parents that matured after one year at sea, and of the bias towards fish
157 maturing after one sea winter in this population. In particular, for the *vgll3* locus, there were no $vgll3^{LL}$
158 individuals, and only one family (out of 29) that could generate $vgll3^{LL}$ offspring (i.e., family 9 in Supplementary
159 Table 1).

160 **Family-wise early life survival in relation to life-history genotype**

161 We performed a generalized linear mixed model to quantify survival among full-sib families within the high and
162 low nutrient streams in relation to their genotype. We measured local survival as the number of individuals
163 recaptured from the 100 eggs per family that were planted in each stream. While emigration is possible,
164 juvenile salmon are predominantly sedentary in their first year of life, with limited movement and a high rate
165 of mortality (Saunders and Gee 1964), suggesting that the local recapture rate can be mostly attributable to
166 survival rather than emigration. Models were run using the *glmmTMB* package in R version 4.2.2 (Brooks et al.
167 2022; R Core Team 2021) and fitted using a negative binomial error structure with quadratic parameterization
168 of mean in relation to variance (the *negbin2* family structure in the *glmmTMB* function).

169 The full model structure is as follows:

170 $Y = \mu + SMR_{family} + MMR_{family} + \text{egg mass}_{mother} + vgll3 + six6 + vgll3{:}six6 + \varepsilon_{family} + \varepsilon_{stream} + \varepsilon_{error}$

171 Whereby Y is the number of surviving individuals per family and stream, μ is the intercept, and *vgll3* and *six6*
172 are the family-wise expected genotype frequency in these genomic regions, and *vgll3:six6* indicating the
173 interaction term between *vgll3* and *six6*. In addition, the model included SMR_{family}, MMR_{family}, and egg $mass_{mother}$
174 which are family-wise mean values for maximum metabolic rate (MMR) and standard metabolic rate (SMR),
175 and mean egg mass per mother, respectively. These physiological indices were added as covariates, since Auer
176 et al. (2018) showed that family-wise local survival was positively related to family-wise MMR and egg mass in
177 the low nutrient streams, and marginally positively related to SMR in the high nutrient streams.

178 Family-wise expected genotype frequencies were modelled continuously, and calculated based on parental
179 genotypes and segregation of alleles according to the Mendelian inheritance principles. For example, in a

family where the parents' genotypes are EE (0) and EL (0.5), the family-wise expected genotype frequency is 0.25, with 50% probability of offspring to be EE and 50% probability to be EL (see Supplementary Table 1 for parental genotype information). Family and stream were included in the model as random terms to account for non-independence among individuals of a given family or in each stream.

We performed a semi-automated model evaluation, using the *dredge* function in the *MuMin* package (version 1.47.1, Barton 2022) in R, by which we evaluated all possible fixed effect structures reduced from the full model, and ranked their fit according to the AICc value (a version of Akaike information criterion that corrects for small sample size), in which models within ΔAICc < 2 to the best model considered equally parsimonious. In a few instances, where convergence have not been archived, models were re-run using *glmer.nb* in *lme4* package (version 1.1.27.1, Bates et al. 2015), which provides nearly identical parameter estimates and AICc values. The model fits were checked using the *DHARMa* package (version 0.4.6, Hartig 2022). Marginal means for genotype effects and their confidence intervals were calculated using the *emmeans* package (version, 1.8.5, Lenth 2023), whereby the values of continuous covariates were fixed at the mean value, and the value of the non-focal locus' genotype was fixed at 0.5 (i.e., the EL genotype). We performed separate analyses for low- and high- nutrient streams to avoid overly complex model structures, since those two environments have been shown to have different associations with physiological indices (Auer et al. 2018).

Partitioning additive and parental genetic effects

Given that the genotype effects for both *vgll3* and *six6* were significant in high nutrient streams (see Results below), we then employed individual level analyses to decompose the genetic variation to its additive (direct genetic effects) and parental genetic effects (indirect genetic effects), and further, to assess the contributions of each parent's effects (i.e., maternal vs paternal, or both). Teasing out additive vs. parental genetic effects requires individual level survival data from the offspring, but we obviously did not have the genotype data for the missing (dead or emigrated) progeny. Therefore, the genotype of the missing progeny was inferred in accordance with Mendelian segregation of the parental genotypes, and after accounting for the known genotypes of the recaptured (surviving) individuals. As an example, suppose that for a family with parental *vgll3*^{EE} and *vgll3*^{EL} genotypes, nine offspring out of initial 100 implanted eggs survived in a particular stream, with seven of them being *vgll3*^{EE} and two of them being *vgll3*^{EL} genotype. In this case, and in accordance to Mendelian segregation laws, we can estimate that N=43 and N=48 offspring are missing (dead or emigrated) for the *vgll3*^{EE} and *vgll3*^{EL} genotype groups, respectively. A small subset of recaptured individuals with no genotype data (3.7% and 2.5% of the recaptured individuals for *six6* and *vgll3*, respectively) were randomly imputed a genotype based on Mendelian segregation of parental genotypes. (As an example, in a family with

211 parental *vgll3*^{EE} and *vgll3*^{EL} genotypes, offspring with missing genotypes would be randomly assigned *vgll3*^{EE} or
212 *vgll3*^{EL} genotypes with an equal (50%) probability). The dataset contained 29000 data points (100 offspring per
213 29 family and 10 streams), of which N=1246 consisted of recaptured individuals. The effect of sampling
214 variation, due to both imputing missing genotypes of the recaptured individuals and missing individuals, was
215 accounted for and quantified by resampling the missing genotypes 1000 times, which then re-analysed as
216 described below.

217 We then built and compared the fit of binomial models with different parametrization of parental effects. All
218 these models included family-wise SMR as a covariate (since this was significant in the high nutrient streams in
219 the family-wise model – see Results), and the additive effects of the genotypes, but they differed in the
220 parametrization of the parental effects, whereby each model contained a different combination of parental
221 effects for *six6* and *vgll3* genotypes. As such, the general model structure could be written as follows:

222 $Y = \mu + SMR_{family} + vgll3_{add.} + six6_{add.} + vgll3_{parent/mother/father} + six6_{parent/mother/father} + \varepsilon_{family} + \varepsilon_{stream} + \varepsilon_{error}$

223 whereby, Y is a Boolean response variable for local survival (with missing and recaptured individuals scored as 0
224 and 1, respectively), SMR_{family} is the family-wise mean SMR value, $vgll3_{add.}$ and $six6_{add.}$ are the additive genetic
225 effects, and $vgll3_{parent/mother/father}$ and $six6_{parent/mother/father}$ are different combinations of parental effects
226 associated with *six6* and *vgll3* loci. In total nine different parental genotype combinations were tested in nine
227 models, whereby the parental covariates included in the models are as follows: (1) $vgll3_{parent} + six6_{parent}$, (2)
228 $vgll3_{parent} + six6_{mother}$, (3) $vgll3_{parent} + six6_{father}$, (4) $vgll3_{mother} + six6_{parent}$, (5) $vgll3_{mother} + six6_{mother}$, (6) $vgll3_{mother} +$
229 $six6_{father}$, (7) $vgll3_{father} + six6_{parent}$, (8) $vgll3_{father} + six6_{mother}$, (9) $vgll3_{father} + six6_{father}$. Family and stream were
230 included in the models as random terms. The parental genotype value is the average genotype value of mother
231 and father genotype, e.g., $vgll3_{parent} = (vgll3_{mother} + vgll3_{father}) / 2$, and $six6_{parent} = (six6_{mother} + six6_{father}) / 2$, which
232 quantifies an overall combined parental genotype effect.

233 Genotypes were modelled additively (i.e., EE, EL, and LL alleles were coded as 0, 0.5, and 1, respectively) with
234 no dominance effects for either genotype. The *vgll3* locus is known to have a sex-dependent dominance effect
235 on sea-age at maturity, hence testing dominance in this locus would have provided further insights on the
236 genetic architecture. However, the lack of *vgll3*^{LL} genotypes in the parental fish and suited cross designs, we
237 had one family with *vgll3*^{LL} offspring (Supplementary Table 1), making predicting dominance effect unreliable.
238 The fit of the models containing different combinations of parental genotypes were then compared according
239 to the AICc criteria, in which models within ΔAICc < 2 to the best model were considered equally parsimonious.

240 To account for uncertainty associated with sampling variation of genotype distributions, we also performed
241 random sampling of genotypes, in which genotypes of missing (dead or emigrated) individuals were randomly
242 drawn from expected genotype probabilities, in accordance with Mendelian segregation of the parental
243 genotypes. In this case, we simulated the genotypes of 100 offspring per family/stream (i.e., the initial number
244 of individuals released per family to each stream) and assigned genotypes for missing individuals after
245 excluding the genotypes of recaptured (surviving) individuals from the simulated set. Similar to above, a small
246 subset of recaptured (survived) individuals with no genotype data (3.7% and 2.5% of the recaptured individuals
247 for *six6* and *vgll3*, respectively) were also randomly assigned a genotype based on Mendelian segregation of
248 parental genotypes in each replicate, to prevent any sampling biases. The random data sampling described
249 here was repeated 1000 times.

250

251 Results

252 The observed local survival per family was dependent on genotype in high but not low nutrient streams (see
253 also the observed family-wise data in Supplementary Figure 1). In the low nutrient streams all parsimonious
254 models (models within ΔAICc = 2 of the best model) contained egg mass and MMR as covariates, a result that is
255 consistent with Auer et al. (2018). While the *vgll3* effect was present in the best model, it was insignificant, and
256 the parameter was not present in all parsimonious models (Figure 1, Supplementary Table 2). In the high
257 nutrient streams, all parsimonious models contained *six6* and SMR as covariates. In the best model, a higher
258 SMR (p = 0.018) and $six6^{E}$ allele (p = 0.025) were significantly and positively associated with local survival, while
259 there was a marginal negative association with the $vgll3^{E}$ allele (p = 0.047). Allelic substitution from $vgll3^{E}$ to
260 $vgll3^{L}$ increased the odds of survival 1.67 times (SE = 0.432, p = 0.047), whereby the marginal survival
261 probability associated with $vgll3^{EE}$ was 3.16% (95% CI 2.46 -4.05), compared to 5.28% (95% CI 3.47 – 8.02) for
262 $vgll3^{EL}$ (Figure 1). Allelic substitution effect from $six6^{E}$ to $six6^{L}$ was in opposite direction, decreasing the odds of
263 survival 1.49 times (SE = 0.118, p = 0.025), whereby the marginal survival probability associated with $six6^{EE}$ was
264 7.85% (95% CI 4.94 -12.46), compared to 5.28% (95% CI 3.47 – 8.02) for $six6^{EL}$ (Figure 1). Models were
265 substantially more parsimonious when both genotype and physiological indices (SMR, MMR and egg mass)
266 were included as covariates compared to the models that included only genotypes. However, family-wise SMR,
267 MMR and egg mass were not significantly associated with either genomic region (Supplementary Table 3),
268 suggesting an independent effect of genotypes and physiological traits on local survival rates. Similarly, an
269 epistasis between *vgll3* and *six6* loci was not supported (Supplementary Table 3).

270 For the high nutrient streams, we then used an individual-based, binomial model to partition the significant
271 family-wise genotype effects into additive effects and different combinations of parental genetic effects. A
272 model with only additive genetic terms had substantially lower fit compared to models that additionally
273 parametrized parental genotypes as covariates (Figure 2). Among different combinations of parental genetic
274 effects, the best model included parental *vgll3* and maternal *six6* genetic effects (Figure 2). This model was
275 superior to the second-best model with an AICc differential 2.08 (SE=0.25, Figure 2). An allelic substitution from
276 *vgll3*^{E} to *vgll3*^{L} in parental genotype increased the odds of survival by 1.98 times (SE = 0.60, p = 0.023), whereby
277 the marginal survival probability associated with parental genotype *vgll3*^{EE} was 2.44% (95% CI 1.71 -3.46),
278 compared to 4.72% (95% CI 3.09 – 7.15) for *vgll3*^{EL} (Figure 3, Table 1). Likewise, an allelic substitution from *six6*^{E}
279 to *six6*^{L} associated with maternal genotype decreased the odds of survival by 1.58 times (SE = 0.10, p = 0.003),
280 whereby the marginal survival probability associated with *six6*^{EE} maternal genotype was 7.25% (95% CI 4.69 -
281 11.07), compared to 4.72 % (95% CI 3.09 – 7.15) for *six6*^{EL} (Figure 3). The additive (direct) *E* to *L* allelic
282 substitutions was insignificant both for *vgll3* (p = 0.51) and *six6* loci (p = 0.36, Figure 3, Table 1). The individual-
283 based analyses were robust to sampling variation associated with imputing the missing genotypes of missing
284 individuals, or recaptured individuals that were not successfully genotyped, since similar effect sizes were
285 obtained across 1000 simulated datasets (Supplementary Figure 2). The results were also robust to some
286 families being invariant in *vgll3* and *six6* genotypes, which may result in lower power for quantifying the
287 additive genetic variance compared to the parental genetic effects. As such, when the analyses included only
288 families which harboured genetic variation in these loci (21 and 14 families for *vgll3* and *six6*, respectively, see
289 Supplementary Table 3), the effect sizes and associated *p-values* were similar to those obtained from the full
290 dataset, and parental genetic effect sizes were substantially higher than the additive genetic effects
291 (Supplementary Table 4).

292 In salmonids, the maternal genotype might be more important to offspring survival than the paternal
293 genotype, since mothers also determine the egg size and composition that influences offspring viability
294 (Fleming 1996). To test the if maternal body size drives the association between local survival and the maternal
295 genetic effects (in *six6* locus), maternal body size traits (i.e., length, weight, and condition factor) were added
296 separately to the most parsimonious models explaining the maternal genotype effects on offspring local
297 survival in the high nutrient streams. None of the maternal size traits had a significant effect on survival and did
298 not improve the model fit, with or without the *six6* maternal effects present in the models (Supplementary
299 Table 5). This suggests that maternal size is not driving the association between offspring survival and maternal
300 *six6* genotypes, although it should be noted that variation in maternal size within the sample was constrained
301 as a result of only using females that had spent a single winter at sea. On the other hand, a maternal *six6*

genotype had strong associations with her size and condition (Supplementary Table 6), with the late genotype being associated with larger size and higher body condition. This indicates that a genetic correlation exists between parental size and early offspring survival via *six6*, but the association between *six6* and offspring survival could be mediated by a different process than female body size.

Discussion

Understanding the genetic architecture of adaptation is crucial for predicting how populations respond to changing environmental conditions at contemporary time scales. Major effect loci may alter phenotypes at early life stages (i.e., during development), leading to phenotypic and fitness changes operated via multiple pathways (Colosimo et al. 2005). This study has demonstrated that the loci that are associated with maturation timing in Atlantic salmon can also affect early life survival, but in a manner that interacts with nutrient levels and the availability of food in the streams that they inhabit. Intriguingly, this effect did not operate via additive genetic effects associated with offspring own genotype, but via a maternal effect in *six6* loci, and via parental effects in *vgll3*. The results suggest that the offspring of parents carrying the *vgll3* late-maturation genotype and of mothers carrying the *six6* early-maturation genotype will benefit from higher survival, regardless of the inherited alleles. Such indirect genetic effects add further complexity to evolutionary dynamics compared to simple Mendelian inheritance (Bonduriansky and Day 2009; Wolf et al. 1998), but have been little studied in wild populations.

Salmon are well known for exhibiting plasticity in life history traits, particularly in response to environmental conditions that influence growth rates (Mobley et al. 2021; Sloat et al. 2014). Age at maturity is an important life history trait that can influence fitness and that has a genetic as well as an environmental component, likely maintained in the population via balancing selection (Barson et al. 2015). Our results suggest that the viability selection acting on *vgll3* and *six6* loci in early juvenile stages of salmon will likely alter the age-structure, hence the dynamics of the evolutionary response in the population. However, the response has a plastic component and operates in environments with higher nutrient levels. As such, the rate of evolutionary response in age at maturity may be attributed, in part, to ecological processes operating very early in life. However, the effects of the freshwater environment on variation in age at maturity are poorly understood, limiting the scope for *a priori* predictions of the effect of these life-history loci on early survival (see also the Introduction). Similarly, while our results indicate that a genetic correlation exists between early- and late-life fitness components, it does not reveal the possible physiological basis or how the observed correlation between fitness components

332 contributes to the complexity of adaptation (Orr 2000). For example, it is unclear if the direction of selection
333 associated with early- and late-life fitness components is aligned (i.e., synergistic pleiotropy) or inflicts a cost to
334 the life-history adaptations (i.e., constraining selection via trade-offs, Orr 2000; Rennison and Peichel 2022;
335 Thorholludottir et al. 2023). A recent study showed that a rapid evolutionary response towards earlier
336 maturation (i.e., younger age structure) in the *vgll3* locus was partly driven by the abundance of prey species
337 once the salmon reach the ocean (Czorlich et al. 2022). However, our results in the high nutrient streams
338 suggest that selection in earlier life stages favours the opposite *vgll3* allele (i.e., late). One might then predict a
339 larger evolutionary cost to age-at-maturity evolution at the *vgll3* loci, i.e., via a slower evolutionary response to
340 a changing environment (and a larger genetic load to the population, Orr 2000). However, we found that the
341 genetic effects on survival was dependent on nutrient levels, and therefore the potential for correlated
342 selection with age at maturity is context dependent, suggesting that the cost of any correlation between fitness
343 components might be population/condition dependent. Finally, the survival effects associated with *six6* and
344 *vgll3* loci are in opposite directions to each other with respect to their effect on maturation timing: while the
345 *vgll3*^{L} allele (the allele linked to later age at maturity) appears to be associated with higher offspring survival, it
346 is the early maturation allele (*six6*^{E}) that positively influences offspring survival in the *six6* region, which
347 necessitates that variation in both loci is accounted for when formulating predictions. Put together, our results
348 highlight the complexity related to predicting the evolutionary dynamics of maturation age in Atlantic salmon,
349 and potentially in other taxa where indirect genetic effects have been found (e.g., Bonduriansky and Day 2009;
350 Tomar and Teperino 2020, Wolf et al. 1998). The observed genetic correlation, however, suggests that a
351 physiological, mechanistic link exists between genetic polymorphisms in the life-history loci and early survival.

352 The indirect genetic effect on viability selection via parental genotypes might have theoretical implications for
353 evolutionary processes (e.g., Bonduriansky and Day 2009; Rausher 1992; Räsänen and Kruuk 2007). In the
354 classical sense, parental effects are a component of phenotypic plasticity, in which the parental environment
355 influence the offspring phenotype, through developmental reprogramming (Kappeler and Meaney 2010). As
356 such, indirect genetic effects via parental genetic variation help to maintain genetic diversity i.e., by reducing the
357 narrow sense heritability by increasing environmental variance, and provide a means for transmission of acquired
358 traits between generations (Bonduriansky and Day 2009; Wolf et al. 1998). However, in our context, the indirect
359 genetic effects of parents are also correlated with the offspring's future life-history and thereby with the fitness of
360 the offspring via the direct effect of genotypes on age at maturity (Wolf et al. 1998). Therefore, selection on
361 offspring survival would alter the phenotypic variation of life-history traits, resulting in deviating from the optimal
362 trait variation maintained under balancing selection (Turelli and Barton 2004), though this prediction is based on
363 a relatively limited range of genotypes (since the *vgll3*^{LL} genotypes was completely absent in the dataset) and

364 phenotypes (since all parents were 1SW fish). Theoretical predictions accounting for such a complexity have not
365 been explored explicitly (e.g., Oomen et al. 2020).

366 Our results highlight that the effect of viability selection on these genomic regions is dependent on the
367 environment, as it appears to only operate under conditions of high nutrient availability. Both loci are linked to
368 a number of different physiological and behavioural traits that mediate energy homeostasis (Mobley et al.
369 2021). However, we did not find a direct link between these genomic regions and SMR or MMR (measured at
370 the family level), thereby suggesting that metabolic rates are not underlying mechanisms for mediating the
371 effects of *vgll3*/*six6* loci on early survival. Earlier studies have shown a broad range of effects on physiological
372 and behavioural traits linked to genetic variation in *vgll3* locus, such as MMR (Prokkola et al. 2022), lipid
373 profiles (House et al. 2021), and aggressive behaviour (Bangura et al. 2022), and that the *six6* genomic region
374 can be broadly expressed during embryonic developmental (Moustakas-Verho et al. 2020). The effect of these
375 on fitness is likely to be context-dependent, supporting our conclusions, although the exact mechanisms are
376 yet to be elucidated. In our study, the genotype dependent selection operating under a more favourable
377 environment (high nutrient) may seem counterintuitive. However, the higher relative fitness (of different
378 genotypes) in a less stressful environment is not only theoretically possible, but an earlier meta-analysis
379 indicated no overall differences in relative fitness under more stressful conditions (Arbuthnott and Whitlock,
380 2018). Furthermore, there were no differences in absolute fitness between low- and high-nutrient conditions,
381 despite substantial differences in juvenile growth rates and different metabolic processes shaping the fitness
382 landscape (Auer et al. 2018), and different impacts of habitat features on the rate of senescence in the fish
383 (McLennan et al. 2021). These suggests a complex landscape is likely underlying the fitness dynamics across
384 environment.

385 The higher local survival of juvenile fish with the early maturation genotype at the *six6* locus was explained
386 solely by the maternal genotype. Indirect genetic effects associated with the maternal environment (i.e.,
387 maternal effects) are commonly observed in salmonids and in other organisms (e.g., Aykanat et al. 2012; Heath
388 et al. 1999; Mousseau and Fox 1998). However, because salmonids lack parental provisioning, these effects are
389 mostly limited to egg size and/or composition, which in turn can be influenced by the size of the mother
390 (Munoz et al. 2014). A significant trait-genotype association (i.e., between $six6_{mother}$ and offspring survival /
391 mother size) despite that the mother's size was constrained (due to using only females that spent a single
392 winter at sea), suggests a robust inference can be drawn to test for a potential effect of an intermediate
393 phenotype (egg mass) mediating the relation. Our results showed that in the high nutrient streams, family-level
394 egg mass was neither correlated with survival (Supplementary Table 3), nor with variation in the $six6_{mother}$

395 (Supplementary Table 2), thereby ruling out a genetic effect of egg mass on survival via *six6*$_{mother}$ (within the
396 constrained size range of mothers). Similarly, we found that maternal size did not explain the correlation
397 between *six6*$_{mother}$ and the survival of her offspring, despite the observed correlation between maternal size
398 and *six6*$_{mother}$ (Supplementary Table 6).

399 A plausible mechanism explaining our results is that that variation in *six6* alters early life survival via changes in
400 egg composition. In oviparous species, the composition of eggs, such as hormone levels, albumin and fat
401 content, may mediate the phenotype and behaviour of the offspring, and subsequently their fitness (Thorn and
402 Morbey 2019; Widowski et al. 2022; Williams 1994). In Chinook salmon, carotenoid composition in the eggs has
403 been shown to be associated with early life survival (Tyndale et al. 2008). Therefore, despite the apparent
404 absence of a link between the *six6* region and family-level egg mass, we cannot rule out potential effects on
405 offspring survival via changes in egg composition. Future studies could test such a hypothesis in a common
406 garden cross design, by quantifying potential markers associated with egg composition, and their effect on the
407 survival of their full sibs. Alternatively, but less parsimoniously, epigenetic mechanisms may be associated with
408 a mothers' *six6* genotype, whereby the maternal *six6* locus controls the epigenetic signature of the offspring
409 genome and thus influences early life developmental pathways (see, Lawson et al. 2013; Venney et al. 2021;
410 Wolf and Wade 2009). *Six6* and other candidate genes located in the same genomic region (i.e., *six1* and *six4*)
411 are known transcription factors, and *six6* expression has been documented in Atlantic salmon in early
412 development (Moustakas-Verho et al. 2020). It is therefore plausible that a mother's *six6* genotype may play a
413 role in the regulation of her offspring's genome.

414 The effect of a parent's *vgll3* genotype on offspring early life survival was not solely limited to the maternal
415 contribution. In salmonids, and generally in fishes, the lack of parental provisioning rules out social
416 environment such as behavioural variation as a potential basis of indirect genetic effects (e.g., Bailey et al.
417 2018, Bonduriansky and Day 2009). A plausible mechanism that is consistent with the observed results is that
418 the genomes inherited from parents are already modified via epigenetic mechanisms, such as via DNA
419 methylation (Bonduriansky and Day 2009; Kappeler and Meaney 2010; Lawson et al. 2013). Epigenetic
420 regulation is known to alter phenotypic variation in natural populations, but the underlying genetic
421 mechanisms and evolutionary predictions are still unclear (Husby 2022). In salmonids, epigenetic effects via
422 DNA methylation have been documented, for example, between hatchery and wild origin fish associated with
423 both parents of origin, with implications for evolutionary genetics and conservation efforts (Koch et al. 2022; Le
424 Luyer et al. 2017; Smith and Kornfield 2002). Our results are consistent with a hypothesis whereby variation in
425 epigenetic signals (associated with genetic variation in the *vgll3* locus) could result in differences in gene

426 expression during early development, subsequently altering offspring survival in the natural settings. Such a
427 hypothesis may be tested by designing cross-breeding experiments, where offspring epigenetic signals, such as
428 genome wide methylation patterns, could be examined among crosses from parents with different *vgll3*
429 genotypes, and in relation to offspring phenotype and survival (i.e., Bossdorf et al. 2008). Alternatively, histone
430 modification is another plausible mechanism that might generate parental genotype-specific modification of
431 chromatin structure, and subsequent survival differences between families (Koch et al. 2022).

432 Even though we have shown that the same genomic regions can account for variance in different fitness
433 components, it is unclear whether covariation between fitness components is causally linked to a single genetic
434 mutation (true pleiotropy), or takes place as a result of physically linked loci acting on different fitness
435 components. While molecular evidence suggests that both *vgll3* and *six6* regulate multiple functions across
436 multiple life stages (Mobley et al. 2021), implying pleiotropy, genetic linkage within the genomic regions cannot
437 be ruled out. There is accumulating evidence to suggest that co-adapted gene complexes are common in wild
438 species (Li et al. 2022; Matschiner et al. 2022; Thompson and Jiggins 2014). Moreover, theoretical models have
439 predicted the evolution of genetic architecture with fewer, larger, and more tightly linked divergent alleles in
440 species that exhibits marked local adaptation between migratory populations (Yeaman and Whitlock 2011). In
441 keeping with this model, Atlantic salmon exhibit local adaptation across closely situated populations with both
442 *six6* and *vgll3* genomic regions harbouring substantial signals of divergence, even between adjacent
443 populations (e.g., Barson et al. 2015; Pritchard et al. 2018). Therefore, it is plausible that the genetic
444 correlations of fitness components via the *six6* and *vgll3* genomic regions might be explained by independent
445 loci with tight linkage within these genomic regions. Such genetic architecture may be instrumental in
446 maintaining the genetic variation and local adaptation of populations amidst high gene flow, although explicit
447 mathematical models and empirical tests of this hypothesis is still lacking.

448 Our study re-purposed a dataset from Auer et al. (2018) in order to test the effect of life history genomic
449 regions on early life survival. While such approaches provide a substantial savings in resources, they come with
450 unavoidable drawbacks. In particular, we could not explicitly test for dominance effects in the *vgll3* locus,
451 which exhibits a (sex-dependent) dominance architecture associated with the age-at-maturity genotype
452 (Barson et al. 2015). This is because the genotypes in the parental fish were either $vgll3^{EE}$ or $vgll3^{EL}$, and only
453 one family (out of 29) had a parental genotype combination that would generate $vgll3^{LL}$ offspring (i.e., both
454 parents heterozygous for *vgll3*), making inferences about dominance confounded with the additive effect, and
455 thus unreliable. For *six6*, we did not have a priori belief that dominance should explain the trait value, and it
456 was not considered in the main framework. However, modelling dominance in the *six6* locus did not improve

457 the model fit ($AICc_{dominance} – AICc_{additive}$ = 2.00), and the *six6* effect was still insignificant, as it is when modelled
458 additively.

459 In this study, we provide a unique example from a natural setting of how indirect genetic effects from large-
460 effect loci influencing adult age at maturity and adaptive divergence shape the early-life survival of offspring.
461 Indirect genetic effects are common across organisms and can alter phenotypic variation and evolutionary
462 trajectories, but most empirical evidence is based on transmission of behavioural traits in higher organisms, or
463 has explored typical maternal effects (Wolf et al. 1998; Bonduriansky and Day 2009). The complex genetic
464 architecture of large effect loci that comprise indirect genetic effects between parents and offspring revealed
465 by this study highlights the challenges associated with predicting evolutionary dynamics in a changing world.
466 Little is known of the fitness landscapes of large effect loci across life stages in the wild, and the generality of
467 our results across different Atlantic salmon populations and taxa needs further work. Our study also calls for a
468 better understanding of the mechanisms, ecological role and evolutionary consequences of indirect genetic
469 effects.

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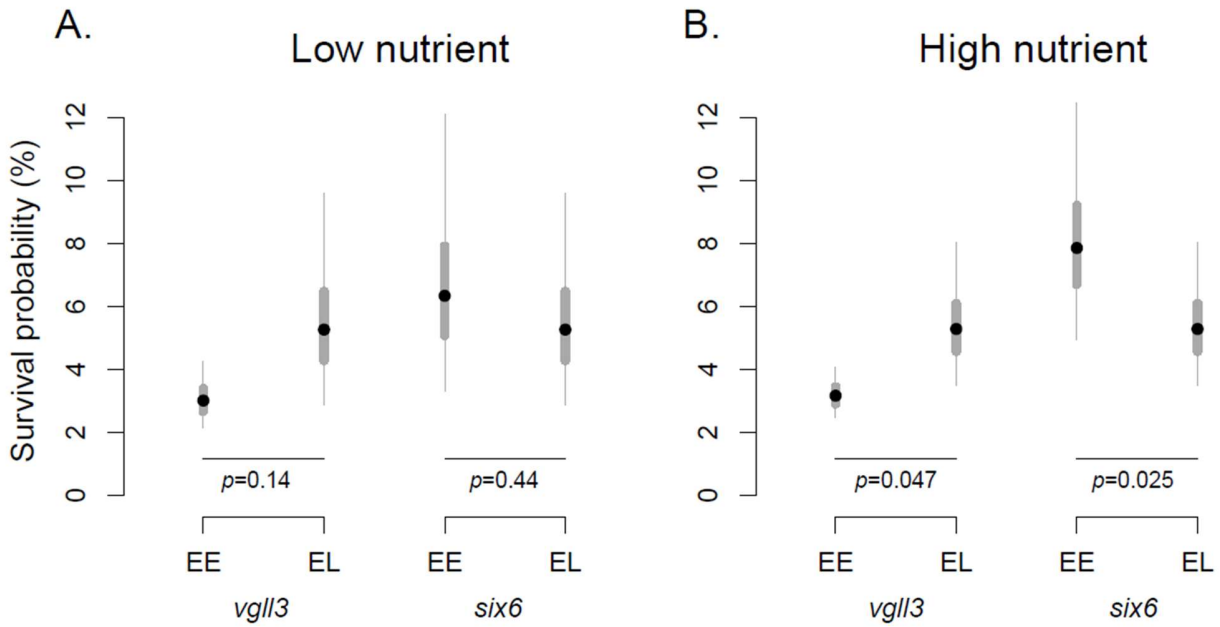
795 Table

796 **Table 1:** Estimated coefficients (fixed effects) and variance (random effects) for individual based binomial
797 model with local survival as the response variable. The coefficients are from the best-fitted model across
798 different parametrization of the parental genetic effects in the high nutrient environment.

Fixed effects	Estimate	Std. Error	*z* value	*p* value
(Intercept)	-5.959	1.156	-5.154	<0.0001
Family SMR	16.142	6.945	2.324	0.0201
vgll3 additive	-0.141	0.213	-0.662	0.5080
six6 additive	0.145	0.159	0.911	0.3625
vgll3 parental	1.368	0.602	2.274	0.0230
six6 maternal	-0.914	0.305	-3.002	0.0027
Random effects	Variance			
Family origin	0.1543			
Stream	0.0047			

799

800 Figures



801

802 **Figure 1:** Marginal means for probability of survival of offspring in relation to family-wise *vgll3* and *six6*
803 genotypes for (a) low, and (b) high nutrient streams. Data are plotted for the homozygote early (EE) and
804 heterozygote (EL) genotypes (no homozygote-LL families were present for either locus). The estimated values
805 are from the most parsimonious models including both *vgll3* and *six6* effects, which is the best fitting model for
806 the high nutrient streams and the fourth best model for the low nutrient streams (see Materials and Methods
807 and Supplementary Table 2 for details). Thin and thick grey bars indicate 50% and 95% confidence intervals,
808 respectively.

809

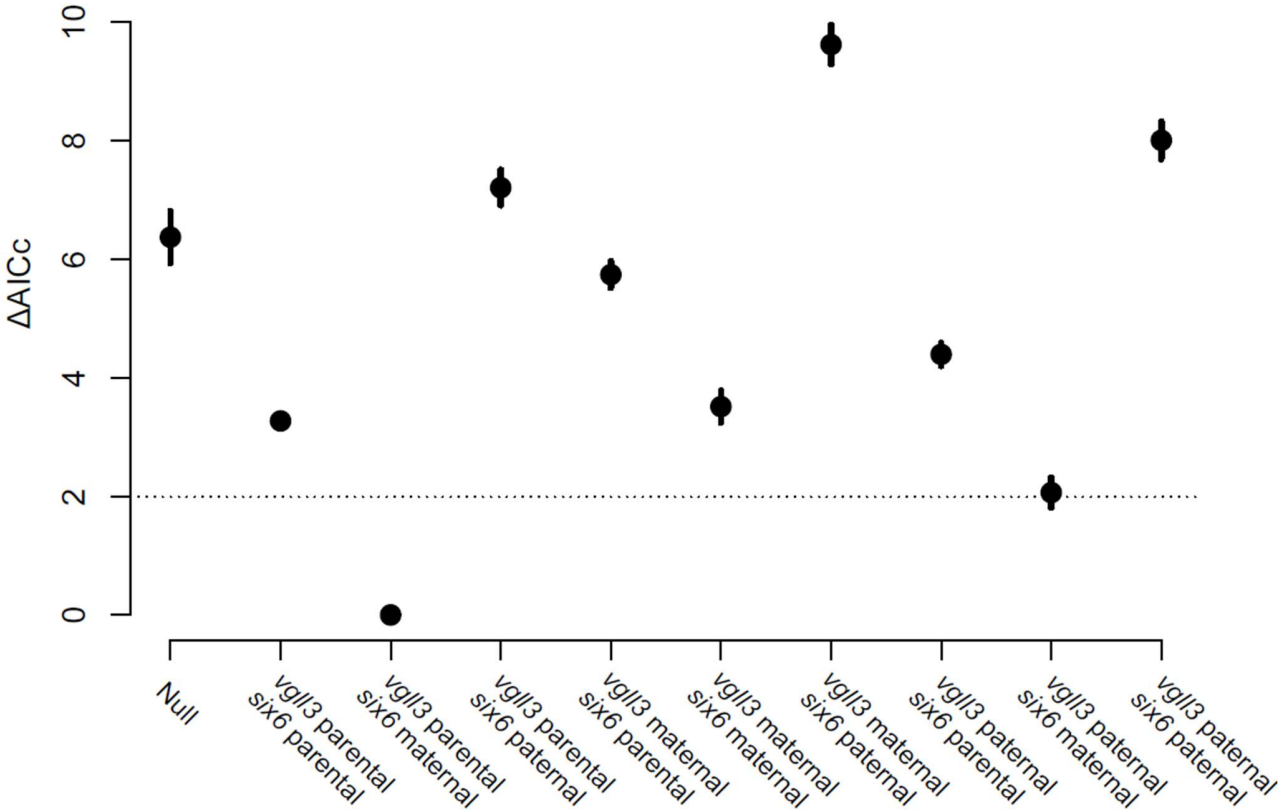


Figure 2: The likelihood differences among individual-based models with different parameterization of the parental genetic effects explaining survival in the high nutrient environment. ΔAICc = 0 indicates the best fitted model. All models contained SMR and additive *vgll3* and *six6* genetic effects as covariates. Y-axis indicates the ΔAICc to the best model, and the dashed line indicates ΔAIC = 2. Error bars represents one standard error of ΔAICc across 1000 models using 1000 data that simulated the genotypes of dead/emigrated individuals (see Materials and Methods for details).

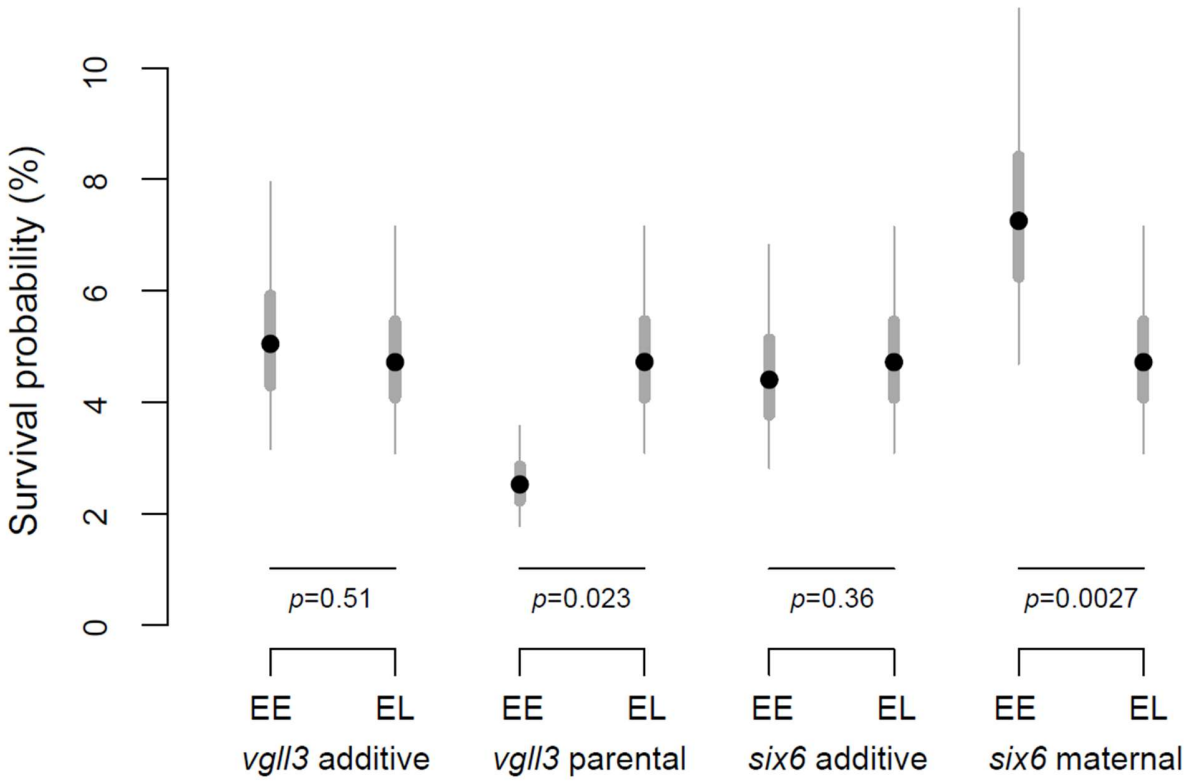


Figure 3: Genetic effects on marginal offspring survival probability for the best-fitted parental genetic structure model in the high nutrient streams. Thin and thick grey bars indicate 50% and 95% confidence intervals, respectively. Data are plotted for the homozygote early (EE) and heterozygote (EL) genotypes (no homozygous-LL families were present for either locus).