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1 **Genome-wide association study and genomic prediction of tolerance to acute**
2 **hypoxia in rainbow trout**

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22

23 **Abstract**

24

25 Hypoxia is one of the major threats to the aquaculture sector resulting in substantial

26 economic losses to the fish farmers. Thus, tolerance to hypoxia is of high economic interest to

27 be genetically improved by breeding programs. Rainbow trout (*Oncorhynchus mykiss*) is one

28 of the most cultured salmonid species worldwide, with well-developed breeding programs.

29 Still, studies of genetic potential to improve hypoxia tolerance in this species are rare. In the

30 present study, 1,320 individuals of rainbow trout were used for a genome-wide association

31 study of acute hypoxia tolerance based on imputed high-density genotypes to explore the

32 genetic architecture and related candidate genes affecting hypoxia response. Three significant

33 (Omy31_1, Omy31_2, Omy20) and two putative (Omy15, Omy28) quantitative trait loci (QTLs)

34 were detected, but each of them only explained between 0.2% and 0.8% of the genetic

35 variance of acute hypoxia tolerance. However, heritability was estimated at a moderate value

36 of 0.24 – 0.28, that suggests a solid potential to improve hypoxia tolerance in the studied

37 rainbow trout population by genetic selection. Moreover, it was shown that genomic

38 prediction for hypoxia tolerance would lead to a relative increase of ~ 11% for genomic

39 selection (GS) accuracy compared to the pedigree-based selection, considering a reference

40 population of 1000 individuals. Finally, sixteen genes (*ids, fmr1, arx, lonrf3, commd5, map4k4,*

41 *smu1, b4galt1, re1, abca1, noa1, igfbp7, noxo1, bcl2a, trim25, mylk3*) were proposed as

42 potential functional candidates involved in hypoxia tolerance. Taking all proposed candidate

43 genes within two main QTLs on Omy31 (12 out of 16 genes), we may hypothesize that the

44 complex response to acute hypoxia in rainbow trout, i.e., the interplay between behavioural,

45 morphological, and physiological responses, is primarily encoded by two supergenes.

46 However, further functional validation of their effects may help to specify the biological

47 mechanisms triggering a response to acute hypoxia in rainbow trout.

48 **Key words:** GWAS, Heritability, Hypoxia resistance, Hypoxia tolerance, *Oncorhynchus mykiss*

49

50 **1. Introduction**

51 A lack of oxygen referred to as hypoxia is one of the greatest challenges that most life
52 can face. In terrestrial ecosystems, conditions of low oxygen are rare. In contrast, low
53 concentration of dissolved oxygen (DO), is much more common in aquatic ecosystems (Diaz,
54 2001; Townhill et al., 2017). The DO is a primary limiting factor in aquaculture because fish
55 have aerobic metabolism requiring DO at efficient levels (Abdel-Tawwab et al., 2019). Hypoxia
56 is also a very complex condition caused by several interrelated factors that might be divided
57 into three main groups: 1) substandard rearing conditions due to the technical failure of water
58 aeration or oxygenation or too high stocking densities regarding post-prandial oxygen
59 consumption (Abdel-Tawwab et al., 2019); 2) eutrophication associated with increased
60 anthropogenic nutrient loading of lakes, rivers and coastal waters leading to blooms of algae
61 and phytoplankton, the dissimilation or death of which subsequently leads massive depletion
62 of dissolved oxygen (Friedrich et al., 2014); 3) global warming as the main aspect of climate
63 change leading to increased microbial respiration rates and reduced oxygen solubility with
64 increasing water temperatures (McBryan et al., 2013; Sae-Lim et al., 2017; Reid et al., 2019).

65 Hypoxia is one of the major threats for aquaculture sector (Farrell and Richards, 2009;
66 Abdel-Tawwab et al., 2019) affecting seriously health and welfare of fish including growth,
67 reproduction, behaviour, immunity, and other energy-demanding activities (Gallage et al.,
68 2016; Abdel-Tawwab et al., 2019; Reid et al., 2019). Consequently, hypoxia often leads to
69 severe losses to fish farmers. Thus, tolerance to hypoxia is of high economic interest to be
70 genetically improved by breeding programs (Sae-Lim et al., 2017).

71 Of the total European aquaculture production, 80 – 83% originated from at least 37
72 different breeding programs that are primarily focused on production traits like growth or
73 processing yields (Janssen et al., 2017). Moreover, improving of disease resistance to several
74 pathogens in both freshwater and marine fishes is under strong interest (Yáñez et al., 2014;
75 Gjedrem and Rye, 2016; Houston et al., 2020). However, improving resilience to
76 environmental variation like e.g., tolerance to temperature, hypoxia or salinity is starting to
77 be an interesting challenge for aquaculture breeding programs (Allal and Nguyen, 2022).

78 Through studies using mammalian model organisms, three hypotheses for oxygen-
79 sensing and downstream response have been proposed: a “membrane hypothesis,” a
80 “mitochondrial/metabolic hypothesis,” and a more recent “gas transmitter hypothesis”.
81 These hypotheses are in close parallel to fish physiological response to hypoxia conditions
82 (Gattuso et al., 2018).

83 Many molecular and physiological responses to hypoxia are regulated by transcription
84 factors named hypoxia-inducible factors (HIFs), heterodimeric proteins with an oxygen-
85 sensitive α -subunit, HIF- α and an oxygen-insensitive β -subunit, HIF- β (Nikinmaa and Rees,
86 2005; Pelster and Egg, 2018; Dzhililova and Makarova, 2020). HIF- α is a key regulator of many
87 hypoxia-related proteins and signalling pathways that facilitate adaptation of organisms to
88 hypoxic environments e.g.: insulin-like growth factor binding protein (*igfbp*, a growth
89 inhibitory protein), vascular endothelial growth factor (VEGF), mitogen-activated protein
90 kinases (MAPK), reactive oxygen species (ROS), reactive nitrogen species (RNS), oxidative
91 phosphorylation (OXPHOS), NADPH oxidase or nitric oxide synthase (NOS, a RNS regulating
92 enzyme) (Fu et al., 2000; Zhu et al., 2013; Fago and Jensen, 2015; Sahoo et al., 2016; Gattuso
93 et al., 2018; Thomas et al., 2019; Dzhililova and Makarova, 2020).

94 The acute response of fish to hypoxia mainly combines physiological changes in order
95 to maintain normal oxygen supply to tissues (hyperventilation, bradycardia, increased blood
96 O₂-carrying capacity and redistribution of blood flow) with metabolic changes to provide
97 adequate amounts of ATP (adenosine triphosphate) with less oxygen through stimulation of
98 anaerobic glycolysis and gluconeogenesis pathways (Farrell and Richards, 2009; Richards,
99 2011; Genz et al., 2013; Gattuso et al., 2018). Due to the use of carbohydrates to produce ATP
100 in the absence of oxygen, glycogen and glucose levels immediately rise and further resulting
101 in lactate accumulation and circulation (Omlin and Weber, 2010; Li et al., 2018; Abdel-Tawwab
102 et al., 2019; Léger et al., 2021). Under chronic hypoxia, lipolysis replaces glycolysis, and lipids
103 are the main energy source of fish (Li et al., 2018). Besides, both acute and chronic hypoxia
104 stress promotes cell apoptosis and oxidative stress leading to DNA damage (Poon et al., 2007;
105 Mahfouz et al., 2015; Mustafa et al., 2015; Birnie-Gauvin et al., 2017; Chowdhury and Saikia,
106 2020), destroys the innate immune system, and makes fish more susceptible to pathogens
107 (Giomi et al., 2016; Esteve et al., 2017; Sae-Lim et al., 2017; Abdel-Tawwab et al., 2019).
108 Furthermore, fishes can show various behavioural responses such as rising to the surface to
109 breathe the uppermost layer of water in contact with air, increasing activity to escape the
110 hypoxic area or decreasing activity to reduce oxygen demand (Domenici et al., 2007; Domenici
111 et al., 2013; Bowyer et al., 2014).

112 Rainbow trout (*Oncorhynchus mykiss*) is one of the most cultured salmonid species
113 worldwide (FAO, 2020), with well-developed breeding programs resulting in significant
114 selection responses in growth, slaughter yields and disease resistance (Gjedrem and Rye,
115 2016; Chavanne et al., 2016; Boudry et al., 2021). In France, four commercial breeding
116 programs are carried out. Besides, French rainbow trout production is mostly developed with
117 all-female diploid or triploid stocks (Piferrer et al., 2009) reared in a land-based facility in a

118 concrete race-way with oxygen enrichment of the water by liquid oxygen injected in the water
119 or mechanical aeration. Precise continuous monitoring of oxygen level is done with electronic
120 probes and adapted software according to oxygen concentration fluctuations due to feeding
121 delivery and consumption. However, an increase in trout robustness is demanded to adapt
122 fishes to the rapid daily changes of oxygen content associated in summer with the increased
123 temperature variation of the river's waters. Both acute and long-term exposure to low
124 dissolved oxygen levels that are less than 4 mg/L (while optimum values are in the range from
125 8 to 10 mg/L) can lead to massive mortality and growth depression caused by reduced growth
126 hormone-I (GH-I) and insulin like growth factor I-II (IGF I-II) levels in rainbow trout (Hou et al.,
127 2020; Aksakal and Ekinci, 2021; Royer et al., 2021). Although hypoxia is a common threat in
128 rainbow trout farming, studies of genetic potential to hypoxia tolerance are still rare (Scott et
129 al., 2015; Borey et al., 2018; Strowbridge et al., 2021; Lagarde et al., Submitted). Thus,
130 understanding the genetic architecture of hypoxia tolerance could help to improve the
131 resilience of rainbow trout stocks by genetic selection.

132 To select for genetically environmental-tolerant individuals, enough genetic variability
133 must exist within the species. Although hypoxia tolerance is an interesting trait for a trout
134 breeding program, heritability estimates for this trait are still missing in salmonids. As far as
135 we know, there were only two estimates in the literature to date showing high heritability for
136 acute hypoxia tolerance (0.50 and 0.61, respectively) in common carp (*Cyprinus carpio*) (Nagy
137 et al., 1980) and large yellow croaker (*Larimichthys crocea*) (Ding et al., 2022).

138 Numerous genome-wide association studies (GWAS) have been run in the last decade
139 to identify genomic regions (Quantitative trait loci – QTLs) and functional candidate genes
140 associated with traits of interest in different aquaculture species (Robledo et al., 2017;
141 Houston et al., 2020). However, only a few GWAS for hypoxia tolerance have been conducted

142 so far, and on limited number of fish species other than salmonids: Nile tilapia (Li et al., 2017;
143 Yu et al., 2021) (*Oreochromis niloticus*), two catfish species (Wang et al., 2017; Zhong et al.,
144 2017) (*Ictalurus punctatus* and *Ictalurus furcatus*), golden pompano (San et al., 2021)
145 (*Trachinotus ovatus*) and large yellow croaker (Ding et al., 2022). These studies revealed
146 multiple QTLs and potential candidate genes that might be responsible for response to
147 hypoxia.

148 The aims of this study were i) to estimate the variance components of hypoxia
149 tolerance; ii) to predict the genomic selection (GS) accuracy compared to pedigree-based
150 BLUP selection for hypoxia tolerance in rainbow trout; iii) to perform GWAS to investigate the
151 genetic architecture of hypoxia tolerance and to propose potential candidate genes for the
152 main QTLs. To our knowledge, this is the first GWAS evaluating the genetic architecture and
153 accuracy of genomic prediction of acute hypoxia tolerance in rainbow trout.

154

155 **2. Material and Methods**

156 **2.1 Ethics Statement**

157 This study used fin clips collected by the breeding company “Milin Nevez” (Bretagne
158 Truite Group, Plouigneau, France) as part of their commercial breeding programs. All
159 challenges were carried out in accordance with the European guidelines (Directive 2010–63-
160 EU) and the corresponding French legislation. Animal experiment procedures were approved
161 by the ethics committee on animal experimentation COMETH ANSES/ENVA/UPC No. 16 and
162 were authorized by the French Ministry of Higher Education, Research, and Innovation under
163 number APAFIS#24441-2020022417122193 v3, project N°20-032.

164

165 **2.2 Establishment and rearing of challenged fish**

166 The experimental stock was established (6.11. 2019) from 190 dams and 98 sex-
167 reversed neomales of a commercial selected all-female line of Milin Nevez breeding company
168 using ten independent full-factorial mating designs. The eggs were split by the dam (meaning
169 190 separated batches, one for each dam), but only the 90 best spawnings were conserved
170 for mixing at the larval stage. So, in the end, the experimental stock came from 90 dams and
171 98 neomales. From each of the parents used in the mating, a fin clip was collected and stored
172 in 98% ethanol for later DNA extraction and genotyping.

173 The progeny stock was then reared under common commercial conditions until 9
174 months. 1,508 individuals were PIT tagged by Bretagne Truite and transferred to the SYSAAF-
175 ANSES Fortior Genetics platform (ANSES, Plouzané, France) and acclimatized for four days
176 before acute hypoxia challenge. Out of 1,508 fish, 1,351 individuals were challenged to
177 hypoxia and fin-clipped for DNA and finally only 1,320 DNA samples were sent for genotyping.

178

179 **2.3 Hypoxia challenge**

180 The challenge to hypoxia was sub-divided into seven batches (one per day starting
181 from 17.8. 2020), and in each batch, a random sample of fish was challenged (Table 1.) At the
182 beginning of each trial, the initial oxygen level was recorded. The gradual decline of oxygen
183 was conducted by bubbling nitrogen and monitored every five minutes until the end of the
184 trial of a given day (Supplementary Fig. S1). Water temperature was constantly monitored
185 during the trial and ranged from 15.2°C to 17.3°C. Hypoxia tolerance phenotype was defined
186 as the time to loss of equilibrium (TLE) in minutes with a value set to 0 for the first fish losing
187 its equilibrium. When fish lost their equilibrium, they were removed from the tank, identified
188 (PIT-tag reading), weighed and euthanized in a concentrated bath of Eugenol (180mg/L). The
189 corresponding TLE and oxygenation levels (mg/l^{-1}) were recorded for each individual. The

190 challenge ended when the last fish lost its equilibrium and was removed from the tank. The
191 parents were not challenged and were only used as a reference population for the imputation
192 of their offspring genotypes.

193 **2.4 Genotyping and imputation**

194 Fin samples from hypoxia-challenged fish (1,320 ind.) and their parents (188 ind.) were
195 sent to the INRAE genotyping platform Gentyane (Clermont-Ferrand, France) for DNA
196 extraction and genotyping. The challenged fish were genotyped for 57,501 SNPs using the
197 medium-density (MD) Rainbow Trout Axiom® 57K SNP array from Thermo Fisher (Palti et al.,
198 2015). Parents were genotyped for 664,531 SNPs using a newly constructed high-density (HD)
199 Rainbow Trout Axiom® 665K SNP array (Bernard et al., 2022).

200 The first round of quality control was done by Thermo Fisher software Axiom Analysis
201 Suite™ with threshold values of 97% for SNP call rate and 95% for sample call rate for both
202 MD and HD SNPs. All parents (288) passed the preliminary quality control, but twenty-three
203 challenged fish samples did not pass quality control, and thus 1,297 progeny samples
204 remained for the following step of quality control. Then, SNPs with probe polymorphism and
205 multiple locations on the Arlee genome reference assembly (accession number:
206 USDA_OmykA_1.1.; Gao et al., 2021) were discarded as described in Bernard et al. (2022).

207 Finally, PLINK v1.9 software (Chang et al., 2015) was used for keeping only SNPs with
208 deviation from Hardy-Weinberg equilibrium with a p-value > 0.0001 and a minor allele
209 frequency (MAF > 0.05). On the HD genotypes, 418,925 SNPs remained for the parents, while
210 29,091 SNPs remained on the MD genotypes of the challenged progeny. Parentage
211 assignment was done using 1,000 randomly sampled markers with the R package APIS (Griot
212 et al., 2020) with a positive assignment error rate set to 2%.

213 The imputation of the MD genotypes into HD genotypes for the 1,297 challenged
214 offspring was run using FIMPUTE3 software (Sargolzaei et al., 2014) utilizing quality-filtered
215 genotypes and pedigree information from 188 parents. The correctness of imputation was
216 checked by mendelian testing and by observation of changes in original MD genotypes that
217 varied from 1 (0.004%) to 106 SNPs (0.37%) per individual. The final dataset contained 1,297
218 phenotyped and genotyped (418,925 imputed SNPs) progeny, which were subjected to
219 genomic analysis.

220

221 **2.5 Estimation of breeding values and variance components**

222 The following statistical model was derived to describe the hypoxia response:

$$223 \quad TLE_{ijk} = \mu + trial_i + dam_j + anim_k + e_{ijkl}$$

224 where TLE_{ijk} is the TLE performance for animal k , produced by dam j and tested day i , μ the
225 overall mean for hypoxia tolerance trait in minutes, $trial$ is the fixed effect of challenge trial (i
226 = 1 – 7); dam is the random maternal effect ($j = 1 – 90$); $anim$ is the random genetic effect of
227 the animal ($k = 1 – 1,297$) and e_{ijkl} is the random residual. In total, 49,402 animals were related
228 through the pedigree relationship matrix (A) for BLUP evaluation, tracing back eight
229 generations of ancestors of the 1,320 phenotyped animals.

230 For genomic-based evaluations, the pedigree matrix A was replaced by a genomic relationship
231 matrix G (VanRaden, 2008), considering either MD (29,091 SNPs) or HD (418,925 SNPs)
232 genotypes.

233 Variance components were estimated using the restricted maximum likelihood
234 method and AIREML algorithm in BLUPF90 software (Misztal et al., 2002).

235 The selection accuracies of a pedigree-based selection approach (BLUP) and a genomic
236 selection approach (GBLUP) were assessed from estimated breeding values (EBV and GEBV,

237 respectively) that were derived through consideration of either the pedigree relationship
238 matrix (A) or the genomic matrix (G) using the software package BLUPf90 (Miształ et al., 2014)

239 To evaluate the accuracy of (G)EBVs, 100 replicates of Monte Carlo ‘leave-one-group-
240 out’ cross-validation tests were run considering the same procedure as described in
241 D’Ambrosio et al. (2020). For each replicate, 297 fish were randomly chosen for the validation
242 set, and 1,000 fish were chosen for the training set. The phenotypes recorded in the validation
243 population were then hidden and breeding values were estimated using BLUP and GBLUP
244 models. The accuracy (r) for each replicate was computed as:

$$245 \quad r = \text{cor}((G)EBV, y^*)/h$$

246 where $\text{cor}((G)EBV, y)$ is the correlation between the (G)EBV and the phenotypes y^* adjusted
247 for batch and maternal effects of the 297 individuals belonging to the validation population,
248 and h is the square root of the pedigree-based heritability. Moreover, the degree of bias in
249 BLUP and GBLUP estimations was evaluated by the regression coefficient of the adjusted
250 phenotypes on the (G)EBVs. In the absence of selection bias, this coefficient is expected to be
251 equal to 1; in the case of EBV over-dispersion (inflation), the coefficient is below 1, and in the
252 case of EBV under-dispersion the value is above 1. The selection accuracies and the inflation
253 coefficients of different tested models (BLUP, GBLUP – MD and GBLUP – HD) were presented
254 as average values over all 100 replicates.

255

256 **2.6 Bayesian-based GWAS**

257 A Bayesian variable selection model with a Bayes $C\pi$ approach (Habier et al., 2011) was
258 used to perform GWAS to locate QTL regions and estimate the proportions of genetic variance
259 explained by the identified QTLs. In this model, only a certain proportion of SNPs (π) are
260 assumed to have a non-zero effect on the phenotype. The marker effects are estimated

261 through the Markov Chain Monte Carlo (MCMC) algorithm that considers a mixture of
 262 markers, of which proportion π has effects that follow a normal distribution $N(0, \sigma_a^2)$ and
 263 proportion $1 - \pi$ have zero effect. The following general model was used:

$$264 \quad TLE_{ijl} = \mu + trial_i + dam_j + \sum_{k=1}^n \delta_{lm} a_k g_{kl} + \varepsilon_{ijlm}$$

265 where TLE_{ijl} is the time to loss of equilibrium of individual l , μ is the overall mean for hypoxia
 266 tolerance trait in minutes, $trial$ is the fixed effect of challenge trial ($i = 1 - 7$), dam is the random
 267 maternal effect ($j = 1 - 90$), n is the total number of SNPs used in the analysis, a_k is the additive
 268 effect of the reference allele for the k^{th} SNP, with genotype g_{kl} (coded as 0, 1, or 2) for
 269 individual l , and ε_{ijlm} is the residual term for the l th individual in the m^{th} cycle of the MCMC
 270 algorithm.

271 At each cycle m , the decision to include SNP k in the model depended on the indicator
 272 variable δ_{lm} . This indicator variable was sampled from a binomial distribution with a
 273 probability π that δ_{lm} was equal to 1 (i.e., the SNP has a non-zero effect a_k) and a probability
 274 $(1 - \pi)$ that δ_{lm} was equal to 0 (i.e., the SNP k is thus not accounted for in the model fit at cycle
 275 m). The proportion $(1 - \pi)$ was sampled from a beta distribution, $B(\alpha, \beta)$, in which parameter
 276 α was set as the total number of markers ($n = 418,925 - \text{HD}$; $n = 29,091 - \text{MD}$) and β was set
 277 at 400, corresponding to a model retaining about 400 SNPs with non-zero effects at each cycle.

278 The BESSiE software (version 1.0) was used to compute this model (Boerner and Tier,
 279 2016). A total of 410,000 cycles of Gibbs sampling were performed with a burn-in of 10,000
 280 iterations using HD imputed genotypes. One Gibbs sample was saved every 40 iterations for
 281 further analysis. For MD analysis, a total of 210,000 cycles of Gibbs sampling were performed
 282 with a burn-in of 5,000 iterations. One Gibbs sample was saved every 20 iterations for further
 283 analysis. To check the convergence, the MCMC algorithm was initiated three times with three

284 different seeds for the random number generator. In addition to checking the consistency of
285 peak SNPs identified across seeds, convergence was assessed by visual inspection of plots of
286 the posterior density of genetic, maternal and residual variances and by high correlations (r
287 >0.99) between the GEBVs estimated from the different seeds of the MCMC algorithm.

288 The evidence for association between the phenotype and each SNP was assessed by
289 the Bayes Factor (BF):

$$290 \quad \text{BF} = \frac{P_i/(1 - P_i)}{\pi/(1 - \pi)}$$

291 where P_i is the probability that the i^{th} SNP has a non-zero effect in the model.

292 The existence of QTL was evaluated considering the values (hereafter named logBF) of
293 twice the natural logarithm of BF for a peak SNP above the threshold value of 6 as proposed
294 by Michenet et al. (2016). All SNPs close to the peak SNP and having a logBF greater than 2.5
295 were considered in the QTL region. The algorithm started at the peak SNP for each
296 chromosome, followed by a sliding window of 150 kb on both sides of the peak SNP. A sliding
297 window was applied until no SNP had a logBF greater than 2.5 in the current window, defining
298 the borders of our QTL region, i.e., the credibility interval for the location of the causal
299 mutation. In addition, we considered the putative existence of a QTL if $5 \leq \log\text{BF} < 6$ for a peak
300 SNP and the corresponding QTL region explained at least 0.1% of the total genetic variance.

301 The genetic variation explained by a QTL region was calculated by the explained
302 variance of each SNP in QTL region as:

$$303 \quad \sigma_{QTL}^2 = \sum_i 2p_i(1 - p_i)a_i^2$$

304 With p_i the MAF of the SNP $_i$ and a_i the effect of the SNP located in the QTL region.

305 All annotated genes within each QTL region are listed in Supplementary Table S1 based
306 on the NCBI annotation released for *Oncorhynchus mykiss* Arlee genome reference assembly

307 USDA_OmykA_1.1. (GCA_013265735.3) (Gao et al., 2021). The potential candidate genes that
308 were meaningfully associated with acute hypoxia were subjected to further discussion.

309 **2.7 Comparison of TLE performances across different genotypes**

310 Homozygote standardized TLE difference was derived as the performance difference
311 between the two homozygous genotypes AA = genotype coded as 0, and BB = genotype coded
312 as 2) expressed in % of genetic standard deviation (σ_a): $(BB - AA) / \sigma_a$. Standardized TLE
313 dominance effect was calculated as the difference between the performance of the
314 heterozygote genotype (AB = genotype coded as 1) and the average performance of the two
315 homozygous genotypes expressed in % of genetic standard deviation: $[(AB - (AA + BB)/2)] / \sigma_a$.

316

317 **3. Results**

318 **3.1 Hypoxia challenge**

319 The mean weight of 1,320 challenged fish was 50.8 ± 11.8 g, and the average time to
320 loss of equilibrium (TLE) was 98.9 ± 71.8 min. (Table 1). The cumulative time to loss of
321 equilibrium within each trial is shown in Figure 1. The initial level of dissolved oxygen (DO)
322 started from 8.7 to 9.2 mg/L⁻¹ and was gradually reduced to 2 – 3 mg/L⁻¹ two hours after the
323 beginning of the challenge (Table 1, Supplementary Fig. S1). Then, after 3 hours of challenge,
324 the DO was kept constant (1 – 2 mg/L⁻¹) until the end of a given trial. The average level (across
325 all trials) of DO when the first fish lost its equilibrium was 3.5 mg/L⁻¹, 50% of fish at 1.7 mg/L⁻¹
326 and the last fish at 1.3 mg/L⁻¹ (Table 1).

327

328 **3.2 Parentage assignment**

329 Of 1,320 genotyped fish, 1,314 (99.5%) were uniquely assigned to a single parental pair
330 using pedigrees. The number of progeny per sire varied from 3 to 27, with an average of 13,

331 and from 1 to 32 per dam, with an average of 14. Assigned fish (single parental pair) belonged
332 to 646 full-sib families.

333 **3.3 Variance components**

334 The estimates of variance components for TLE using different models and density of
335 genotypes are shown in Table 2. The highest heritability estimate was based on pedigree
336 (0.28). Genomic heritability estimates (0.22 – 0.24) were slightly lower than the pedigree
337 estimate. Maternal effects explained a modest but significant part of phenotypic variance
338 across all studied models (0.09 – 0.10).

339

340 **3.4 Efficiency of genomic selection**

341 The criteria for assessing the efficiency of the selection (pedigree or genomic) are
342 summarized in Table 3 (accuracy (r) and bias (b)).

343 Inflation coefficients were statistically not indistinguishable from 1, while slightly lower
344 for GBLUP than for BLUP EBVs, so (G)EBVs were not biased. On average, GBLUP accuracy was
345 similar for MD and HD genotypes (0.65) and was 11% higher than BLUP accuracy (0.59).
346 However, of the 100 replicates of the validation and training populations, a gain in accuracy
347 between GBLUP and BLUP was observed for only 82 replicates (Figure 2).

348

349 **3.5 QTLs for acute hypoxia tolerance**

350 In summary, GWAS detected three significant and two putative QTLs using HD imputed
351 genotypes (Figure 3) with the statistical characteristics described in Table 4. However, none
352 of them explained over 1% of genetic variation. Hence, the genetic architecture of hypoxia
353 tolerance seems to be highly polygenic.

354 The main QTL was named Omy31_1. It explained 0.8% of the genetic variance and
355 spanned the region from 19.93 to 21.56 Mb on the chromosome Omy31. This was the only
356 significant QTL that could be identified using MD genotypes (results not presented). All genes
357 annotated within the QTL Omy31_1 are graphically visualized in Figure 4. The peak SNP for
358 this QTL was located at 20.876 Mb in the intergenic region between *aff2* (AF4/FMR2 family
359 member 2) and *ids* (iduronate 2-sulfatase isoform X1 – X2) genes. The Bayesian analysis
360 identified the same peak SNP position of the QTL using two different seeds.

361 A second QTL region was found on the same chromosome (Omy31_2), spanning from
362 33.43 to 33.97 Mb and explaining only 0.3% of the genetic variance. The peak SNP for this QTL
363 was located at 33.812 Mb, in the *smu1* gene (WD40 repeat-containing protein SMU1).

364 The third significant QTL explained only 0.2% of the genetic variance and spanned the
365 region from 22.62 to 22.99 Mb on Omy20. Its SNP was located on 22.880 Mb in the gene *noxo1*
366 (NADPH oxidase organizer 1).

367 Two other putative QTLs were also identified for hypoxia tolerance. The first one was
368 on Omy15, spanned the region from 17.58 to 18.32 Mb, and explained 0.2% of the genetic
369 variance. The peak SNP for this QTL was located at 17.668 Mb in the *bcl2a* (apoptosis regulator
370 Bcl-2) gene. The second putative QTL was located on Omy28 between 14.92 and 15.09 Mb
371 and also explained 0.2% of the genetic variance. The peak SNP for this QTL was located close
372 to the *mylk3* (myosin light chain kinase 3) gene.

373

374 **3.6 Comparison of TLE performances across different genotypes**

375 Homozygote standardized TLE difference and standardized TLE dominance effect were
376 calculated for the peak SNPs of all significant and putative QTLs (Table 4). Statistical

377 differences ($p < 0.05$) in the TLE performance for genotypes at all identified QTLs are listed in
378 Supplementary Table S2.

379 The performance difference between the two homozygous genotypes ranged from
380 56.5% to 118.5% of genetic standard deviation in favour of the homozygotes BB (coded 2 in
381 the GWAS). The TLE performance comparisons for genotypes at QTLs on Omy31_1 and Omy28
382 are illustrated in Figure 5. For Affx-569844518 (peak SNP of QTL Omy31_1), the TLE
383 performance of the homozygote (GG) was better (128.6 ± 91.4 min.) in comparison to the
384 homozygote (AA) (89.6 ± 65.7 min.) and heterozygote (112.3 ± 77.3 min.) (Figure 5A). For Affx-
385 1237683396 (peak SNP of QTL Omy28), the TLE performance of the homozygote (CC) was
386 higher (120.9 ± 81.3 min.) compared to the homozygote (AA) (93.5 ± 69.5 min.) and
387 heterozygote (91.2 ± 65.2 min.) (Figure 5B). A complete dominance effect of the unfavourable
388 allele (A) was observed at Affx-1237683396 (QTL on Omy28) as the performances of the
389 heterozygous individuals were similar to those of the (AA) homozygotes (Supplementary Table
390 S2). A full additive QTL with codominance effects of the two alleles was observed on Omy20
391 (the dominance effect was estimated close to zero, 1.7%).

392

393 **4. Discussion**

394 Besides major diseases such as flavobacteriosis, IPN or SHV (Yáñez et al., 2014; Fraslin
395 et al., 2020b), hypoxia is one of the most critical threats to rainbow trout aquaculture
396 production (Van Raaij et al., 1996; Hou et al., 2020). Yet, a limited number of studies dealing
397 with the genetic basis of hypoxia tolerance have been conducted on salmonid species (Anttila
398 et al., 2013; Scott et al., 2015; Borey et al., 2018; Lagarde et al., Submitted), and genetic
399 determinism of this trait is still unknown. Hence, we aimed to estimate the genetic

400 architecture of acute hypoxia tolerance by estimating this heritability of this trait and its
401 potential for genomic selection and by proposing potential candidate genes for the main QTLs.

402 A new high-density (HD) 665K SNP array (Bernard et al., 2022) was used for the first
403 time for GWAS on a rainbow trout population. This HD chip was used for the imputation step
404 using HD genotypes of parents to get imputed HD genotypes of challenged offspring.
405 Genotype imputation of challenged fish from MD (medium-density) to HD showed a high
406 potential for identifying new QTLs and refining positions of QTL identified on MD genotypes.

407

408 **4.1 Estimation of the variance components of hypoxia tolerance: potential for selective** 409 **breeding**

410 We found a maternal effect explaining a significant part of the phenotypic variance of
411 hypoxia tolerance (Table 2.), mostly typical for growth at early stages in salmonids (Blanc,
412 2002; Fishback et al., 2002; Haffray et al., 2012). One explanation might be the
413 transgenerational epigenetics effect of dams (Wolf and Wade, 2009). Accordingly, Ho and
414 Burggren (2012) demonstrated that parental hypoxic exposure in adult zebrafish (*Danio rerio*)
415 has profound epigenetic effects on the morphological and physiological phenotype of their
416 offspring. However, as the females and their previous generations were reared in the same
417 conditions, additional investigations are needed to identify the rearing factors that may have
418 indirectly induced this potential epigenetic effect. Another hypothesis could be based on
419 different hypoxia-tolerant mitochondrial genomes as was reported in mitochondria
420 differences of cerebral cortex cells of tolerant- and susceptible-to-hypoxia rats (Dudchenko et
421 al., 1993; Luk'yanova et al., 1995). However, in fish, no data are to date available concerning
422 the involvement of mitochondria in O₂ sensing, and thus this hypothesis could be of interest
423 for further research investigation (Gattuso et al., 2018).

424 Regardless of the evaluation model applied, we estimated moderate heritability of TLE,
425 with similar values estimated through MD or HD genomic relationship matrices, as previously
426 observed in rainbow trout by Fraslin et al. (2020a). To our knowledge, there were only two
427 estimates in the literature to date showing high heritability for hypoxia tolerance (0.50 and
428 0.61, respectively) in common carp (Nagy et al., 1980) and large yellow croaker (Ding et al.,
429 2022). Furthermore, previous studies dealing with acute hypoxia challenges showed
430 significant inter-family differences in Atlantic salmon (Anttila et al., 2013) or catfish (Wang et
431 al., 2017; Zhong et al., 2017), as well as between-isogenic lines differences (Borey et al., 2018;
432 Lagarde et al., Submitted) and between-strains differences (Scott et al., 2015; Strowbridge et
433 al., 2021) in rainbow trout. So, there is substantial evidence for standing additive genetic
434 variation in hypoxia tolerance in fishes, which might be exploited by genetic selection.
435 However, genetic correlations between hypoxia tolerance and other production traits (e.g.,
436 harvest weight, slaughter yields, muscle fat etc.) need to be further assessed before
437 integrating hypoxia tolerance in a future breeding program of rainbow trout.

438

439 **4.2 Genomic prediction for hypoxia tolerance: increased accuracy compared to pedigree-** 440 **based selection**

441 Genomic selection (GS) is currently implemented in several aquaculture breeding
442 programs (Boudry et al., 2021) and has been shown to improve selection accuracy, thus
443 leading to higher genetic gains (Robledo et al., 2017). Besides, in fish species, GS is especially
444 interesting for traits that cannot be measured directly on selection candidates (R2D2
445 Consortium et al., 2021), for example, disease resistance and meat quality, but also for traits
446 associated with environmental changes like salinity, thermal or hypoxia tolerance (Gjedrem
447 and Rye, 2016; Robledo et al., 2017; Houston et al., 2020).

448 Our results showed that genomic prediction for TLE would lead to a relative increase
449 of ~ 11% for GS accuracy compared to the pedigree-based selection, considering a reference
450 population of 1000 individuals. However, only a few studies investigated selection accuracy
451 for environmental stress-related traits such as heat tolerance in Pacific abalone (*Haliotis discus*
452 *hannai*) (Liu et al., 2022) and salinity tolerance in eastern oyster (*Crassostrea virginica*)
453 (McCarty et al., 2022) or growth-related traits under chronic thermal stress in rainbow trout
454 (Yoshida and Yáñez, 2022). Still, both genomic prediction accuracies and relative increase in
455 accuracy in comparison to PBLUP were in a similar range as in this study. Genomic selection
456 may thus significantly improve tolerance to hypoxia and other environmental stress-related
457 traits, supported by the advantage of phenotyping only the reference population, but the
458 relative expected gains need to be balanced with the operational costs of genotyping
459 (Sonesson and Meuwissen, 2009).

460 Even though genotyping costs are gradually decrease yearly, dense SNP arrays are still
461 expensive. Genotype imputation to generate high-density markers is thus a cost-effective
462 method. In general, the accuracy of genomic prediction is highly associated with the genotype
463 density used, which means that increasing marker densities should generate higher accuracies
464 (Tsai et al., 2016; Correa et al., 2017; Yoshida et al., 2019). However, we observed no increase
465 in prediction accuracy using HD-imputed genotypes compared to MD genotypes. It illustrated
466 that high-density (imputed) markers might not be necessary for genomic prediction as
467 previously reported in pigs (Song et al., 2019), cattle (Gunia et al., 2014; Van Binsbergen et al.,
468 2015), and salmonids (Yoshida et al., 2018a; Yoshida et al., 2018b). Accordingly, recent
469 genomic studies are widely focused on optimising low-density SNP panels to get strong
470 predictive accuracy still outperforming BLUP (Vallejo et al., 2017; Vallejo et al., 2018; Kriaridou
471 et al., 2020; Griot et al., 2021).

472

473 **4.3 Genetic architecture of hypoxia tolerance: a highly polygenic trait and identification of**
474 **potential candidate genes**

475 As far as we know, this is the first study that identified significant QTLs associated with
476 tolerance to hypoxia in rainbow trout. We found three significant QTLs (one on Omy20 and
477 two on Omy31) and two putative QTLs (on Omy15 and Omy28), but they explained each only
478 a limited proportion of genetic variation (0.2% – 0.8%). It suggests a highly polygenic nature
479 of hypoxia tolerance controlled by many loci of small effect (Houston et al., 2020). In previous
480 studies, multiple significant and suggestive SNPs associated with hypoxia tolerance explained
481 between 4.22 – 12.44% (four linkage groups – LGs) of phenotypic variation in catfish strains
482 and hybrids (Zhong et al., 2017; Wang et al., 2017), 6.6 – 14.7% (five LGs) in Nile tilapia (Li et
483 al., 2017), up to 32% (four LGs) in golden pompano (San et al., 2021) and 5.5 – 18% (four LGs)
484 in large yellow croaker (Ding et al., 2022). Thus, identified SNPs had a significantly stronger
485 effect on hypoxia tolerance than in our study. However, those studies were focused on a
486 limited number of tolerant/sensitive fish from a few number of different families used for
487 GWAS, which may explain this difference – 208 fish (Zhong et al., 2017), 376 fish (Wang et al.,
488 2017), 45 fish (Li et al. 2017), 100 fish (San et al., 2021) and 398 fish (Ding et al., 2022) in
489 contrast to our study population – 1,320 fish from hundreds of families. Consequently,
490 comparing these studies might be difficult and partially irrelevant. In any case, all studies
491 reinforce the evidence of the polygenic architecture of hypoxia tolerance regardless of the
492 studied species and populations, statistical models or marker densities. However, HD imputed
493 genotypes significantly refined our QTL regions by filling the gaps of missing genotypes on the
494 MD SNP panel. This is consistent with previous studies that also led to refining QTL and
495 candidate genes associated with various performance traits of dairy cattle (Höglund et al.,

496 2014; Wu et al., 2015; Nayeri et al., 2016), pigs (Yan et al., 2017; Xu et al., 2019) and fishes
497 (Palaiokostas et al., 2018; Fraslin et al., 2020a; Yoshida and Yáñez, 2021) using imputed HD
498 genotypes or sequence data.

499 Although each QTL does not explain a large part of the genetic variance at the
500 population level, significant phenotypic differences between individuals of different
501 genotypes at peak SNPs across all significant and putative QTLs were observed. The
502 association of favourable homozygous genotypes significantly prolonged TLE in the range of
503 17% to 30% (Supplementary Table S2). Thus, these SNPs might be used in marker-assisted
504 selection for producing juveniles with tolerance for hypoxia in rainbow trout. Similarly,
505 significant individual differences among different genotypes of the main SNPs associated with
506 hypoxia tolerance were previously observed in golden pompano (San et al., 2021) and large
507 yellow croaker (Ding et al., 2022).

508 Within the list of 113 genes annotated in our 5 identified QTL regions (see
509 Supplementary Table S1), we proposed sixteen functional candidate genes with a meaningful
510 biological association to hypoxia tolerance (*ids*, *fmr1*, *arx*, *lonrf3*, *commd5*, *map4k4*, *smu1*,
511 *b4galt1*, *re1*, *abca1*, *noa1*, *igfbp7*, *noxo1*, *bcl2a*, *trim25*, *mylk3*). The potential candidate genes
512 were firstly assessed with the database of Fish Hypoxia Responsive Genes (HRGFish) (Rashid
513 et al., 2017). Furthermore, we also focused on the functional information given in the Mouse
514 Genome Informatics (MGI) resource studied phenotypes in mutant mice (Eppig, 2017) or the
515 zebrafish database (ZFIN) related to phenotypes in mutant zebrafish (Sprague et al., 2006).

516 The peak SNP of the main QTL (Omy31_1) was located in the intergenic region between
517 *aff2* (AF4/FMR2 family member 2) and *ids* (iduronate 2-sulfatase) genes. Interestingly, a
518 mutation of the *ids* gene in a zebrafish line (*ids*^{ia200/ia200}) led to a significantly larger liver
519 (Bellesso et al., 2018). The liver is a significant source of glycogen which is the first mobilized

520 energy reserve during acute hypoxia leading to the glycogenolysis process and immediate
521 increase of plasma glucose and glycogen, further increasing blood lactate concentration
522 (Omlin and Weber, 2010; Li et al., 2018; Abdel-Tawwab et al., 2019; Léger et al., 2021).
523 Therefore, liver size and glycogen level play a significant role in fish survival cope with acute
524 hypoxia (Li et al., 2018), physiological stress response (Crespel et al., 2011) and energy
525 mobilization during starvation (Crespel et al., 2013; Zhao et al., 2021). Similarly, male knockout
526 mice (IdS-KO, ID MGI:259752) phenotypes for the *ids* gene exhibited significantly larger liver,
527 spleen, and lungs and were hypoactive compared to wild mice (Garcia et al., 2007). This agrees
528 with typical behaviour under hypoxia when some fish species remain static at the tank bottom
529 to save their energy for facing the hypoxic condition (Abdel-Tawwab et al., 2019). Therefore,
530 the *ids* gene might be suggested as a potential functional candidate. Besides, the *fmr1* gene
531 (synaptic functional regulator FMR1) was annotated in the close vicinity of the peak SNP. The
532 *fmr1* zebrafish mutant lines showed hyperactivity and abnormal swimming behaviour (Hu et
533 al., 2020) and decreased startle reflex in case of loss of function of *fmr1* in mice (Chen and
534 Toth, 2001; Pietropaolo et al., 2011; Rossignol et al., 2014). Abnormal behaviour under
535 hypoxia conditions has been previously observed in fishes manifesting as rapid swimming in a
536 circular motion with a wide mouth gape (Domenici et al., 2013; Bowyer et al., 2014) or as
537 decreased startle reflex known as antipredator behaviour (Domenici et al., 2007). Moreover,
538 *arx* gene (homeobox protein ARX-like) might also be proposed as an interesting functional
539 candidate belonging to this QTL. Loss of function of this gene may cause hypoglycemia in mice
540 (Collombat et al., 2003) and thus may block the natural response to acute hypoxia by upsetting
541 the metabolism of carbohydrates (Polakof et al., 2012; Abdel-Tawwab et al., 2019). Let us also
542 mention genes *lonrf3* (LON peptidase N-terminal domain and RING finger protein 3), *commd5*
543 (COMM Domain-Containing Protein 5), and *fam199x* (protein FAM199X), which are in our QTL

544 region as well as in the vicinity of the main SNP associated to hypoxia tolerance in golden
545 pompano (San et al., 2021). Interestingly, mouse mutant genotype hm1 of *lonrf3* (Dickinson
546 et al., 2016) and *commd5* gene in rats (Matsuda et al., 2014) are linked to calcium influx, which
547 is strongly modified under hypoxia conditions and inhibits the expression of myoglobin
548 (Kanatous et al., 2009). Myoglobin is an oxygen-binding hemoprotein that is widely thought
549 to be expressed exclusively in oxidative skeletal and cardiac myocytes, where it plays a crucial
550 role in coping with both acute and chronic hypoxia by the supply of oxygen to the fish heart
551 (Rashid et al., 2017), as previously reported, for example, in the Tibetan Plateau fish
552 (*Glyptosternum maculatum*) (Qi et al., 2018), Japanese medaka (*Oryzias latipes*) (Wawrowski
553 et al., 2011) and zebrafish (Jaspers et al., 2014). Besides, MAPK (mitogen-activated protein
554 kinases) signalling pathway have been shown to be involved in low oxygen tolerance in fishes
555 (Wang et al., 2017; Tian et al., 2019; Yu et al., 2021). Thus, the candidate gene *map4k4*
556 (mitogen-activated protein kinase 4) may also play an important role in response to hypoxia
557 challenges.

558 The second significant QTL was also detected on chromosome 31 (Omy31_2) between
559 33.43 Mb and 33.97 Mb, with the peak SNP positioned within the *smu1* gene, a member of
560 the WD40-repeat protein family. Loss of *smu1* function leads to multiple cellular defects,
561 including chromosomal instability, aberrant DNA replication and alternative RNA splicing
562 events. Accordingly, the DNA damage is also closely linked to hypoxia, as was previously
563 described in common carp and Nile tilapia (Poon et al., 2007; Mahfouz et al., 2015; Mustafa
564 et al., 2015). Besides, the *smu1* gene in zebrafish was upregulated under acute hypoxia
565 (Ragsdale et al., 2020). Thus, the *smu1* gene might be proposed as an interesting candidate
566 gene. We also identified three other potential candidate genes linked to hypoxia: *b4galt1*, *re1*
567 and *abca1*. *B4galt1* (beta-1,4-galactosyltransferase 1) and its exclusive function in the Golgi

568 compartment is a prerequisite for full catalytic activity. In contrast, a lack of this function is
569 associated with cancers and intracellular hypoxia in human (Hassinen et al., 2019; Khoder-
570 Agha et al., 2019). *Re1* was responsible for regulating approximately 20% of the hypoxia-
571 repressed genes in human embryonic kidney cells. Hence, this gene was proposed as a key
572 mediator of gene repression in hypoxia (Liang et al., 2014; Cavadas et al., 2016). *Abca1*
573 (Phospholipid-Transporting ATPase ABCA1) is closely linked with hypoxia inducible factor α
574 (HIF- α) which increases *abca1* promoter activity. Thus, an expression of *abca1* might further
575 stimulate the regulation of other hypoxia-inducible genes (Zhu et al., 2013; Pelster and Egg,
576 2018; Dzhililova and Makarova, 2020). Moreover, not far from the peak SNP, an interesting
577 gene *noa1* encodes nitric oxide-associated protein 1. It is involved in regulating mitochondrial
578 protein translation and respiration, thereby controlling mitochondrial metabolism under
579 acute and long-term hypoxia as previously described in goldfish (*Carassius auratus*) (Farhat et
580 al., 2021), mice (Heidler et al., 2011) and humans (Tang et al., 2009). Mitochondria play a
581 crucial role in coordinating responses to low oxygen because of their ability to detect
582 physiological changes and supply the body with ATP through oxidative phosphorylation
583 (OXPHOS) (Thomas et al., 2019). Moreover, the nitric oxide synthase (NOS) expression was
584 observed to enhance the expression of HIF-1 α that activates several pivotal genes (Zhu et al.,
585 2013; Dzhililova and Makarova, 2020) linked to hypoxia tolerance in goldfish and crucian carp
586 (*Carassius carassius*). We thus hypothesize that *noa1* gene may have a complex role in
587 rainbow trout response to hypoxia. In addition, the *igfbp7* gene (insulin-like growth factor-
588 binding protein 7 precursor) might also be considered a potential candidate gene. Genes
589 belonging to IGFs group are hypoxia-inducible genes involved in response to hypoxia and may
590 have an important impact on fish growth during hypoxia conditions (Kajimura et al., 2006;
591 Olsvik et al., 2013; Rashid et al., 2017; Hou et al., 2020; Aksakal and Ekinci, 2021). Moreover,

592 the *igfbp7* gene may inhibit the stimulatory effect of vascular endothelial growth factor (VEGF)
593 (Tamura et al., 2014; Ma et al., 2016), a key regulator of angiogenesis, hematopoiesis and
594 vascular density under low-oxygen conditions that activate genes involved in a series of
595 responses to hypoxia (Rehn et al., 2011; Dzhililova and Makarova, 2020). In line with our
596 finding, Yu et al. (2021) annotated a candidate gene (*igf1ra*) belonging to the IGFs group in a
597 genome-wide association analysis of adaptation to long-term oxygen stress in Nile tilapia.

598 Within the two main QTLs on Omy31, seven and five genes are thus very convincing
599 functional candidates whose interplay may lead to behavioural, morphological, and
600 physiological responses to acute hypoxia stress. The response to acute hypoxia in rainbow
601 trout could then be explained through the supergene concept (Schwander et al., 2014).
602 Supergenes are tight clusters of multiple neighbouring genes inherited together because of
603 close genetic linkage, each affecting a different developmental, physiological or behavioural
604 characteristic. In combination, they provide integrated control of complex adaptive
605 phenotypes segregating within species (Schwander et al., 2014). Recently, a supergene was
606 identified in rainbow trout as a 55-Mb double-inversion region on Omy5 that mediates sex-
607 specific migratory tendency (Pearse et al., 2019). Here we suggest that two supergenes on
608 Omy31 may explain such enrichment of the QTL regions for involved hypoxia-responsive
609 genes.

610 On Omy20, the peak SNP was located in the intergenic region of the *noxo1* gene
611 (NADPH oxidase organizer 1), which is associated with NADPH oxidase — the enzyme
612 responsible for the production of reactive oxygen species (ROS) (Fu et al., 2000; Sahoo et al.,
613 2016). ROS can lead to oxidative stress during periods of environmental stress for fish
614 (Wischhusen et al., 2020). However, ROS are usually balanced by an antioxidant (redox)
615 defence and are considered a potent bactericide that actively destroys invading pathogens

616 (Birnie-Gauvin et al., 2017; Chowdhury and Saikia, 2020). But acute hypoxia commonly results
617 in a disbalance between the production of oxidant and antioxidant components (oxidative
618 stress) and thus significantly damages cell structures and DNA. In addition, hypoxia-tolerant
619 fish appear to have an anticipatory response during low-oxygen availability by enhancing their
620 ability to eliminate ROS production upon return to normoxia (Birnie-Gauvin et al., 2017; Qi et
621 al., 2020). Hence, the *nox01* gene seems to be a promising functional candidate, playing an
622 essential role in oxidative response pathways.

623 The peak SNP of the putative QTL on Omy15 was located within the gene *bcl2a*
624 (apoptosis regulator Bcl-2). Bcl-2 proteins are a family of regulatory proteins that regulate cell
625 apoptosis by either inducing or repressing cell death and are involved in several biological
626 processes related to immune responses (Kratz et al., 2006). *Bcl-2a* gene was repressed after
627 acute hypoxia stress in zebrafish (Cai et al., 2018) and channel catfish (Yuan et al., 2016),
628 indicating that this gene is potentially involved in the hypoxia response by reducing cell
629 apoptosis or autophagy, and could be considered a potential candidate gene. We may also
630 propose *trim25* as a convincing candidate gene because the peak SNP is located just before
631 this E3 ubiquitin/ISG15 ligase protein, with a major role in the initiation of intracellular
632 antiviral response to herpesviruses (Gack et al., 2008). It is well known that hypoxia has
633 substantial effects on fish's physiological and immune responses, which can depress their
634 immune system leading to greater susceptibility to diseases (Giomi et al., 2016; Esteve et al.,
635 2017; Sae-Lim et al., 2017; Abdel-Tawwab et al., 2019). Hence, loss of function of this gene
636 may block an appropriate antiviral response as previously observed in common carp
637 susceptible to koi herpesvirus (Palaiokostas et al., 2018).

638 Concerning the second putative QTL on Omy28, the candidate gene *mylk3* (myosin
639 light chain kinase 3) was found close to the peak SNP. MGI mutant phenotype for the *mylk3*

640 gene was associated with several heart-related changes such as the increased response of the
641 heart to induce stress, abnormal heart morphology, cardiac hypertrophy and necrosis (Ding
642 et al., 2010; Bischof and Krishnan, 2016; Yuan et al., 2016) or influenced smooth blood
643 pressure and angiogenesis in humans (Gordeuk et al., 2012). We thus hypothesise that acute
644 hypoxia stress might lead to severe heart and blood changes causing limited oxygen transport
645 to tissues and organs (Gattuso et al., 2018; Abdel-Tawwab et al., 2019).

646

647 **5 Conclusions**

648 In the present study, a newly designed HD chip was used to impute MD to HD markers
649 in fish exposed to acute hypoxia. The GWAS showed clearly refined QTL regions and SNP peak
650 position using HD-imputed markers but confirmed that hypoxia tolerance is of highly
651 polygenic nature. Three significant and two putative QTLs explaining between 0.2% and 0.8%
652 of the genetic variance, were identified for acute hypoxia tolerance, defined as TLE. However,
653 moderate heritability suggests a solid potential to improve TLE in the studied rainbow trout
654 population by genetic selection. As the variance explained by the five QTLs altogether is less
655 than 5% of the total genetic variance, genomic selection should be promoted rather than
656 marker-assisted selection to improve the selection efficiency of the broodstock population.
657 However, marker-assisted selection may help to multiply broodstock producing offspring with
658 high tolerance to hypoxia for production purposes. Finally, sixteen genes (*ids, fmr1, arx, lonrf3,*
659 *commd5, map4k4, smu1, b4galt1, re1, abca1, noa1, igfbp7, noxo1, bcl2a, trim25, mylk3*) were
660 proposed as potential functional candidates involved in hypoxia tolerance. Taking all proposed
661 candidate genes within two main QTLs on Omy31 (12 out of 16 genes), we may hypothesize
662 that the complex response to acute hypoxia in rainbow trout is encoded by two supergenes.

663 However, further functional validation of their effects may help to specify the biological
664 mechanisms triggering a response to acute hypoxia in diploid rainbow trout.

665

666

667

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1286

1287 **Table 1.** Summary statistics of average body weight and hypoxia tolerance phenotypes and
 1288 dissolved oxygen levels during hypoxia challenge trials

Trial	Phenotypes			Dissolved oxygen level mg/L ⁻¹			
	N ^a	BW (g) ^b	TLE (min.) ^c	Initial	First fish	50%	Last fish
1.	202	46.1±11.1	100.1±65.0	9.4	2.2	1.6	1.2
2.	205	47.3±10.6	65.3±60.1	9.6	2.1	1.5	1.3
3.	202	47.4±10.7	111.3±80.0	9.1	2.3	1.6	1.2
4.	203	52.9±11.8	115.7±64.4	9.3	4.4	1.7	1.2
5.	206	52.5±10.7	74.6±71.0	8.8	2.4	1.7	1.5
6.	217	55.3±11.5	129.3±75.2	8.7	5.9	1.9	1.3
7.	85	57.4±12.7	89.8±44.2	9.6	5.1	2.2	1.5
Mean	189	50.8±11.8	98.9±71.8	9.2	3.5	1.7	1.3

1289 ^a number of fish

1290 ^b body weight

1291 ^c time to loss of equilibrium

1292 **Table 2.** Variance components for acute hypoxia tolerance in rainbow trout estimated with
 1293 three models (BLUP, GBLUP, Bayes C π) and two genotype densities (MD, HD)

Model	σ_a^2	σ_m^2	σ_e^2	h^2	m^2
BLUP	1332	416	2984	0.28 (0.09)	0.09 (0.04)
GBLUP_MD	1126	481	3081	0.24 (0.05)	0.10 (0.03)
GBLUP_HD	1118	471	3100	0.24 (0.05)	0.10 (0.03)
Bayes C π _MD	1054	502	3218	0.22 (0.04)	0.11 (0.03)
Bayes C π _HD	1084	484	3215	0.23 (0.04)	0.10 (0.03)

1294 σ_a^2 : additive genetic variance; σ_m^2 : maternal variance; σ_e^2 : residual variance; h^2 : heritability (standard
 1295 error); m^2 : proportion of the phenotypic variance explained by maternal effect (standard error)

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1297 **Table 3.** Mean \pm standard deviation over 100 replicates of the selection accuracy (r) and
1298 inflation coefficient (b) for BLUP and GBLUP evaluation for hypoxia tolerance using MD or HD
1299 genotypes

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	r	b
BLUP	0.594 \pm 0.079	1.456 \pm 0.260
GBLUP_MD	0.656 \pm 0.072	1.121 \pm 0.174
GBLUP_HD	0.653 \pm 0.071	1.202 \pm 0.172

1302 **Table 4.** Summary statistics for GWAS for acute hypoxia tolerance in rainbow trout using Bayes
 1303 π method

Chr.	Peak SNP	Peak position (pb)	MAF	logBF	QTL start (Mb)	QTL end (Mb)	Var (%)	Homozygote standardized TLE difference ^A	Standardized TLE dominance effect ^B
Omy15	Affx-1237442714	17668393	0.32	5.16	17.58	18.32	0.22	82.07	6.99
Omy20	Affx-569843766	22880000	0.42	6.14	22.62	22.99	0.19	59.88	-1.67
Omy28	Affx-1237683396	15091174	0.49	5.13	14.92	15.09	0.17	90.27	38.15
Omy31_1	Affx-569844518	20875730	0.22	7.37	19.93	21.56	0.78	118.54	-9.73
Omy31_2	Affx-1237632075	33812474	0.49	6.27	33.43	33.97	0.33	56.53	13.37

1304 **Chr.:** Chromosome; **logBF:** Twice the natural logarithm of the Bayes Factor; **MAF:** Minor allele
 1305 frequency; **Var(%):** The percentage of genetic variance explained by the QTL
 1306 ^A the performance difference between the two homozygous genotypes (BB-AA) expressed in
 1307 % of genetic standard deviation
 1308 ^B difference between the performance of the heterozygote genotype (AB) and the average
 1309 performance of the two homozygous genotypes (AA+BB)/2 expressed in % of genetic
 1310 standard deviation

1311 **Figure Captions**

1312 **Fig. 1.** The cumulative loss of equilibrium in response to hypoxia challenge across seven trials.
1313 Time represents the time since the first fish lost its equilibrium.

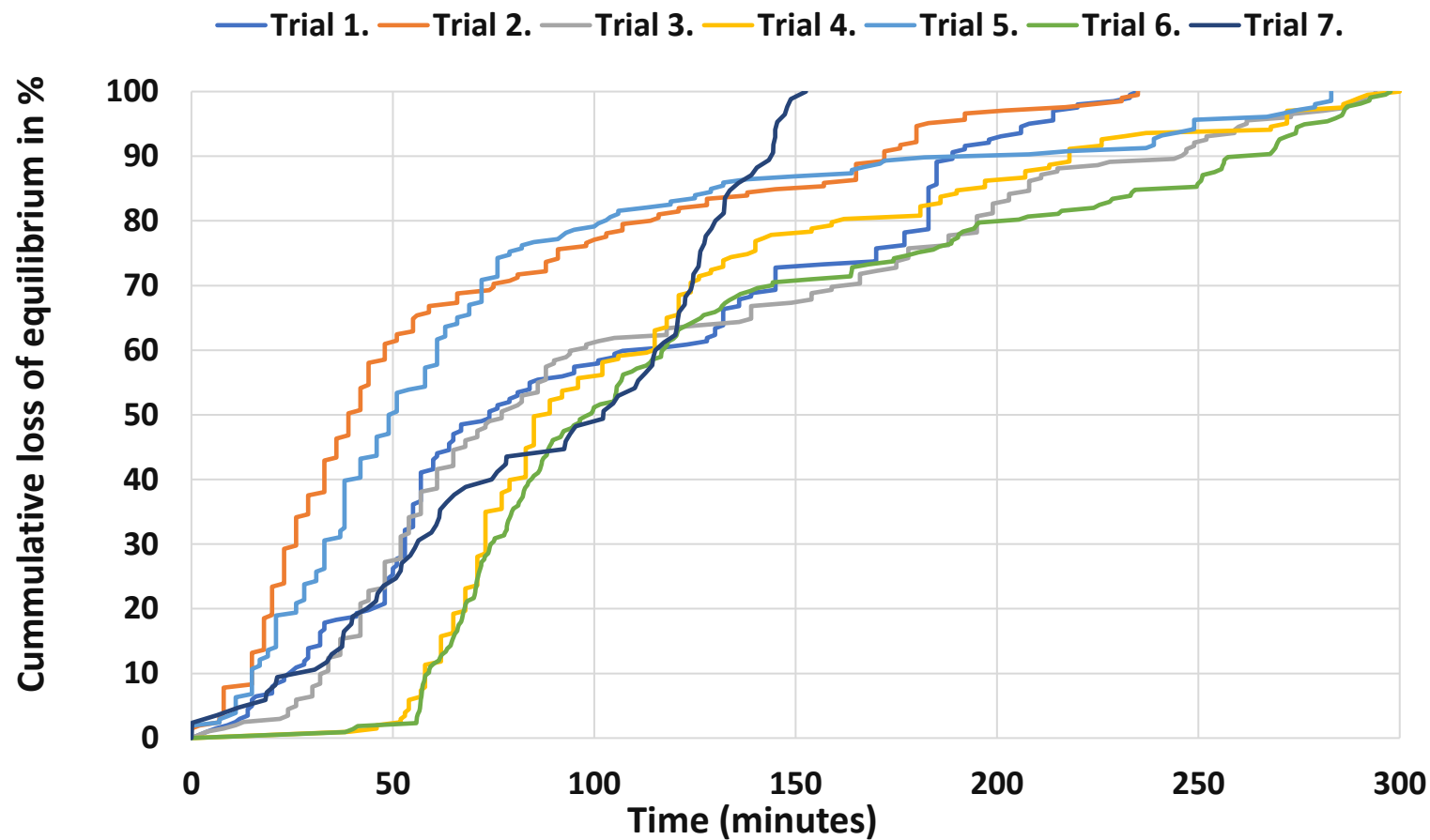
1314 **Fig. 2.** Boxplot of accuracy difference of GBLUP versus BLUP of hypoxia tolerance for each of
1315 100 replicates.

1316 **Fig. 3.** Manhattan plots of QTL detected under Bayesian GWAS for hypoxia tolerance. The
1317 dashed red line corresponds to the threshold $\log_{BF} > 6$ for defining evidence for a significant
1318 QTL and dashed blue line corresponds to the threshold $\log_{BF} > 5$ for defining evidence for a
1319 putative QTL.

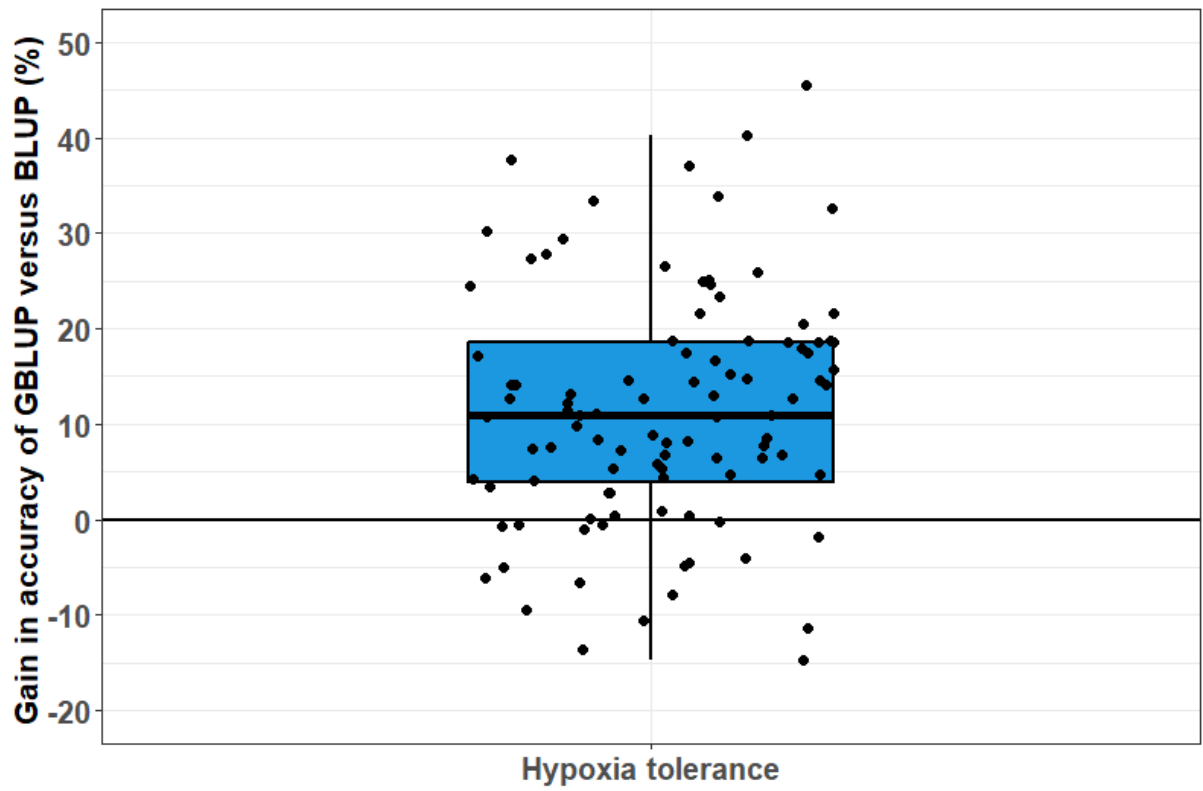
1320 **Fig. 4.** Annotated genes within the main QTL region on Omy31_1. The red dots correspond to
1321 significant SNPs that have $\log_{BF} > 6$ (dashed red line). The positions of the five genes located
1322 within the QTL region are figured by rectangles of a different colour: *slitrk4* (SLIT and NTRK-
1323 like protein 4), *slitrk2* (SLIT and NTRK-like protein 2), *fmr1* (synaptic functional regulator
1324 FMR1), *aff2* (AF4/FMR2 family member 2), *ids* (iduronate 2-sulfatase), *cracd1* (CRACD-like
1325 protein isoform), *lonrf3* (LON peptidase N-terminal domain and RING finger protein 3),
1326 *commd5* (COMM domain-containing protein 5), *fam199x* (protein FAM199X), *arx* (homeobox
1327 protein ARX-like), *il1rapl2* (X-linked interleukin-1 receptor accessory protein-like 2), *map4k4*
1328 (*mitogen-activated protein kinase 4*).

1329 **Fig. 5** Violin box plots of time to loss of equilibrium (TLE) with different genotypes of peak
1330 SNPs at QTLs located on Omy31_1 (A) and Omy28 (B). The vertical axis is the TLE of the
1331 individuals, and different colours represent different genotypes.

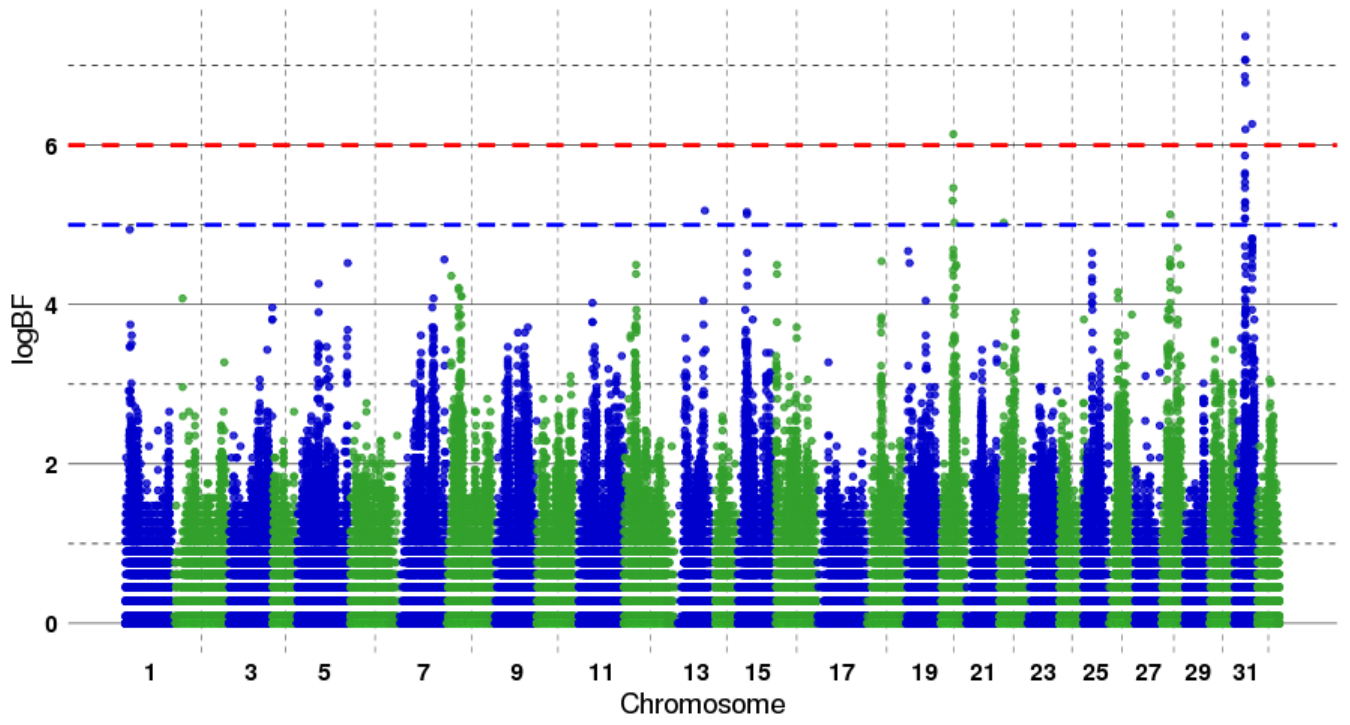
1332



1335 Fig 2.

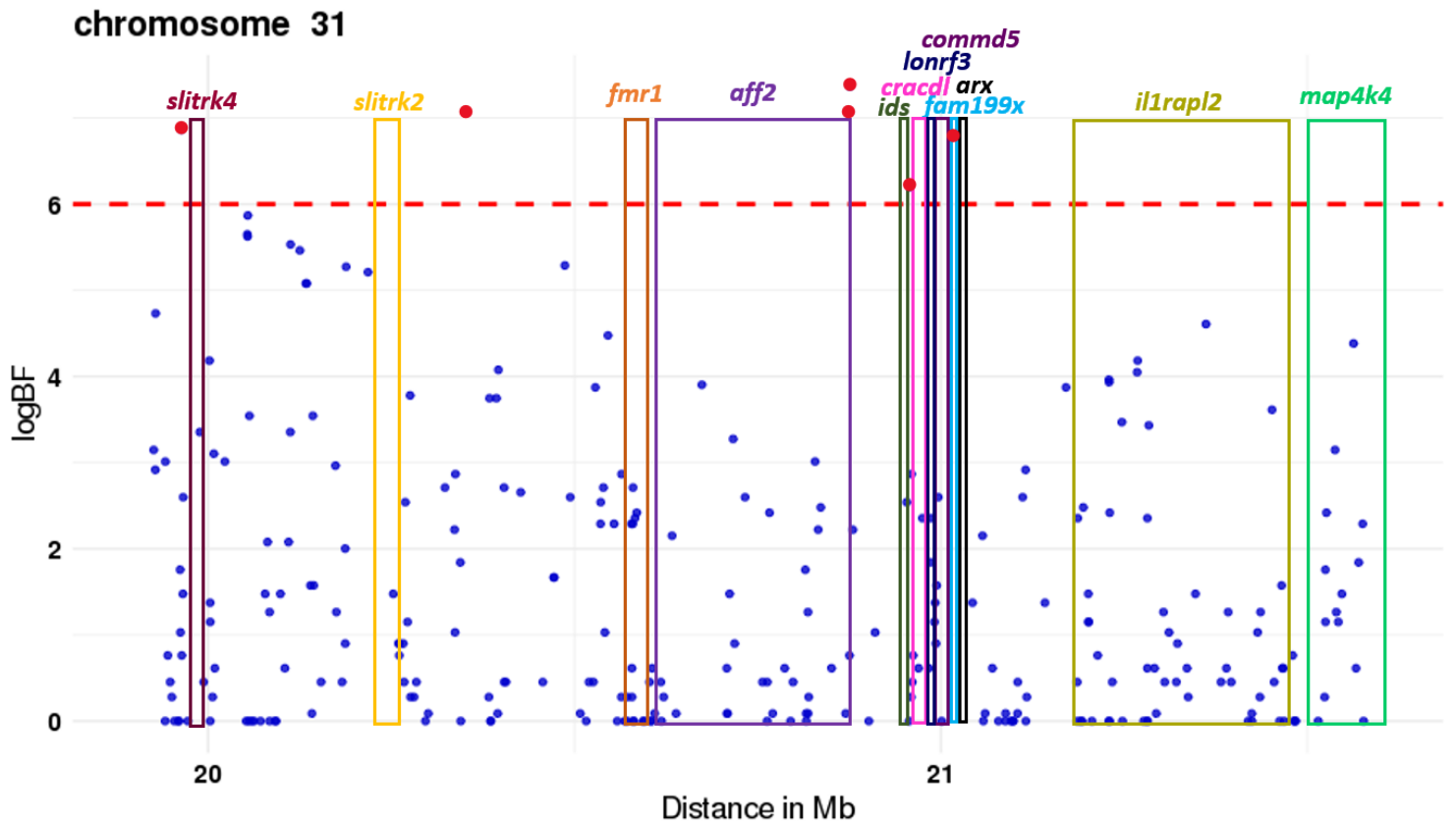


1336 Fig. 3



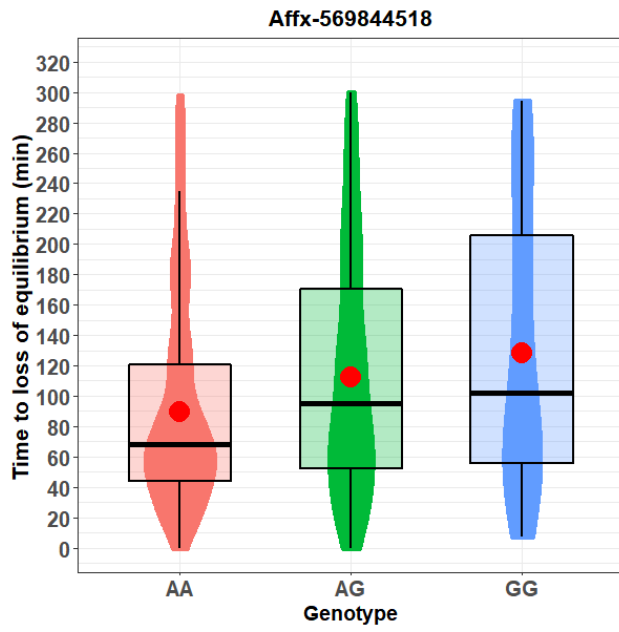
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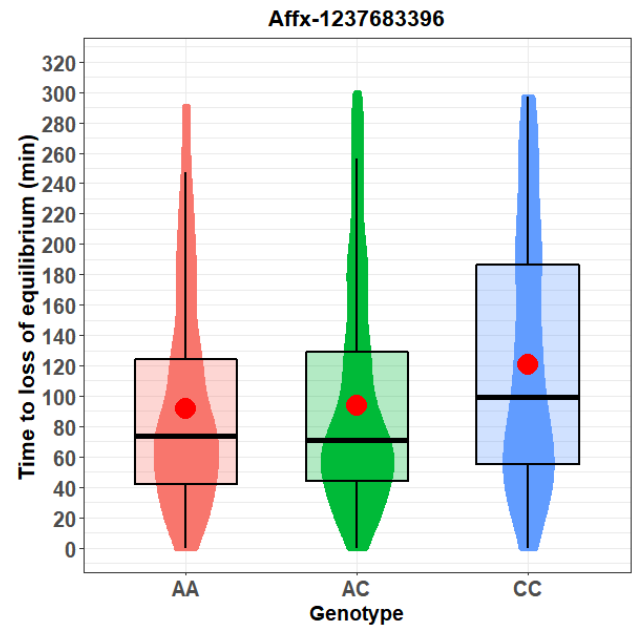


1341 Fig. 5

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B)



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