Large single-locus effects for maturation timing are mediated via body condition in Atlantic salmon

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Abstract

Maturation timing is a pivotal life-history trait balancing probabilities between mortality and reproduction. Environmental vs. genetic contributions to traits associated with maturation initiation, such as growth and body condition, remain uncertain because of difficulties in determining causality. In Atlantic salmon, maturation timing associates with a large-effect locus around *vgll3*, but how this locus affects maturation remains unknown. We combined controlled breeding with common-garden experimentation at two temperatures and show that *vgll3* effects on maturation of males express primarily via body condition, which we demonstrate in the males' non-maturing female relatives, thus avoiding reverse causality. Between homozygous *vgll3* genotypes, maturation probability differed several folds and female condition differed 2% in both temperature environments. *Vgll3* effects explained 25 and 16% of maturation probability heritability and 15 and 6% of female condition heritability, in the warm and cold environment, respectively. Non-significant *vgll3* effects on female length were antagonistic to those on condition but of equal proportional size. When controlling for *vgll3* effects, genetic correlations changed antagonistically between both maturation and condition vs. growth, suggesting *vgll3* as a resource-allocation locus. The results support large *vgll3* maturation effects being mediated via environmentally stable body condition effects, enabling rapid co-evolution between the life-history traits.

Introduction

Sexual maturation is a central life-history trait that contributes to maximizing individual survival and reproductive success and, thereby, per *capita* population growth rate (Stearns 1992; Roff 2002; Wells et al. 2017). Maturation initiation is assumed to be genetically and environmentally controlled via factors including growth or size and body condition (Stearns 1992; Roff 2002; Taranger et al. 2010; Wells et al. 2017; Andersson et al. 2018), which may signal current energy status (Danielsen et al. 2013; Dupont et al. 2014). However, disentangling cause and effect is a major challenge in studies on maturation and associated traits (Kause et al. 2003; Cousminer et al. 2013; Bell et al. 2018). For example, as opposed to growth controlling maturation, ongoing maturation can temporally boost growth, such as the human puberty growth spurt. Likewise, the maturation process can reduce somatic growth by competing with resources and lower condition by depleting reserves, or affect both growth and condition via appetite (Stearns and Koella 1986; Taranger et al. 2010; Andersson et al. 2018). Related to this problem, fundamental evolutionary knowledge on presence and relative importance of genetic vs. environmental contributions to maturation timing and their link to maturation component traits, such as growth or condition, remains limited (Gjedrem and Baranski 2005; Law 2007; Dunlop et al. 2009; Enberg et al. 2012).

Contrary to the assumption that life-history traits are comprised of several underlying component traits with polygenic architecture (Lande 1982; Roff 2002), each coded by many loci with small effect on phenotypic variation (Lynch and Walsh 1998; Hill 2010), maturation timing in Atlantic salmon (*Salmo salar*) associates with a locus explaining a large proportion of phenotypic variation (33-39%; Ayllon et al. 2015; Barson et al. 2015). This finding bears implications on evolutionary predictions because the

51 expected selection response differs depending on whether a trait is governed by only small- or also
52 large-effect loci (Roff 2002; Kuparinen and Hutchings 2017). For example, initial allele frequencies for
53 the latter, but not the former, may govern evolutionary responses (Kardos and Luikart 2019). The large-
54 effect locus also offers outstanding opportunities for understanding the role of age-specific body size
55 and condition and for quantifying the relative importance of genetic vs. environmental contributions of
56 these traits to maturation timing. The large-effect locus positions close to a transcriptional co-factor
57 gene (*vgll3*), hypothesized as a strong candidate gene (Ayllon et al. 2015; Barson et al. 2015). Known
58 functions of Vgll3, such as inhibition of adipocyte differentiation in cell lines in favor of somatic growth
59 processes and its negative transcriptional correlation with body mass and fat content in mice (Halperin
60 et al. 2013), suggest a mechanistic link of *vgll3* with maturation via control of resource allocation
61 between energy reserves and somatic growth. Genetic markers in the genome region around *vgll3* have
62 also been associated with salmon length (Barson et al. 2015), and human maturation and growth
63 (Cousminer et al. 2013), body condition (Nakayama et al. 2017), or condition change during maturation
64 (Tu et al. 2015), fostering the idea that the link between this locus and maturation, somatic growth, and
65 condition underlies a common functional phenotype. However, a comprehensive joint assessment of
66 independent *vgll3* effects on maturation, growth, and condition, which also requires that the latter two
67 traits are estimated free of maturation-induced changes, is still missing.

68 In Atlantic salmon, sexual maturation studies have a long history (Meerburg 1986; Marschall et al. 1998;
69 Andersson et al. 2018) and this species offers features allowing for a joint assessment of maturation,
70 growth, and condition, thus enabling independent assessment of their links with *vgll3*. Specifically,
71 readily available pedigreed hatchery populations allow for planned breeding of highly fecund

72 individuals. Many offspring with tightly connected pedigrees combined with common garden
73 experimentation followed by quantitative genetic analyses enable i) dissection of genetic from
74 environmental effects, ii) estimation of genetic correlations between environments or iii) estimation of
75 genetic, environmental, and phenotypic correlations between traits. Perhaps the biggest advantage,
76 however, is the observation that Atlantic salmon males, but usually not females, can mature during their
77 first year (Marschall et al. 1998). This provides opportunities to estimate environmental and genetic
78 contributions, including those of *vgll3*, to maturation in males and to growth and condition in non-
79 maturing females. By genetically relating male maturation to maturation-component traits of their
80 female relatives, it is possible to infer the presence and relative importance of genetic vs. environmental
81 components of maturation timing and its maturation-unbiased component traits.

82 Here, we implemented a quantitative genetic breeding design for 42 pedigreed Atlantic salmon parents
83 with known homozygous *vgll3* genotypes and studied >5,000 male and female offspring from 41 families
84 with all *vgll3* genotypes (**figure 1A, B**). The study of these families in a common-garden environment
85 enabled general estimates of genetic vs. environmental contributions for maturation timing of first-year
86 Atlantic salmon and its component traits in conjunction with an assessment of specific *vgll3* effects on
87 maturation, growth, and condition. Further, we evaluated whether a known association of the *vgll3*
88 locus with maturation (co)expresses via growth, condition, or both. We did so by testing whether male
89 maturation probability correlates genetically with maturation-unbiased female somatic growth or body
90 condition (or with both) and by quantifying the *vgll3* contribution to the genetic between trait
91 correlation between sexes. By replicating all families in two environments with a life-time 2 °C water-
92 temperature difference across a seasonal temperature curve (a likely global-warming scenario (IPCC

93 2014); **figure 1C, D**), we were also able to assess environmental effects and their influences of wide

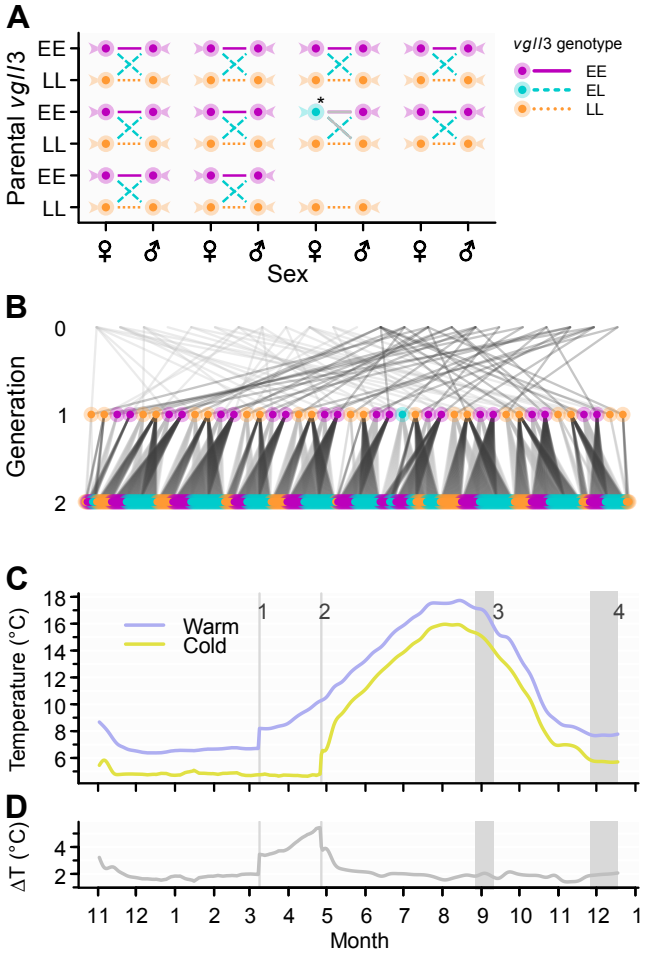
94 relevance to our estimates. We show that large *vgll3* effects on maturation timing are mediated via

95 large *vgll3* effects on body condition and that allele specific phenotypic effects are environmentally

96 stable, although the relative contributions to the phenotypic variance differ with water temperature.

97 Combined, our results also suggest *vgll3* as a candidate locus for controlling the resource allocation

98 trade-off between energy reserves and somatic growth.



99

100 **Figure 1:** Breeding design for *vgll3*, pedigree, and water temperatures during the experiment.

101 (**A**) Realized breeding design with anticipated 2x2 factorial for 24 *vgll3* homozygous dams by 24 *vgll3* homozygous

102 sires that was successful for nine factorials. One factorial curtailed because of low egg survival, whereas one dam

103 (marked by asterisk) was determined to be *vgll3* heterozygous upon confirmatory genotyping after spawning. (**B**)

Pedigree depicting relationships among studied salmon (generation 2; N = 5,145; only every 10th individual plotted to facilitate viewing) via parents (generation 1; N = 42) up to their grandparents (generation 0; N = 23). Upward links to dams and sires in the pedigree are colored in light and dark gray, respectively. *Vgll3* genotypes for created families (lines, **A**) and breeders (fish shapes, **A**), or in generations 1 and 2 (circles, **B**), are depicted corresponding to the legend next to **A**. (**C**) Average temperature across eight tanks in the warm or cold temperature environments. Experimental events are indicated by light gray vertical lines with 1: transfer from egg incubators (N = 2) to tanks (N = 8) and first feeding in the warm environment; 2: transfer from egg incubators (N = 2) to tanks (N = 8) and first feeding in the cold environment; 3: phenotyping of length and condition as used in analyses described in the manuscript; 4: maturation status and sex confirmation assessments. (**D**) Average temperature differences between the warm and cold temperature environments resulting from **C.**

Methods

Fish population, breeding and experimental design, data collection

The experimental cohort was parented by pedigreed hatchery fish maintained by the Natural Resources Institute Finland (Laukaa, Finland). The hatchery-stock ancestors originated from the River Neva, Russia, which drains into the Baltic Sea. In November 2017, we crossed 48 parents with known *vgll3* genotype as 12 2x2 factorials of unrelated *vgll3* homozygous individuals; each factorial yielded four reciprocal *vgll3* offspring genotypes (EE, EL, LE, LL; details on realized design and resulting pedigree in **figure 1A, B**). We reared the experimental cohort in two recirculation systems controlled for water temperature, oxygen, dissolved nitrate components, and natural light cycle, which affect growth or sexual maturation timing (Taranger et al. 2010; Andersson et al. 2018). We split each family by randomizing ~400 eggs across four egg-incubator replicates in two water temperatures (kept in darkness). At first feeding, we randomized an equal number of individuals from each incubator into eight similar tank replicates for each temperature (due to differential egg mortality: mean = 5, range: 1-7, total per family across 16 tanks: mean = 155, range: 21-234). Due to mortality, removal of sick individuals, unknown genotype or

128 sex, culling of random individuals to reduce densities, and removal of individuals with mismatch
129 between genotypic and phenotypic sex (see below), an average of 125 individuals (range: 11-199) per
130 family existed for analysis. Water temperatures in egg incubators and tanks followed a seasonal cycle
131 with a 2 °C difference, referred to as "warm" or "cold" (warm, range: 6.3-17.7 °C; cold, range: 4.1-16.0
132 °C; **figure 1C, D**). Fish were fed *ad libitum* using a commercial salmon diet starting 2018-03-09 (warm)
133 or 2018-04-27 (cold) (**figure 1C**). Once fish size allowed passive integrated transponder tagging (warm:
134 August 2019; cold: September 2019) to enable re-identification, we anesthetized (using
135 methanesulfonate), fin clipped, and tagged individuals; fin clips allowed for genotyping individuals to
136 assign family, determine molecular sex, and confirm *vgll3* genotype. We measured fork length (± 1 mm)
137 and weighed wet mass (± 0.01 g) in September (the earliest time point when all fish were individually
138 tagged), and in December (at final spawning time) when we also determined maturity status by checking
139 for extruding milt while gently pressing the abdomen (**figure 1C**). During December sampling, we culled
140 and dissected 84% of all fish (N = 4,318; others were kept for later studies). Genotypic and phenotypic
141 sex matched in 99.9% of the culled fish (five culled fish, i.e., 0.1%, diverged between genotypic and
142 phenotypic sex and were removed from analysis), and we used phenotypic sex in 109 fish with unknown
143 genotypic sex. We confirmed maturity status in 100% of the culled fish. Once individual identification
144 was possible, we applied a feed-restriction treatment (either *ad libitum* feeding for seven days per week
145 or *ad libitum* feeding for two days per week with no feeding for two or three days between feedings)
146 that was crossed with the temperature treatment for a five-week period (September - October 2018),
147 but we did not detect any feed-restriction effect on maturation (**figure A1A**, appendix). Because length
148 and condition data analyzed originated from before the feed restriction, we omitted the feed restriction

149 term from further analyses. Animal experimentation was conducted according to European Union
150 Directive 2010/63/EU and under license ESAVI-2778-2018 by the Animal Experiment Board in Finland
151 (ELLA).

152 Genotypes and genotypic sex of both parents and the experimental cohort were determined using a
153 multiplex-PCR for 177 single nucleotide polymorphisms (SNPs) of a previously described SNP panel
154 (Aykanat et al. 2016), followed by Ion Torrent (984 broodstock individuals from which we drew parental
155 individuals) or Illumina platform (MiSeq or Next-Seq) sequencing (parental individuals, experimental
156 offspring cohort). Using a subset of unlinked, polymorphic SNPs, we reconstructed the experimental
157 cohort's grandparents, i.e., parents of the used parents (with 131 SNPs), under maximum likelihood
158 (Jones and Wang 2010) ("Settings for the parental reconstruction" in the appendix, available online).
159 and we assigned the experimental individuals to their 48 parents (with 141 SNPs) with a likelihood
160 approach (Anderson 2010). Merged information about reconstructed grandparents and assigned
161 parents yielded a three-generation pedigree (**figure 1B**) on which we based the relationship matrix
162 utilized in animal-model analyses (Henderson 1973).

163 **Data analysis**

164 We fitted a series of uni- and multivariate general and generalized linear animal models to data for
165 maturation binaries recorded in December and for length and condition recorded in September. We
166 defined condition as deviation from the (temperature-specific) slope of logarithmic mass on logarithmic
167 length - a correlate of first-year salmon lipid content (Sutton et al. 2000). Length and condition data
168 were first log-transformed, then mean-centered and variance scaled (across temperatures) to allow for
169 estimating biologically meaningful proportional and phenotypic variance-standardized effects.

170 To determine the multivariate model structure and allow for comparisons between uni- or bivariate
171 with multivariate model estimates (**figure A2**, appendix), we first fit univariate models for the binary
172 response of male maturation and bivariate models for the continuous responses of sex-specific length
173 or condition. We estimated models effects for the binary maturation response (including the
174 multivariate model) using Bayesian Markov Chain Monte Carlo simulations, which is recommended for
175 binary animal models (de Villemereuil et al. 2013), with the R-package MCMCglmm v. 2.28 (Hadfield
176 2010) in R v. 3.5.3. For the continuous responses, we initially fitted bivariate models under REML, which
177 is recommended for continuous animal models (de Villemereuil et al. 2013), using ASReml-R v. 3 (Butler
178 et al. 2009) in R v. 3.0.2. For Bayesian models, we removed mean and variance terms when all estimates
179 included zero in their 95% credible intervals (see below; **figures A1, A3**, appendix). For REML models,
180 we removed fixed terms with $P \geq 0.05$ for Wald's *F*-test with denominator degrees corrected for small
181 samples (Kenward and Roger 1997) and removed random terms with $P \geq 0.1$ for likelihood ratio tests if
182 parameters were restricted to be ≥ 0 and with $P < 0.05$ otherwise (Stram and Lee 1994) (see below;
183 **table A1,** appendix). We then fitted the multivariate model corresponding to the chosen univariate
184 (maturation) or bivariate models (sex-specific length or condition), and by adding the required between-
185 trait covariances for the additive genetic effects (i.e., 2,599 [males] or 5,209 [both sexes] relationship-
186 matrix-predicted breeding values) (Henderson 1973), common environmental effects (i.e., 16 tanks),
187 maternal effects (i.e., 21 dams), and individual environmental effects including measurement error and
188 non-additive genetic effects (i.e., 2534 [males] or 5145 [both sexes] residuals). We fitted the models
189 with probit-link function and residual variance fixed to one for maturation, corresponding to genetic
190 threshold models (Hadfield and O'Hara 2015), and with identity link function for length and condition.

191 We did not detect maternal effects on any trait (**figure A1B, table A1**, appendix; we removed dam
192 effects as a consequence) and no common environmental effects on maturation (**figure A1B**, appendix;
193 we still kept the experimental tank effects), but on length and condition, which contributed up to 6 and
194 15% to the total phenotypic variance, respectively (**figure A2**, appendix). We started model selection
195 with mean-effect interactions and removed non-significant effects (**figures 2; A1A, A3,** appendix). Final
196 models followed the general equation (per trait), with colon indicating term interaction and variance
197 terms in italic: y ~ Intercept + Temp + Vgll3 + *Temp:Tank* + *Temp:Animal* + *Temp:Residual*. The Vgll3
198 model term refers to either three genotypes (reciprocal heterozygote differences were absent;
199 posterior EL-LE contrast, 95% CI: MAT_{EL}-MAT_{LE} = 0.00, -0.47-0.49), or to the additive allelic effect (we
200 fitted both; see below); the Temp model term refers to a factor for warm or cold environments.
201 Covariance matrices across temperatures for initially fit univariate models were diagonal for tank and
202 residual effects and unstructured for dam and animal effects. The latter allows estimating dam- and
203 additive genotype-by-environment effects (Falconer 1952). For the multivariate models (five response
204 traits: sex-specific length, sex-specific condition, male maturation) we expanded the covariance
205 matrices to temperature-specific block-diagonals for *Trait:Temperature:Tank* (two 5x5 blocks), a full
206 *Trait:Temperature:Animal* genetic covariance matrix (10x10), and temperature- and sex-specific block-
207 diagonals for *Trait:Temperature:Residual* (two 2x2 female and two 3x3 male blocks; **files A1-3,**
208 electronic enhancements). We used recommended (co)variance priors following a χ_1^2 distribution in
209 Bayesian univariate threshold models (de Villemereuil et al. 2013) or priors that resulted in flat priors
210 for heritabilities and correlations in multivariate models. We based estimates on 5,000 or 1,000 retained
211 iterations after 50,000 burnin iterations and sampling every 1,250 and 2,500 or 3,000 iterations (uni-

212 and multivariate models, respectively). We invoke latent variable truncation between -7 and 7 to avoid
213 numerical errors. We confirmed model convergence by trace plot inspection and ensuring lag-two
214 autocorrelation < 0.1 for all estimates.

215 We tested and estimated additive and dominant *vgll3* effects by replacing the factorial Vgll3 term by
216 appropriate covariates (α: -1, 0, 1; δ = 0, 1, 0). To obtain observed-scale maturation probability
217 parameter estimates, we integrated over marginal model predictions and used methodology
218 implemented in the R-package QGglmm v. 0.7.2 (de Villemereuil et al. 2016) in R v. 3.5.3, applied to
219 each retained MCMC iteration to estimate credible intervals. We calculated heritability as the ratio of
220 additive genetic over total phenotypic variance, and estimated genetic, environmental, and phenotypic
221 correlations following Searle (1961). All necessary data and an R-script mirroring the final uni- and
222 multivariate modeling have been deposited in the Dryad Digital Repository (during review:
223 https://datadryad.org/stash/share/FLBZRu6qosNz909duxMd6Tw-LeGo16cPHlfprRaqKb0; after
224 acceptance: https://doi.org/10.5061/dryad.jh9w0vt6k).

225 Results and Discussion

226 We used a multivariate generalized animal model to test for associations between *vgll3* and each of the
227 investigated traits of male maturation probability (maturation, MAT), sex-specific somatic growth
228 (length, LEN), and sex-specific body condition (condition, CON). To avoid reverse causality (i.e., inferring
229 condition- or length-mediated *vgll3* effects on maturation that are truly maturation-mediated *vgll3*
230 effects on somatic growth or condition) we focused on *vgll3* effects on maturation in males and on *vgll3*
231 effects on length and condition in females (of which none matured). To allow for wider interpretation
232 and relevance of our results, we report maturation results, consistent with a genetic threshold model,

233 on the probit or observational probability scale, which are relevant for breeding-value based or
234 phenotypic selection, respectively (de Villemereuil et al. 2016). Likewise, we report results for length
235 and condition on the proportional scale, which is relevant to growth processes at the individual level, or
236 on the standardized effects size scale (phenotypic standard deviation across environments, psd), which
237 is relevant among individuals at the population level.

238 ***Vgll3* dominance effects are absent**

239 We first formally tested jointly for additive (α) and dominant (δ) effects for all traits, because sex-specific
240 dominance (i.e., *vgll3*-by-sex epistasis) has been reported for sea age at maturity in two of three
241 previous studies (Barson et al. 2015; Czorlich et al. 2018; but see Ayllon et al. 2019). When fully
242 accounting for experimental randomization and relatedness, we did not detect dominance for any trait
243 (**figure 2**). This result suggests that previous inferences about *vgll3*E* dominance on maturation age in
244 males from wild populations (Barson et al. 2015; Czorlich et al. 2018) cannot be generalized to all
245 situations. However, dominance absence verifies a requirement for meaningfully associating *vgll3*
246 effects between male and female traits that would not be fulfilled under a sex-by-locus interaction, such
247 as sex-specific dominance, although we cannot exclude the presence of non-additive allelic effects on
248 prospective female maturation, which, however, does not affect inferences for any trait in the present
249 study.

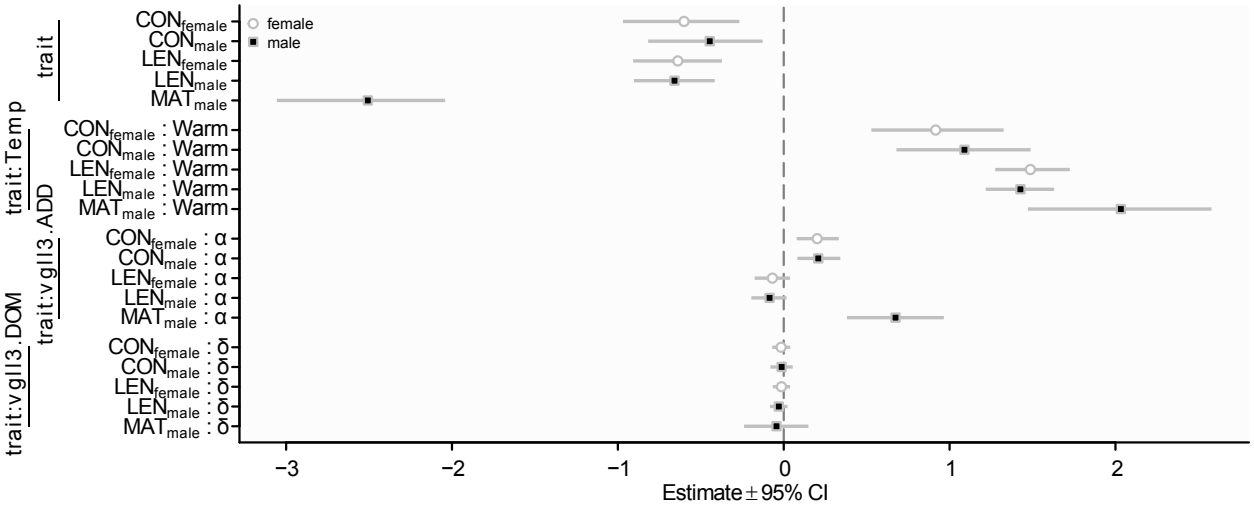


Figure 2: *Vgll3* dominant effects are absent.

Mean and contrast effect estimates (grouped by term, with term level indicated) with 95% credible intervals for the multivariate animal model on traits of male maturation (MAT_{male}; probit scale), male length (LEN_{male}; standardized log of cm), female length (LEN_{female}; standardized log of cm), male condition (CON_{male}; standardized log of g, adjusted to common size), and female condition (CON_{female}; standardized log of g, adjusted to common size). Traits were modelled as a linear function of temperature effects (Temp; levels: Cold, Warm), additive *vgll3* effects (vgll3.ADD), and dominant *vgll3* effects (vgll3.DOM). Dominant *vgll3* effects for all traits were removed because their 95% credible intervals included zero. All effects estimates originate from a common multivariate generalized animal model ($N_{families}$ = 41, N_{male} = 2,534, N_{female} = 2,611).

***Vgll3* associates with maturation timing and body condition across environments**

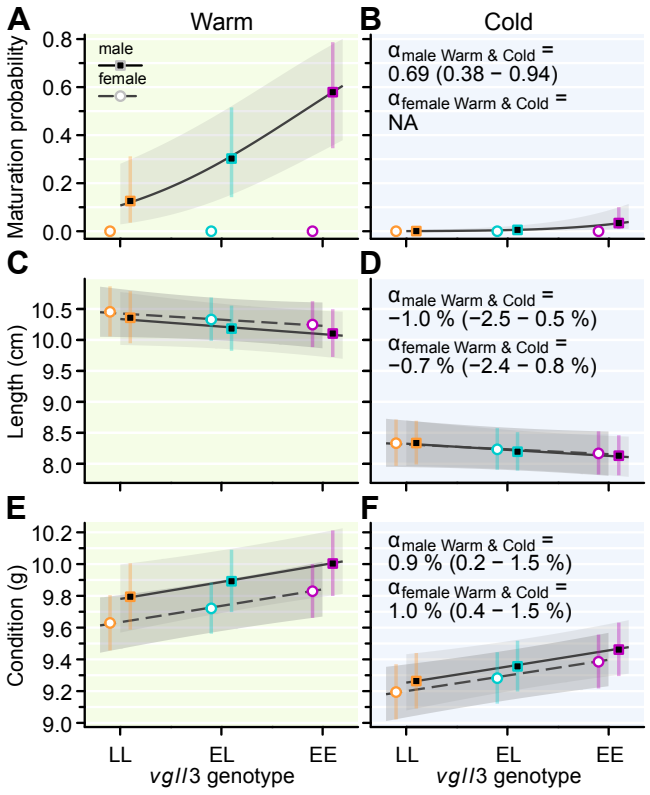
After removing dominance effects, we detected *vgll3* effects on maturation probability and, in both sexes, on condition, but not on length (i.e., the 95% credible intervals included zero), in both temperature environments; the *vgll3*E* allele associated with both higher maturation probability and higher condition (**figure 3**). These results provide experimental confirmation that the allele associated with earlier maturation following marine migration (Ayllon et al. 2015; Barson et al. 2015; Ayllon et al. 2019) has consistent effects in males maturing in freshwater, and that the same allele also associates with a higher condition. All focal trait means were much higher in the warm than in the cold environment

268 (**figure 3;** posterior temperature contrasts, 95% credible interval [95% CI]: probit scale, MAT_{Warm} -
269 MAT_{Cold} = 2.0, 1.5-2.6; psd scale, female LEN_{Warm} - LEN_{Cold} = 1.5, 1.3-1.7; female CON_{Warm} - CON_{Cold} = 0.92,
270 0.57-1.29). Despite these strong environmental effects on trait means (discussed below), *vgll3* effect
271 estimates did not differ between temperature environments for any trait (**figure 3; figure A3**, appendix).
272 For male maturation probability, we estimated a positive additive *vgll3**E allele effect on the probit scale
273 that translated to considerable maturation probability differences among *vgll3* genotypes (**figure 3A,**
274 **B)**. For female length, we estimated a non-significant and negative additive *vgll3**E allele effect on the
275 psd scale of α = -0.06 (95% CI = -0.16-0.05). This effect translates to a non-significant 1% lower body
276 length per *vgll3**E allele (**figure 3C, D**). For female condition, we estimated an additive *vgll3**E allele
277 effect on the psd scale of α = 0.20 (95% CI = 0.09-0.33). This among-individual additive *vgll3* effect on
278 condition is much larger than that estimated for length. However, it translates to the same proportional
279 effect as estimated for length, but in the opposite direction. Specifically, a non-significant 1% body
280 length decrease per *vgll3**E allele is accompanied by a significant 1% body mass increase (**figure 3E, F**).
281 Although the *vgll3* effect on length is non-significant and of little, if any, importance at the population
282 level (but may still represent a within-individual trade off, discussed below), the same effect size of 1%
283 body mass (condition) increase per *vgll3**E allele is very likely relevant for maturation. Specifically, male
284 salmon gonad development is dependent on body reserves, such as fat (Taranger et al. 2010; Andersson
285 et al. 2018), and gonads constitute 5-12% of body mass at spawning for the investigated freshwater life
286 stage (Rowe et al. 1991; Fleming 1996; Trombley et al. 2014). Thus, ignoring unknown reserve-to-gonad
287 mass conversion factors, condition variation explained by *vgll3* genotype may finance up to 40% of the
288 required extra mass (in *vgll3* EE vs. LL; assuming minimum gonad proportion; 2% / 5% = 0.4;). These

289 results provide the first indication that the large effect of *vgll3* on maturation is, at least partly, mediated

290 by a large effect of *vgll3* on condition. We strengthen this further by providing additional evidence below

291 where we quantify *vgll3* effects on trait-specific heritabilities and between-trait genetic correlations.



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293 **Figure 3**: *Vgll3* associates with maturation and body condition across environments.

294 (**A-F**) Back-transformed mean and additive effect (α) estimates with 95% credible interval per *vgll3* genotype for

295 male maturation probability (**A**, **B**; α on probit scale; no female maturation occurred), sex-specific body length (**C**,

296 **D**) sex-specific body condition (**E**, **F**; standardized mass for a geometric mean-sized fish of 9.1 cm). Mean effect

297 estimates are valid for either a warm (**A, C, E**) or a 2 °C colder (**B, D, F**) environment. All *vgll3* genotype mean or

298 additive effects estimates originate from common multivariate generalized animal models (one for mean effects,

299 one for additive effects; $N_{families}$ = 41, N_{male} = 2,534, N_{female} = 2,611). Additive *vgll3* effect estimates with 95%

300 credible intervals (**B, D, F**) are valid for both environments (see also **figure A3**, appendix).

301 ***Vgll3* explains heritability for maturation timing and body condition, and the genetic between-trait**
302 **correlation between sexes**

303 The same multivariate models also enabled us to estimate environment- and trait-specific heritabilities
304 (h^2) and trait-specific genetic correlations (R_G) between temperature environments (both contribute to
305 genotype-by-environment interactions; Sae-Lim et al. 2016) and also to estimate how much *vgll3*
306 contributes to either. The heritability of a trait quantifies the proportion of phenotypic variance
307 explained by the sum of all underlying additive genetic effects and predicts the response to phenotypic
308 selection. The genetic between-environment correlation quantifies the genotype re-ranking between
309 environments and predicts, in conjunction with heritability estimates, the response to selection across
310 environments (Falconer 1952). Fitting each model with and without specified additive *vgll3* effects,
311 enabled us to quantify the relative genetic and phenotypic contributions of additive genetic *vgll3* effects,
312 and thus the trait-specific evolutionary importance of *vgll3* within and across environments. It should
313 be noted that significance of *vgll3* effects is tested via the above-reported phenotypic effects, not via
314 heritability differences when *vgll3* effects contribute or not.

315 Remarkably, male maturation heritability (h^2MAT) on both the probit and the observed scale was 1.4
316 times larger in the warm environment than in the 2 °C colder environment (**figure 4A, B; file A4**,
317 electronic enhancement; probit scale, posterior temperature contrast, 95% CI; h^2MAT_{Warm} - h^2MAT_{Cold} =
318 0.32, 0.21-0.41; observed scale, posterior mean, 95% CI; h^2MAT_{Warm} = 0.41, 0.32-0.50; h^2MAT_{Cold} = 0.10,
319 0.04-0.16; posterior temperature contrast, 95% CI; h^2MAT_{Warm} - h^2MAT_{Cold} = 0.28, 0.17-0.38;). In addition
320 to heritability differences, the between-temperature genetic correlation estimate for maturation
321 ($R_GMAT_{Warm \cdot Cold}$) was < 0.8 (posterior mean, 95% CI; $R_GMAT_{Warm \cdot Cold}$ = 0.70, 0.45-0.93), which is

322 somewhat lower than most previous genotype-by-temperature environment estimates for maturation
323 of related species (Sae-Lim et al. 2016). Importantly, $R_G < 0.8$ indicates breeding value re-ranking
324 between environments with a mere 2 °C temperature difference and thus is of relevance to natural and
325 aquaculture settings (Robertson 1959; but see Sae-Lim et al. 2016). This genetic correlation estimate is
326 of particular relevance to predicting selection response across environments in combination with the
327 pronounced environmental differences in maturation heritability (Falconer 1952), and the values
328 reported here readily apply to a 2 °C global-warming scenario (IPCC 2014). For maturation, additive *vgll3*
329 effects on the probit scale explained 24.8 and 16.1% of heritability in the warm and cold environments,
330 which explains (by multiplication with *vgll3*-unadjusted heritability) 16.7 and 7.5% of phenotypic
331 variance, respectively. On the observed-scale, *vgll3* effects explained 32.9 and 28.1% of heritability and
332 13.6 and 2.7% of phenotypic variance, respectively. Additive *vgll3* effects also considerably reduced the
333 between-environment genetic correlation for maturation (**figure 4C; file A4**, electronic enhancement),
334 which supports an interpretation that the abovementioned result for non-significant temperature-by-
335 *vgll3* interaction effects imply environmentally stable *vgll3* effects relative to other, less environmentally
336 stable additive genetic effects on maturation.

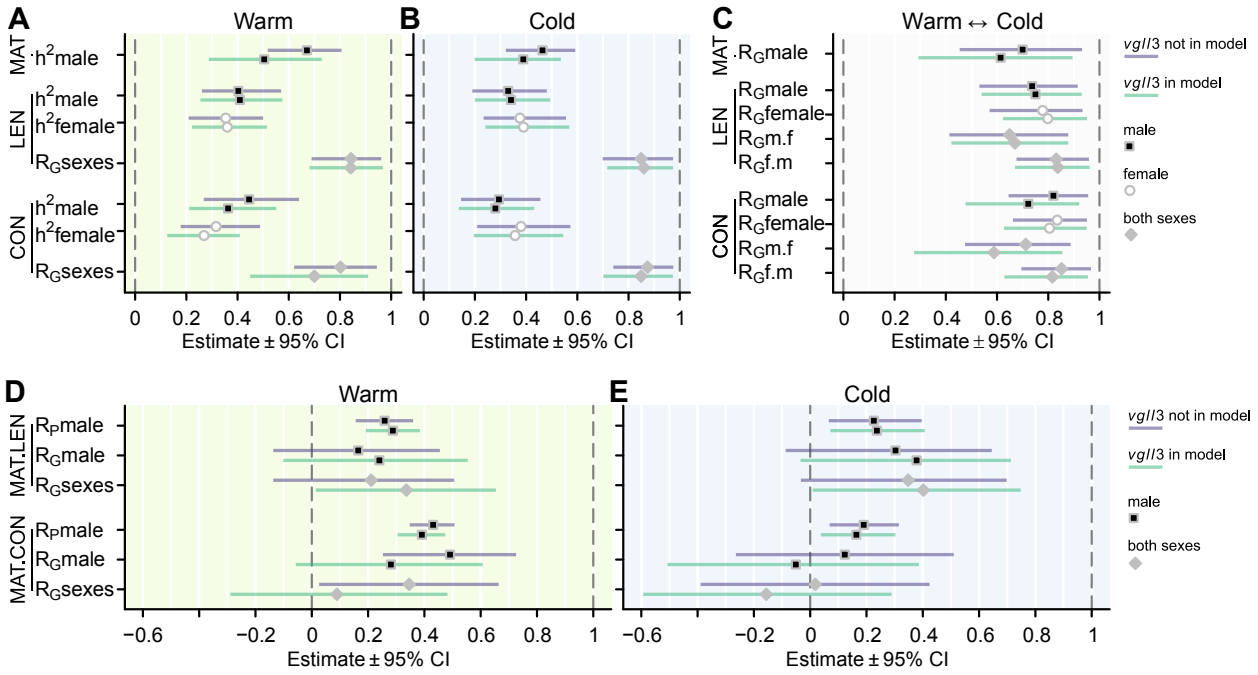

Figure 4: *Vgll3* explains heritabilities and genetic between-trait correlations.

(**A, B**) Environment- and sex-specific heritability (h^2) and between-sex genetic correlation ($R_G$sexes) estimates with 95% credible intervals for male maturation (MAT), sex-specific body length (LEN), and sex-specific body condition (CON). Estimates are valid for either a warm (**A**) or 2 °C colder (**B**) environment. (**C**) Between-environment genetic correlation (R_G) estimates with 95% credible interval within sex ($R_G$male, $R_G$female) and reciprocally between sexes (R_Gm.f, R_Gf.m) for male maturation (MAT), sex-specific length (LEN), and for sex-specific condition (CON). Estimates refer to the correlation between a warm and a 2 °C colder environment. (**D, E**) Between-trait phenotypic correlation (R_P) estimates with 95% credible intervals between male maturation and male length (MAT.LEN) or male maturation and male condition (MAT.CON) and between-trait genetic correlation (R_G) estimates with 95% credible intervals between male maturation and sex-specific length (MAT.LEN) or male maturation and sex-specific condition (MAT.CON). Estimates are valid for either a warm (**D**) or 2 °C colder (**E**) environment. All estimates were obtained by two similar multivariate models ($N_{families}$ = 41, N_{male} = 2,534, N_{female} = 2,611), differing in whether additive *vgll3* additive effects were included (the same model underlying estimates in **figure 3**) or excluded as indicated in the legends.

Female length heritability was, in contrast to that for maturation probability, similar between environments (posterior mean, 95% CI; h^2LEN_{Warm} - h^2LEN_{Cold} = -0.03, -0.19-0.13) and the between-

354 environment genetic correlation of $R_G LEN_{Warm.Cold}$ = 0.78 (0.57-0.93) indicated less genotype re-ranking
355 between environments than that for male maturation (**figure 4A-C**). This between-environment genetic
356 correlation contrasts with much lower estimates in other fish species (Sae-Lim et al. 2016). Accounting
357 for *vgll3* effects, unexpectedly, increased female length heritability, as opposed to lowering it as
358 observed for maturation heritability, though by only 1.5 and 3.5% in the warm and cold, respectively
359 (**figure 4A, B).** When we investigated underlying variance components between models for length, we
360 found that including *vgll3* effects re-allocated variance from the additive genetic to the residual
361 component (**files A2, A4**, electronic enhancements), which is not expected if *vgll3* comprises additive
362 genetic effects on length.

363 Female condition heritability was, like that for female length and in contrast to that for maturation
364 probability, similar between environments (h^2CON_{Warm} - h^2CON_{Cold} = -0.09, -0.30-0.08) and the between-
365 environment genetic correlation of $R_G CON_{Warm.Cold}$ = 0.83 (95% CI = 0.66-0.95) indicated very little
366 genotype re-ranking between environments (**figure 4A-C**). Additive *vgll3* effects explained 15.0 and
367 6.0% of the condition heritability and 4.7 and 2.3% of the phenotypic variance in the warm and cold
368 environments, respectively. And, *vgll3* effects explained some of the between-environment genetic
369 correlation for female condition (**figure 4C; file A4**, electronic enhancement), although less than what
370 *vgll3* explained for maturation of the same parameter. Thus, unlike for maturation, for which we
371 detected stable *vgll3* effects that explained a large share of the genetic between-environment
372 correlation in the presence of a significant heritability difference between environments, the
373 environmentally stable *vgll3* condition effects were detected in the presence of a relatively more stable
374 genetic background for condition.

375 We collected additional evidence for determining the phenotypic path how *vgll3* affects maturation
376 timing by estimating between-trait genetic correlation between sexes. By quantifying the proportion of
377 the additive *vgll3* effect contribution to trait-specific heritability, we were unable to support a
378 hypothesized *vgll3* association for maturation via length but support an association for maturation via
379 condition. Quantitative contribution estimates of the genetic marker to the heritability were sufficiently
380 large to consider *vgll3* a large-effect locus for both maturation and condition. Nonetheless, *vgll3*
381 contributions to the phenotypic maturation-timing variance were lower than previous estimates at a
382 later life stage (Ayllon et al. 2015; Barson et al. 2015; Ayllon et al. 2019), agreeing with the assumption
383 that initially detected genetic-marker effects tend to be overestimated (Hill 2010), and which could have
384 several biological, methodological, or statistical reasons (discussion of which goes beyond the scope of
385 this manuscript). Furthermore, by having observed the same direction for *vgll3* effects between male
386 maturation and female condition, we had obtained the first indication that *vgll3*-induced variation for
387 maturation and condition may underlie a common *vgll3*-related molecular process. We wanted to
388 further foster this idea by quantifying the *vgll3* contribution to the genetic correlation between male
389 maturation and female length (MAT.LEN) or female condition (MAT.CON), and thus estimated the
390 between-trait genetic correlation between sexes.

391 We did not detect genetic correlations between male maturation and female (or even male) length,
392 although estimates in both environments were positive and the relationship-controlled phenotypic
393 correlation estimate (R_P) (Searle 1961) between male maturation and male length was significant in both
394 environments (**figure 4D, E**). Furthermore, all correlation estimates (genetic and phenotypic) between
395 male maturation and female or male length increased after accounting for *vgll3* effects (**figure 4D, E**).

396 Thus, we were able to further exclude length as a mediator of *vgll3* effects on maturation, which
397 requires inferring a positive genetic covariance among *vgll3* effects between traits, but instead found
398 support for a negative genetic covariance among *vgll3* effects between maturation and length.
399 Between male maturation and female (and male) condition, we, however, detected a positive genetic
400 correlation, although only in the warm environment (we discuss this environmental difference below)
401 (**figure 4D, E**). After accounting for *vgll3* effects, all genetic correlation estimates between male
402 maturation and female (or male) condition decreased, as is expected under scenarios of either the
403 presence of pleiotropic *vgll3* effects on condition and maturation, or when one trait mediates the
404 genetic-marker associated variation of the other. The decreasing effect was strongest for the genetic
405 correlation between male maturation and female condition, which even rendered non-significant when
406 accounting for *vgll3* effects (**figure 4D**). Ignoring a *vgll3* pleiotropy scenario, this latter result suggests a
407 positive genetic covariance among the significant *vgll3* effects between male maturation and female
408 condition. This covariance may even be dominated by *vgll3* effects and, thereby, suggests a *vgll3* effect
409 mediation on maturation via condition and not *vice versa* (because maturation variation cannot account
410 for condition variation in immature females).

411 ***Vgll3* as a candidate gene for a resource allocation trade-off?**

412 Although many effects for length were statistically non-significant, we cannot entirely rule out small
413 *vgll3* effects on length. Generally, growth or length and maturation initiation are assumed to associate
414 positively (Taranger et al. 2010; Andersson et al. 2018). By inferring a negative covariance among *vgll3*
415 effects between maturation and length we were able to rule out length mediating *vgll3* effects on
416 maturation with a high certainty. However, the inferred negative genetic covariance among *vgll3* effects

417 between maturation and length support a scenario for a *vgll3*-governed resource allocation trade-off.
418 Such a trade-off was also, albeit weakly, indicated by the non-significant 1% length decrease per *vgll3**E
419 allele that was accompanied by a significant 1% condition increase. This result is typical in life-history
420 research for traits that represent within-individual resource allocation trade-offs in the presence of
421 relatively much larger among-individual variation for resource acquisition (de Jong and van Noordwijk
422 1992; Roff 2002). The idea of a *vgll3*-mediated resource allocation trade-off also makes biological sense.
423 This is not only because resource allocation theory predicts that, regardless of underlying genetics,
424 energy allocated to condition cannot concurrently be allocated to growth, but also due to the suggested
425 role of Vgll3 in controlling mesenchymal cell fate into either adipocytes (thus increasing body condition)
426 or bone and cartilage lineages (thus increasing somatic growth) (Halperin et al. 2013). However, a final
427 conclusion for our tentative results requires additional research, also because there are other plausible
428 candidate genes in the same genome region as *vgll3*, e.g., *akap11* (Ayllon et al. 2015; Barson et al. 2015).

429 **The presence of strong temperature effects on maturation timing and body condition**

430 A remaining question is why we detected a significant genetic correlation between male maturation and
431 female condition in the warm, but not the cold, environment. We suspect that one reasons may be that
432 the higher maturation rate and maturation heritability in the warm provided sufficient information to
433 detect the genetic correlation, because higher heritabilities decrease the error of the genetic correlation
434 estimate (Robertson 1959). Furthermore, many males in the cold environment with "high" breeding
435 values for condition (adjusted for temperature environment) did not mature, possibly because of the
436 much lower average condition in the cold, or due to other lower temperature-related causes, such as

437 not exceeding growth or size thresholds needed for maturation (Taranger et al. 2010; Andersson et al.
438 2018), masking an otherwise positive genetic correlation.

439 Extending these thoughts, we detected environmental effects on condition that were consistent with
440 the notion that both condition and maturation covary positively with temperature. Specifically, when
441 translated to the proportional scale, we detected a 4.6% (95% CI = 2.9-6.4%) higher female condition in
442 the warm relative to the cold environment, where we had also detected a much higher maturation
443 probability (0.41, 0.27-0.58 vs. 0.05, 0.02-0.08; **figure 3A, B, E, F**). Thus, the environmental effect of a
444 global-warming-relevant 2 °C temperature difference (IPCC 2014) on condition (4.6%) was more than
445 twice the maximum genetic *vgll3* effect (EE vs. LL: 2%) and may have contributed considerably to the
446 large environmental temperature effect on maturation probability. Similar positive relationships
447 between body condition and water temperature have previously been observed (Dwyer and Piper 1987;
448 Jonsson et al. 2013; Tromp et al. 2018). We suspect that temperature effects on maturation via
449 condition explain, at least partly, unexpectedly high maturation rates in heated salmon rearing facilities
450 (Good and Davidson 2016) and why effects on size and maturation timing vary between growth
451 acceleration through increase in feed vs. temperature (Berrigan and Charnov 1994; Shapiro Goldberg et
452 al. 2019). Important for consistency of natural and human selection success across temperatures
453 (Falconer 1952), the large average temperature difference for condition observed here was evident in
454 the presence of both high genetic correlations (> 0.8 for both sexes) and similar female condition
455 heritabilities between temperatures (**figure 4A-C**). Furthermore, *vgll3* effect estimates on both female
456 condition and on male maturation did not differ between temperature environments, and *vgll3* effects
457 contributed to the between-environment genetic correlations for both traits. Thus, the environmental

stability of *vgll3* condition effects contributes to the general environmental stability of additive genetic condition effects.

These new results suggest - together with the previous results on maturation (Ayllon et al. 2015; Barson et al. 2015; Ayllon et al. 2019) - the presence of environmentally stable *vgll3* effects on both condition and maturation. A large share of *vgll3* effects for the positive genetic correlation between maturation and condition predicts rapid evolutionary co-responses to selection for either trait, but also predicts that their genetic correlation and importance is sensitive to *vgll3* allele frequencies. The sex-specific results, together with previous biological knowledge on their causal association (Taranger et al. 2010; Andersson et al. 2018), indicate that large *vgll3* effects on maturation are likely mediated via large condition effects and suggest *vgll3* as a candidate locus for controlling the resource allocation trade-off between energy reserves and somatic growth.

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