Genome-wide detection of positive and balancing selection signatures shared by four domesticated rainbow trout populations (Oncorhynchus mykiss)

K Paul, G Restoux, Florence Phocas

1 *Molecular ecology*

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Genome-wide detection of positive and balancing selection signatures shared by four domesticated rainbow trout populations (*Oncorhynchus mykiss*)

5 Paul, K.[1], Restoux, G. [1], Phocas, F. [1]

6 1. Université Paris-Saclay, INRAE, AgroParisTech, GABI, 78350 Jouy-en-Josas, France

7 Corresponding author: Florence Phocas - florence.phocas@inrae.fr

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9 **Abstract**

10 Evolutionary processes leave footprints across the genome over time. Highly homozygous

11 regions may correspond to positive selection of favourable alleles, while maintenance of

12 heterozygous regions may be due to balancing selection phenomena. We analyzed 176 genomes

13 coming from 20 sequenced US fish and 156 fish from three different French lines that were

14 genotyped using a HD Axiom Trout Genotyping 665K SNP Array. Using methods based on

15 either Run of Homozygosity or Extended Haplotype Homozygosity, we detected selection

16 signals in four domesticated rainbow trout populations. Nine genomic regions composed of 253

17 genes, mainly located on chromosome 2 but also on chromosomes 12, 15, 16, and 20, were

18 identified under positive selection in all four populations. In addition, four heterozygous regions

19 containing 29 genes putatively under balancing selection were also shared by the four

20 populations and located on chromosomes 10, 13, and 19. Whatever the homozygous or

21 heterozygous nature of the region, we always found some genes highly conserved among

22 vertebrates due to their critical roles in cellular and nuclear organisation, embryonic

23 development or immunity. We identify new promising candidate genes involved in rainbow

24   trout fitness, as well as genes already detected under positive selection in other fishes (*auts2,*

25   *atp1b3, zp4, znf135, igf-1α, brd2, col9a2, mrap2, pbx1, emilin-3*). These findings represent a

26   genome-wide map of signatures of selection common over rainbow trout populations, which is

27   the foundation to understand the processes in action and to identify what kind of diversity

28   should be preserved, or conversely avoided in breeding programs, in order to maintain or

29   improve essential biological functions in domesticated rainbow trout populations.

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31   Keywords: Runs of Homozygosity, Extended Haplotype Homozygosity, domestication, fitness,

32   selection, fish.

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1| Introduction

Any population, whether animal or plant, wild or domesticated, evolved through continuous and cumulative changes over time (Wright, 1931). It relies on various evolutionary forces, mutation, migration, selection, and genetic drift, whose relative effects may vary depending on population history and structure. For example, genetic drift is more substantial when the effective population size is small and randomly induces fixation of alleles, which may lead to degeneration and extinction due to the fixation of deleterious alleles in small populations (Smith & Haigh, 1974). When modifications of environmental conditions occur, allele frequencies will change to a new relevant equilibrium, as a result of natural selection. Indeed, favorable alleles in a particular environment due to either new mutations or standing variation, will be positively selected. In wild populations, favourable alleles are generally affecting fitness through individual survival, mating, or fertility (East, 1918; Fisher, 1958). Natural selection can also act by negative (or purifying) selection that hinders the spread of deleterious alleles (Charlesworth et al., 1995). These two processes tend to reduce the genetic diversity at the target genes but had different effect on the genome, positive selection leading to stronger selection signatures (selective sweep) than negative one. Conversely, the population's polymorphism can be actively maintained in some rare genomic regions through balancing selection that keeps an equilibrium in the frequencies of alleles. The two main biological causes of balancing selection are heterozygote advantage at a single locus, known as overdominance effect, and frequency-dependent selection with a rare-allele advantage that tends to restore a frequency equilibrium between alleles at the population level (Charlesworth, 2006, Fijarczyk & Babik, 2015).

Domestication is the evolutionary process of genetic adaptation over generations of a wild population to handling by humans and breeding in captive environments (Darwin, 1859, 1868; Price, 1984). During domestication, humans exert artificial selection pressure on the initial

68   population by choosing and organizing the reproduction of the most adapted individuals to

69   cohabitation or more globally to those whose aptitudes correspond the best to their expectations

70   (Price, 1999; Russell, 2002), such as a less fearfulness of humans (Price, 2002; Harri et al.,

71   2007). Domestication induces severe genetic bottlenecks due to the selection and reproduction

72   of only a few adapted animals from the wild population. Thus, many genetic evolutionary

73   processes, such as selection, genetic drift, and inbreeding, have a significant role in the

74   evolution of farmed animal populations (Helmer, 1992; Mignon-Grasteau et al., 2005). The

75   domestication process affects life history traits due to changes in morphological, physiological,

76   reproductive, behavioural, and immune functions (Mignon-Grasteau et al., 2005; Pulcini et al.,

77   2013; Milla et al., 2021 for review in fishes) compared to their wild relatives (Darwin, 1859,

78   1868). Wilkins et al. (2014) suggest that these specific modifications, called domestication

79   syndrome, may be due to mild deficit of neural-crest cells during embryonic development in

80   domesticated animals. In addition, both natural and artificial selection in domesticated species

81   leaves footprints across the genome, known as selection signatures, which can point to regions

82   harboring essential genes for domestication or natural fitness (Dobney & Larson, 2006; Qanbari

83   & Simianer, 2014; Wright, 2015).

84   Compared to domestication in terrestrial animals (Mignon-Grasteau et al., 2005), fish

85   domestication is recent and was first documented with carp about 2,000 years ago. The precise

86   date and location (Neolithic China or at the Roman period in Central and East Europe) of the

87   carp domestication are still debated (Balon, 1995; Balon, 2004). However, most farmed fish

88   species have only been domesticated since the last century. The rainbow trout is native to the

89   Pacific drainages of North America and to Kamchatka in Russia and its domestication started

90   in the 1870s in California (Hershberger, 1992; Gall & Crandel, 1992). It was then introduced

91   in Western Europe at the beginning of the 20th century (Fabrice, 2018).

Numerous studies have been carried out over the last ten years to detect signatures of selection in farmed fish species (Channel Catfish: Sun et al., 2014; Atlantic salmon: Mäkinen et al., 2015; Gutierrez et al., 2016; Liu et al., 2016; Pritchard et al., 2018; López et al., 2019; Carp: Su et al., 2018; Nile Tilapia: Hong et al., 2015; Cádiz et al. 2020; Yu et al., 2022; Rainbow trout: Cádiz et al., 2021; Coho salmon : López et al., 2021; Australasian snapper: Baesjou & Wellenreuther, 2021; Brown trout: Magris et al., 2022) in order to identify genomic regions involved in recent adaptation or domestication processes (Smith & Haigh, 1974; Pennings & Hermisson, 2006). In this study, we were interested in farmed rainbow trout populations as it is one of the oldest farmed fish and the analysis of genes under either positive or balancing subsequent selection in. Indeed, only a few studies on selection signatures were performed in rainbow trout. Three of them only focused on wild populations and showed signatures of selection linked to life-history variation, egg development, spawning time (Martínez et al., 2011), immune response (Limborg et al., 2012), and smoltification (Weinstein et al., 2019). The first study in domesticated rainbow trout was performed on a single Chilean population (Cádiz et al., 2021) genotyped with a 57K SNP array; identified signatures of selection were associated with early development, growth, reproduction and immune system. Recently, a high-density array (665K SNPs) was developed for rainbow trout (Bernard et al., 2022), allowing us to potentially more accurately detect signatures of selection and to compare them across various domesticated rainbow trout populations. The existence of signatures of selection shared by farmed populations from different geographical areas is essential to understand the importance of genetic diversity in several genomic regions in rainbow trout and then to identify genes having key roles in either the domestication process or fitness because conserved by all populations (Bruford et al., 2003; Yáñez et al., 2022).

115   Various approaches have been developed to reveal selection signatures within population based

116   on site frequency spectrum, linkage disequilibrium (LD), or reduction of local variability (Vitti

117   et al., 2013; Saravanan et al., 2020). Among these approaches, we will use two strategies, one

118   based on the reduction of local variability using Run of Homozygosity (ROH) metrics and the

119   second one relying on allele frequencies and the extent of LD based on Extended Haplotype

120   Homozygosity (EHH). ROH is a large homozygous stretch in the genome of an individual

121   inherited from a common ancestor to his parents (McQuillan et al., 2008; Purfield et al., 2012),

122   while EHH measures the extent of shared haplotypes through the association between a single

123   core haplotype and multiple loci at various distances from the core region (Sabeti et al., 2002).

124   In our study, we considered four populations: one INRAE experimental line (with no intentional

125   selection), two French selected lines from two different breeding companies, and a pooled

126   American population gathering samples from one wild river and four hatchery populations, all

127   coming from the North-West of the USA and closely genetically linked (Gao et al., 2018). Our

128   work aimed to discover the main genomic regions sharing strong homozygosity (positive

129   selection) or heterozygosity (balancing selection) across the four rainbow trout populations and

130   to get further insights into the nature of genes spanning these regions.

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2 | Material and methods

2.1 | Populations

135   Three French populations were considered: 14 breeding females from the INRAE synthetic line

136   SY and, 90 and 72 females from two selected lines LB and LC from the breeding companies

137   "Bretagne Truite" (Plouigneau, France) and "Viviers de Sarrance" (Sarrance, France)

6

138   respectively. The SY was developed by intercrossing several domesticated lines of rainbow

139   trout, in order to create a population with a large diversity (D'Ambrosio et al., 2019).

140   In addition, we considered an American pooled population, hereafter named HA, using the

141   whole genome sequence data of 20 fishes obtained by Gao et al. (2018). The sampling strategy

142   consisted in collecting DNA from 4 individuals in each of five locations from the North-West

143   of the USA: wild fish from Elwha River, and farmed fish from Dworshak, L. Quinault,

144   Quinault, and Shamania hatcheries. We pooled together the 20 individuals, as these five

145   populations were genetically close to each other (Supplementary Figure 1; Gao et al., 2018) and

146   greatly distant from the three French populations (Figure 1).

147

148   2.2 | Genotyping and quality control

149   High-density genotypes were obtained at the INRAE genotyping Platform Gentyane

150   (Clermont-Ferrand, France) for all the 176 French samples using the Affymetrix 665K SNP

151   array recently developed for rainbow trout (Bernard et al., 2022). We only considered the

152   genotypes for the 576,118 SNPs of the Rainbow Trout Axiom® 665K SNP array that were

153   positioned on the Arlee genome (GCA_013265735.3, Gao et al., 2021; Bernard et al., 2022).

154   From the whole-genome sequence information of the 20 American samples (Gao et al., 2018),

155   we extracted the genotypes for the same 576,118 SNPs of the HD chip.

156   Among the 177 French genotyped fish, 19 individuals with more than 30% identity-by-state

157   (IBS) with other individuals were removed from the dataset. We thus kept for the analysis 76,

158   67, 20, and 14 fish sampled from LB, LC, HA, and SY populations, respectively.

159   Then, SNP quality control was performed using PLINK v1.9 software (Chang et al., 2015).

160   Note that, to avoid limitations due to the low number of individuals in SY, quality filters were

161   made considering LC and SY together, as both populations were genotyped on the same SNP

162   plate and are close genetically (D'Ambrosio et al., 2019). About 4,000 SNPs randomly

163   distributed over all the genome were removed for all populations due to extreme deviation from

164   Hardy-Weinberg equilibrium (p-value < 10-7). It allowed us to discared SNPs with high risk of

165   wrong genotyping, in addition to the edit for SNP call rate lower than 97%. We retained 571,319

166   SNPs, 569,030 SNPs, and 573,793 SNPs on LB, 'LC- SY', and HA populations, respectively.

167   Finally, crossing the three SNP lists, we kept the 546,903 common SNPs for the analysis.

168

169   2.3 | Genetic structure of the populations

170   Genetic differentiation between populations was measured with a pairwise Fst estimate using

171   the VCFtools v0.1.13 software (Danecek et al., 2011). In addition, a principal component

172   analysis (PCA) was performed with the R package *Adegenet* (function *glPca*) (Jombart &

173   Ahmed, 2011) to visualize the genetic structure of the populations.

174

175   2.4 | Runs of homozygosity

176   Runs of homozygosity (ROH) were identified for each fish using the PLINK v1.9 *homozyg*

177   function (Chang et al., 2015) with the following options *'--homozyg-kb 500 –homozyg-window-*

178   *snp 40 –homozyg-snp 40 –homozyg-gap 500 –homozyg-density 40 –homozyg-het 1*'. ROH was

179   defined by a sliding window with a minimum length of 500 kb containing at least 40

180   homozygous SNPs. This minimum number of homozygous SNPs was chosen using the formula

181   described by Purfield et al. (2012) in order to limit the number of ROHs that might only occur

182   by chance.

183

184   2.4.1 | Estimation of inbreeding coefficients

185 The individual inbreeding coefficients (F_{ROH}) were calculated according McQuillian et al

186 (2008) as $F_{i,ROH} = \frac{\sum length(ROH_i)}{LGenome}$

187 With $\sum length(ROH_i)$ the sum of ROH length in an individual i and $LGenome$ the total length

188 of the autosomal genome covered by SNPs.

189

190 2.4.2 | Identification of ROH islands

191 For each SNP, the number of individuals with this SNP included in a ROH was calculated in

192 order to identify the regions of the genome that were frequently homozygous in each

193 population, i.e. constituting ROH islands (Nothnagel et al., 2010). These ROH hotspots may

194 then be considered as signatures of positive selection (Saravanan et al., 2021).

195 To allow the comparison of ROH islands across populations, we implemented population-

196 specific thresholds based on the ROH occurrence to define ROH islands, as proposed in many

197 studies (Purfield et al., 2017; Mastrangelo et al., 2017; Zhang et al., 2018; Peripolli et al., 2018;

198 Grilz-Seger et al., 2018; Gorssen et al., 2021; Illa et al., 2022). The number of individuals

199 corresponding to the top 5% of SNPs most often found in a ROH within each population was

200 chosen as a threshold to define a ROH island.

201 These top 5% values were equivalent to 35, 27, 5, and 10 individuals for LB, LC, SY, and HA,

202 respectively. Values chosen within each population corresponded to 48.6%, 40.3%, 35.7%, and

203 50% of individuals with a ROH in LB, LC, SY, and HA, respectively. In addition, two close

204 SNPs in the top 5% were considered in the same ROH island if there were separated by a

205 distance lower than 500 kb with less than 40 SNPs in the gap stretch. The ROH island was

206 delimited by a number of individuals, with ROH falling below the top 10% of the SNPs, which

207 correspond to 30, 22, 3, and 7 individuals for LB, LC, SY, and HA populations, respectively.

9

208   2.4.3 | Detection of balancing selection signals based on regions without ROH

209   We used the ROH occurrence information per SNP to detect extreme heterozygous regions, i.e.

210   without ROH. In these regions, we have an enrichment of heterozygous SNP relative to the

211   genome-wide prevalence that may be due to balancing selection phenomena (Szpiech et al.,

212   2013).

213   Applying the same criteria as for defining ROH, the minimal size and number of SNPs to define

214   a heterozygous region were fixed to 500 kb and 40 SNPs, respectively. Moreover, two

215   successive SNPs were considered in the same region if they were separated by a distance lower

216   than 50 kb. A region was detected in extreme heterozygosity if less than 5% of individuals (per

217   population) have SNPs in ROH in the region, corresponding to a maximum of respectively 4

218   and 3 individuals with a ROH in LB and LC populations, and to 0 individual with a ROH in

219   SY and HA.

220

221   2.5 | Detection of signatures of selection based on Extended Haplotype Homozygosity (EHH)

222   For a given core allele, the EHH is defined as 'the probability that two randomly chosen

223   chromosomes carrying the core haplotype of interest are identical by descent for the entire

224   interval from the core region to the point x' (Sabeti et al., 2002). EHH measures the association

225   between a single allele from the study locus (the core region) with multiple loci at various

226   distances x (Sabeti et al., 2002). The iHS (Integrated Haplotype Homozygosity Score) proposed

227   by Voight et al. (2006) aims to compare the integrated EHH profiles obtained for a SNP in the

228   ancestral versus derived states. An extreme value of iHS corresponds to a positive selection

229   because a core haplotype with unusually high EHH and high frequency in the population

230   indicates the presence of a mutation that has spread through the population faster than the

231   haplotype broke down.

232   EHH methodology requires haplotype information. Thus, genotype data must be phased before

233   their calculation. We used FImpute3 (Sargolzaei et al., 2014) to phase the genotypes of the

234   study females, considering all parents (including our study females) and offspring genotyped

235   in LB, LC, and SY populations for different purposes (see respectively Prchal et al., 2022,

236   Lagarde et al., 2022 and Paul et al., 2022). All parents (except 8 SY sires) were genotyped with

237   the HD chip (Bernard et al., 2022), while offsprings (and 8 SY sires) were genotyped with a

238   57K chip only (Palti et al., 2015). Information used for phasing is given in Table 1. Due to the

239   lack of genotyped offsprings, only the HD genotypes information was used to phase the

240   genotypes of the HA population.

241   Once phasing was performed, the *rehh* R package (Gautier & Vitalis, 2012; Gautier et al., 2017)

242   was used to conduct EHH-based analyses. EHH detection was stopped when the EHH value

243   declined under 0.1 or when the gap between two consecutive SNPs was higher than 20 kb

244   (*scan_hh* function with the following options: limehh = 0.1; maxgap=20 kb).

245

246   <u>2.5.1 | Cross population Extended Haplotype Homozygosity (XP-EHH)</u>

247   From EHH information, we used the XP-EHH statistic (*ies2xpehh* function) to compared the

248   integrated EHH profiles (iES), two by two, between a French (popA) and the HA (popB)

249   populations at the same focal SNP (Sabeti et al., 2007) as:

250    $$XP\_EHH = \frac{\ln\left(\frac{iES_{popA}}{iES_{popB}}\right) - Med\left[\ln\left(\frac{iES_{popA}}{iES_{popB}}\right)\right]}{SD\left[\ln\left(\frac{iES_{popA}}{iES_{popB}}\right)\right]}$$

251   The median (*Med*) and standard deviation (*SD*) of ln(iES$_A$/iES$_B$) were computed over all the

252   analysed SNPs.

253

254   2.5.2 | Integrated Haplotype Homozygosity Score (iHS)

255   In the same way, we used the iHS test (Voight et al., 2006) to evaluate the evidence of positive

256   selection based on haplotype frequencies in a single population, using the *ihh2ihs* function of

257   the package *rehh*. This statistic was based on the log-ratio of the integrated EHH (iHH) for

258   haplotypes with the ancestral (A) *versus* the derived (D) alleles and was computed for each

259   autosomal SNP as $iHS = \dfrac{\ln\left(\frac{iHH_A}{iHH_D}\right) - Mean_p\left[\ln\left(\frac{iHH_A}{iHH_D}\right)\right]}{SD_p\left[\ln\left(\frac{iHH_A}{iHH_D}\right)\right]}$

260   The average (*Mean$_p$*) and standard deviation (*SD$_p$*) of ln(iHH$_A$/iHH$_D$) were computed over all

261   the SNPs with a derived allele frequency *p* similar to that of the core SNP. In our study, the

262   ancestral allele state is unknown. Therefore, we assumed that the most frequent allele represents

263   the ancestral state as proposed by Bahbahani et al. (2015).

264

265   2.5.3 | Detection of candidate regions

266   To detect candidate regions for signatures of selection based on the iHS test, we used *the*

267   *calc_candidate_region* function of the R package *rehh* (Gautier & Vitalis, 2012). We

268   considered windows of 500 kb across the genome containing at least 30 SNPs, with 10 kb of

269   overlapping. A region was considered as under positive selection if at least one SNP had a

270   log(p-value) > 4 and extreme iHS value *i.e.* |iHS| ≥ 2.5.

271

272   2.6 | Identification of common regions under positive selection

273   ROH islands and regions identified by iHS were pooled within each population. Then, the

274   intersection set of the regions identified by one or another method across the four studied

275   populations was established. We eliminated an intersection from the study if one population

276   does not have at least one SNP with an |iHS|≥ 2.5 or enough individuals with an ROH in the

277   intersected region. So, only intersections containing either ROH island or extreme iHS (|iHS| ≥

278   2.5) for the four populations were thus further analyzed.

279

280   2.7 | Gene analysis

281   The genes annotated in the regions under positive or balacing selection were identified from

282   the NCBI *Oncorhynchus mykiss* genome assembly (GCA_013265735.3). Gene symbols were

283   checked, and, if necessary, familiar names were added using the information available from

284   GeneCards (https://www.genecards.org/).

285   Gene ontology (GO) terms study was performed with 'g:profiler' (Raudvere et al., 2019;

286   https://biit.cs.ut.ee/gprofiler/gost) for the list of genes identified in the regions of interest.

287   Percent identity of rainbow trout proteins with nine other vertebrate species (human, mouse,

288   cow, goat, pig, chicken, zebrafish, medaka, and Atlantic salmon) was established using the

289   blastp tool (Basic Local Alignment Search Tool on proteins).

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3| Results

3.1 | Genetic diversity within and across populations

The ROH statistics and inbreeding coefficients are presented in **Table 2** for all the populations. The average number of ROH per individual varied between 141 (SY) and 168 (LB). French selected lines had larger average sizes of ROH than populations SY and HA. The average inbreeding coefficients of HA individuals were between three (compared to SY) and five (compared to LB) times lower than those of the French lines.

Based on genome-wide Fst values, large differentiation of around 0.28 was observed between HA and any of the French populations (Table 3). In the PCA figure (Figure 1), the three French lines differed strongly from the American pooled populations, and the first two PCA axes explained 29% of the total genetic variation. In addition, Fst values indicated that all the French lines were moderately differentiated (0.104 – 0.122).

Using the XP-EHH statistic, we identified 93, 105 and, 135 regions that strongly discriminated HA from LB, LC and SY, respectively. Among these regions, 34 regions were shared, spanning about 32 Mb in total over 21 chromosomes, and differentiated any of the French lines from the American HA pooled population (Supplementary information S1).

The distribution of the proportion of individuals having a ROH at each SNP position is presented in Figure 2. In average, ROH were more shared between individuals for selected lines (LB and LC, on average, 23.39% and 19.82% of individuals respectively) than for other populations (SY and HA, on average, 13.67% and 8.91% of individuals respectively). Probably linked to the composite nature of the HA population (5 sub-groups of 4 individuals), HA contained the lowest number of shared ROH among the individuals but also showed the most shared ROH among individuals.

3.2 | Signatures of positive selection

3.2.1 | ROH islands

The sharing of ROH among individuals, regardless of the population considered, was presented Figure 3. Eight ROH islands were shared by at least 2 populations, and a minimum of 50% of individuals concerned. However, only three of these regions were defined as ROH island in each of the 4 populations.

We listed all ROH islands within each population which resulted in the identification of 270 ROH islands distributed among the four populations (Supplementary Informations S2 to S5, for LB, LC, SY, and HA, respectively). The ROH islands were not evenly distributed across populations and chromosomes. The average ROH island size was 2,737 kb, varying from 1,593 kb to 4,465 kb, depending on the population. The longest ROH island was observed in SY (21.4 Mb), while the shortest one was observed in LC (16.1 kb).

3.2.2 | Identifying selection signatures using iHS

The log(p-values) of iHS calculated along the genome are presented in Figure 4 for each population (all regions identified with *calc-candiate_region* are described in Supplementary Informations S6-S9). While numerous regions have been detected as under positive selection overall, fewer candidate regions were detected for the French lines (LB, LC and, SY) than for the Amercian pooled population (HA). The genome-wide highest estimated values of |iHS| were 8.97, 7.24, 5.67, and 9.09 for LB, LC, SY, and HA, respectively (with log(p-values) > 7.8).

In total, 72, 68, 76, and 54 ROH islands were identified in LB, LC, SY, and HA populations respectively (Figure 5). Using iHS statistics, 55, 69, 73, and 362 signatures of selection were detected for LB, LC, SY, and HA populations, respectively. Only 10.4%, 8.7%, 8.0%, and 5.6%

340   of the regions were detected by both methods (ROH + iHS) for LB, LC, SY, and HA

341   populations, respectively.

342

343   ### 3.2.3 | Regions under positive selection shared by the four studied populations

344   Among the numerous regions identified for each population by either ROH or iHS methods,

345   only nine regions were shared by the four studied populations (Table 4). The average size of

346   these shared regions was 1135 kb. Five of them were located on chromosome 2, and the four

347   other regions were on chromosomes 12, 15, 16, and 20, respectively.

348   Depending on the population, six regions were identified by either ROH or iHS metrics. Two

349   regions, chr2_c and chr15_a, were only detected by ROH in all four populations, while a single

350   region, chr16_a, was only identified through significant iHS statistics in all the four populations

351   (Supplementary Information S10). The list of genes annotated in the nine shared genomic

352   regions is given in Supplementary Informations S11.

353

354   ### 3.3 | Signatures of balancing selection

355   ### 3.3.1. Regions under balancing selection detected within population

356   In total, 14, 24, 158, and 265 hot spots of polymorphism (i.e. without ROH) were identified in

357   LB, LC, SY, and HA populations, respectively. The numbers of heterozygous regions detected

358   for SY and HA populations were drastically larger than those observed for the LB and LC

359   selected lines. The average size of the detected heterozygous regions was 1,400 kb, varying

360   from 1,086 kb to 1,828 kb, depending on the population.

361   Tables listing all heterozygous regions within each population are presented in Supplementary

362   Informations S12 to S15, for LB, LC, SY, and HA, respectively.

363

364 3.3.2. Regions under balancing selection shared by the four studied populations

365 A substantial lack of ROH was observed in four regions of all studied rainbow trout populations

366 (Table 5). Two of them, chr10_a and chr19_a, were particularly small (53 kb and 70 kb,

367 respectively), but still contained at least 20 SNPs. The region chr10_a only encoded one of the

368 introns of the *ctnna2* (= catenin alpha 2*)* gene while chr19_a was composed of two genes,

369 *smarca5* (=SWI/SNF-related matrix-associated actin-dependent regulator of chromatin

370 subfamily A member 5) and *frem2* (= FRAS1-related extracellular matrix protein 2). A second

371 heterozygous region on chromosome 19 was larger (163 kb) but contained a single annotated

372 gene, *pou4f2* (= POU domain, class 4, transcription factor 2-like). A last region chr13_a

373 spanned over 1,100 kb) on chromosome 13 and was composed of 25 genes. The list of genes

374 annotated in the four shared genomic regions is given in Supplementary Informations S16.

375

376 3.4 | Identification and roles of genes underlying the regions under selection across all

377 populations

378 3.4.1. Common homozygous regions under positive selection

379 The nine common homozygous regions contained a total of 253 genes (listed in Supplementary

380 Information S11). A gene ontology (GO) study was performed and showed a significant over-

381 representation (p-value < 0.01) among the 253 genes of functions related to the following GO

382 terms: membrane (GO:0016020, CC: Cellular Component*, p-value = 1.3e10^{-5}*), intrinsic and

383 integral component of membrane (GO:0031224; GO:0016021, CC, *p-value = 0.001/0.005*), ion

384 binding (GO:0043167, MF: Molecular Function*, p-value = 0.002*), and nuclear speck

385 (GO:0016607, CC, *p-value = 0.008*).

386   Among the nine studied regions, the three regions chr2_a, chr2_c, and chr15_a, that contain

387   less than ten genes annotated in each, were analyzed in further detail to accurately define the

388   roles of underlying genes. The 17 genes located in these three regions are listed in Table 6 with

389   their associated biological functions. These genes play key roles in protein

390   transduction/maturation, genome stability, embryonic development, growth, energetic function,

391   reproduction, or immune function. In addition to this list of genes, a subset of 15 genes in the

392   six other homozygous regions already identified as signatures of selection in the literature were

393   further studied in terms of their biological functions. Detailed information for these genes is

394   also given in Table 6.

395   We studied the degree of protein identity among 10 vertebrate species for all the 17 genes of

396   regions chr2_a, chr2_c, and chr15_a (Table 7), considering a protein as highly conserved if its

397   identity between rainbow trout and other species was higher than 85%. Except for the proteins

398   linked to *cep162* (centrosomal protein of 162 kDa) and *zp4* (zona pellucida sperm-binding

399   protein 4-like) genes, all other proteins were highly conserved at least between the two studied

400   salmonids. In each of the three regions, one or two genes were highly conserved across the all

401   ten study species: in chr2_a, rainbow trout *cdk14* (cyclin-dependent kinase 14) protein had a

402   percent identity between 86 and 99.6% with the other species; in chr2_c, rainbow trout *brsk2a*

403   *(*serine/threonine-protein kinase *brsk2*) protein had between 92 and 96.3 % of percent identity

404   with the other species; in chr15_a, two genes, *chn1*(n-chimaerin) and *atp5mc1* (ATP synthase

405   lipid-binding protein, mitochondrial)*,* also had protein percent identity ranging from 85% to

406   98% depending of the species.

407   Some other rainbow trout proteins (*tsnare1,* t-SNARE domain-containing protein 1*; pttg1IP,*

408   pituitary tumor-transforming gene 1 protein-interacting protein*)* were conserved to a lesser

409   extent (minimum 65% of percent identity) with the three other fish species, some being also

18

410 conserved at least with chicken (*adgrb1,* adhesion G protein-coupled receptor B1*;b4galnt4a,*

411 N-acetyl-beta-glucosaminyl-glycoprotein 4-beta-N-acetylgalactosaminyltransferase 1) or even

412 with all the nine study species (*zc3h15,* zinc finger CCCH domain-containing protein 15).

413

414 <u>3.4.2. Common heterozygous regions under balancing selection</u>

415 The four common heterozygous regions (Table 5) contained 29 genes (listed in Supplementary

416 Information S16). A gene ontology (GO) terms study showed no significant over-representation

417 of specific GO terms.

418 The degree of protein percent identity among 10 various vertebrate species for these 29 genes

419 are presented in supplementary information S17.

420 Regions chr10_a, chr19_a, and chr19_b contained only a few genes and were then analyzed in

421 further detail to accurately determine the role of underlying genes (Table 8). These genes play

422 key roles in cellular and nuclear organisation and in embryonic development.

423

424

4| Discussion

426 The objective of our study was to detect signatures of selection into domestic rainbow trout. To

427 reach that goal we studied four genetically distinct populations coming from different locations

428 either in France or in the North-West of the USA. We used two different approaches, ROH and

429 EHH, to detect the genomic regions shared by all populations using a HD SNP. We were able

430 to detect 9 very conserved regions and 4 hotspots of polymorphism, corresponding to 253 and

431 29 annotated genes, respectively.

432

4.1 | Genetic structure

First, we described the genetic structure of the populations under scrutiny. The three French lines were moderately differentiated with Fst ranging from 0.10 to 0.12. These estimations were congruent with those computed by D'Ambrosio et al.'study (2019) with the same populations that ranged between 0.09 and 0.14, but were estimated using a 38K SNPs array. These moderate differences between the 3 French populations were consistent with the PCA we performed and the history of these populations with a partly common INRAE origin (D'Ambrosio et al., 2019). This trend is shared between European populations with for instance an average Fst of 0.13 between 12 European rainbow trout strains (Gross et al., 2007) or 0.12 among 9 Norwegian populations (Glover, 2009). Similarly, US farmed populations are also weakly to moderately differenciated with an average Fst of about 0.09 (Silverstein et al., 2004) or 0.13 (Liu et al., 2017) and pairwise values ranging from 0.06 and 0.16. We observed a similar pattern in the present study with the HA population that consisted in samples from 5 locations, which all clustered together in the PCA. Reversely, we observed a large differentiation between our French and US populations revealed by large Fst values (0.27-0.29). This is likely the result of numerous factors, including selection, genetic drift and absence of gene flow between these very geographically distant populations. In addition, the European farmed populations originated from Californian domesticated strains, that have been shown to differ from strains of North-Western USA (Stanković et al., 2015). We found 34 haplotypes distributed over 21 chromosomes that differed between the American pooled population (HA) and all French populations (Supplementary information S1).

Due to the moderate to large differentiation between the 4 populations, the conserved regions across all populations are likely to be the result of ancient natural selection traces.

457   <u>4.2 | Comparison of methods to detect common signatures of positive selection</u>

458   We used a double check of positive selection traces in the genome by using both ROH and EHH

459   approaches. However, for each population, only a few regions were identified by both methods.

460   These regions detected by more than one method represent stronger evidence of selection

461   signatures since outlier markers detected by various genome scan methods help to uncover true

462   selection signatures by reducing the number of false positives.

463   Even if both methods evaluate the homozygous large stretches in the genome, iHS also

464   considers information based on haplotypic version and linkage disequilibrium from a core SNP.

465   ROH approach detects homozygous regions regardless of their haplotypic versions, contrary to

466   iHS. Thus, it may detect a signature of positive selection even if various haplotypes were

467   present at the homozygous state in the population. In addition, while the ROH approach only

468   detects the homozygous large stretches (at least 500 kb in the present study), iHS can detect

469   small regions under positive selection as the only limitation in EHH region size is based on a

470   threshold value for a minimum LD (0.10). Consequently, the sizes of the detected homozygous

471   region varied between 1,065 kb and 2,857 kb based on ROH metrics and between 1,000 kb and

472   1,600 kb with iHS statistics.

473   The high number of regions (55, 69, 73, and 362) detected by iHS in our study was consistent

474   with numbers detected in either Atlantic salmon (López et al., 2019) or cattle (Saravanan et al.,

475   2021). However, these two previous studies used a lower threshold than ours (log(p-value) = 3

476   and 2, respectively vs 4 in the present study). Lower numbers of regions were previously

477   detected by iHS in rainbow trout by Cádiz et al. (2021) and in Coho salmon by López et al.

478   (2021). We speculate that these differences in the numbers of detected signals may be linked to

479   the lower density of SNPs they used in both studies (57K or 200K chip versus 665K chip for

480   our study) and the subsequent lower ability to detect LD and haplotypes at fine scale. Indeed,

481   in the Chilean rainbow trout study (Cádiz et al., 2021), only one signal of positive selection was

482   detected by iHS located at 6.398-14.936 Mb on chromosome 20 of the Swanson reference

483   genome, which corresponds to the region 7.488-16.111 Mb on chromosome 20 of the Arlee

484   reference genome. Nevertheless, we also detected by iHS signals of selection in each of our

485   four studied populations, located at 10.5-16.5 Mb for LB, 11.2 – 13.3 Mb for LC, 13.0 – 14.2

486   Mb for SY and 12.3-13.2 Mb for HA (Supplementary Informations S6 to S9 for LB, LC, SY,

487   and HA, respectively). Thus, all these signals were consistent with the larger region identified

488   by Cádiz et al. (2021).

489   A common putative selection signature located at 13.0-13.2Mb could also be shared by all

490   studied populations. In this 200kb-region, we observed at least one iHS value over |2.5| for LB,

491   LC and SY lines, but not for HA population. In this region of 200 kb on chromosome 20, six

492   genes were identified (*lgi1, noc3l, plce1, slc35g1, fra10ac1, tbc1d12*). Among these genes,

493   Cádiz et al. (2021) identified two candidates genes associated with domestication,

494   *noc3l* (nucleolar complex protein 3 homolog**)** and *plce1* (1-phosphatidylinositol 4,5-

495   bisphosphate phosphodiesterase epsilon-1). Both are related to early development traits in

496   zebrafish (*noc3l*: Walter et al., 2009; *plce1*: Zhou et al., 2009).

497

498   4.3 | Biological functions of genes under positive or balancing selection

499   Among the 282 genes in the 13 regions detected under either positive or balancing selection,

500   most genes seem to play essential roles in fitness as expected with such a dataset comprising

501   both European and US populations. They are related to all main biological functions (genome

502   stability, cell organization, neuronal and embryonic development, energy metabolism, growth,

503   reproduction, and immunity). All identified biological functions were already described in other

504 studies of signatures of selection in farmed rainbow trout (Cádiz et al., 2021) and other

505 domesticated species (López et al., 2018, 2018; Naval-Sanchez et al., 2020; Baesjou &

506 Wellenreuther, 2021; Signer-Hasler et al., 2022).

507

508 <u>4.3.1 Hotspots of heterozygosity and balancing selection for fitness traits</u>

509 In livestock species, many variants under balancing selection are known to improve

510 performance in heterozygote state but cause defect in homozygous state (Hedrick, 2015;

511 Georges et al., 2019). However, in such cases of balancing selection, there is generally only one

512 homozygous state, which is deleterious at a locus level, while the alternative homozygous state

513 is observed in the population. In our study, we highlight four regions potentially involved in

514 balancing selection for which we observed a lack of any kind of long streches of homozygosity.

515 Even if these regions are extremely heterozygous, the proteins associated with these genes are

516 highly conserved among vertebrates (Supplementary information S17). Many processes may

517 explain these surprising observations at first glance. First of all, these regions may concentrate

518 polymorphism in non-coding parts of the genome. Polymorphism in intronic regions may

519 promote various proteins by allowing alternative splicing. We may also observe an excess of

520 synonymous polymorphism in exons without effects on proteins. Further analyses must be

521 conducted to better understand the mechanisms underlying the maintenance of extreme

522 polymorphism, whether to validate the hypothesis of balancing selection or the existence of

523 high mutation and recombination rates in these specific regions.

524

525 In the heterozygous region chr10_a, the gene *ctnna2 (*Table 8) enables actin filament binding

526 activity and is involved in the regulation of neuron migration and neuron projection

527 development. Thus, *ctnna2* plays an essential role in brain development among vertebrates

528   (Uvarov et al., 2014). In yonlong grouper, *ctnna2* seems implicated in vertebral development,

529   because significantly differentially expressed between normal and fish with lordosis (Li et al.,

530   2022). In mice, a homozygous for a mutation of *ctnna2* reduced body weight, male fertility,

531   and induced brain abnormalities (hypoplastic cerebellum, abnormal foliation pattern, ectopic

532   Purkinje cells, and abnormal pyramidal cells in the hippocampus). While the protein associated

533   to this gene is highly conserved among vertebrates (Uvarov et al., 2014; Supplementary

534   information S17), the gene exhibits a strong polymorphism in all the four studied rainbow trout

535   populations. However, a large part of its polymorphism is located in one intronic region (intron

536   6-7) of *ctnna2*. In the zfin database, five transcripts of this gene were identified (three mRNA

537   and two non-coding RNA). We hypothezise that the polymorphism in the intronic region of

538   *ctnna2* is essential for alternative splicing.

539   In the heterozygous region chr13_a (Supplementary information S16), *mmd* and *map2k4* are

540   identified as highly conserved across vertebrates (Supplementary information S17). The

541   gene *mmd* plays an important role in maturing macrophages, which is essential for immune

542   response as observed in mice (Lin et al., 2021). The gene *map2k4* is implicated in a variety of

543   cellular processes (proliferation, differentiation, transcription regulation, development), seems

544   to play a role in liver organogenesis and embryonic development during gastrulation, as

545   demonstrated by morpholino-mediated knockdown in zebrafish (Seo et al., 2010), and

546   implicated in immune response in yellow catfish (Zheng et al., 2022). The inflammatory

547   process in immune response seems linked to the polymorphism of the *map2k4* gene, which is

548   consistent with our hypothesis of balancing selection, and more precisely potential ancestral

549   trans-species polymorphism in this genomic region (Gu et al., 2016; Fijarczyk & Babik, 2015).

550   Trans-species polymorphism is a crucial evolutionary mechanism for sharing adaptative genetic

551   variation across taxa (Klein et al., 1998). The study of this mechanism has primarily

552 concentrated on major histocompatibility complex genes, but a few studies described this

553 process for other immune genes (Ferrer-Admetlla., et al., 2008; Leffler et al., 2013; Těšický &

554 Vinkler, 2015). Maintaining genetic diversity in regions related to the immune system may be

555 essential to resilience against various pathogens. In addition, this region of chromosome 13 has

556 been recently detected as a significant QTL playing a role on resistance to temperature (Lagarde

557 et al., 2022).

558 In the heterozygous region chr19_a (Table 8), the protein encoded by *smarca5* is a component

559 of chromatin remodeling and spacing factor RSF, a facilitator of the transcription of class II

560 genes by RNA polymerase II (zebrafish: Armas et al., 2013; Ding et al., 2021; mice: Limi et

561 al., 2018). The protein is highly conserved among vertebrates (Supplementary information

562 S17), which is consistent with its essential role thought to regulate the transcription of many

563 genes by altering the chromatin structure around those genes. In the same region

564 chr19_a, *frem2* codes for an extracellular matrix protein required for maintenance of the

565 integrity of skin and renal epithelia in zebrafish (Gautier et al., 2008). This protein is moderately

566 conserved across vertebrates (Supplementary information S17). In a study searching for

567 genomic regions with ancestral trans-species polymorphism shared between humans and

568 chimpanzees (Leffler et al., 2013), *frem*3, an important paralog of *frem2,* was identified under

569 balancing selection. However, further studies should test the hypothesis of trans-species

570 conservation of *map2k4* and *frem2* genes that may help to understand the various cellular

571 processes in which the gene is implicated.

572 In the heterozygous region chr19_b (Table 8), *pou4f2* protein is highly conserved among

573 vertebrates (Supplementary information S17) and is a tissue-specific DNA-binding

574 transcription factor involved in the development and differentiation of specific cells. It

575 maintains the visual system neurons in the retina and the lateral line (DeCarvalho et al.,

576 2004) and seems also related to cardiac development in zebrafish (Maskell et al., 2017).

577

578 4.3.2 Hotspots of homozygosity and positive selection for essential biological functions

579 4.3.2.1 | Regions and genes involved in cellular and nuclear organization, and embryonic

580 development

581 In homozygous region chr2_a, three genes plays important roles in embryonic development and

582 then fitness (*cep162*, *tsnare1*, *mrap2*, Table 6). In the homozygous region chr2_b (Table 6), the

583 gene *pbx1* (pre-B-cell leukemia transcription factor 1) is related to early development in

584 zebrafish (Teoh et al., 2010). Mutations in this gene generally cause major malformations,

585 which seem to play an essential role in survival in various species (zebrafish: Teoh et al., 2010;

586 mouse: Selleri et al., 2001; human: Le Tanno et al., 2017). It was detected under positive

587 selection in a Chilean farmed rainbow trout population (Cádiz et al., 2021). However only

588 moderate percent identity ($> 65\%$) is observed between *pbx1* proteins across vertebrates.

589 In the homozygous region chr15_a, many genes *(chn1, atp5mc1, zc3h15, nid2 and brca2)* were

590 playing essential roles in cell functioning and early development (Table 6). However only two

591 of them were highly conserved among vertebrates ($> 85\%$; *chn1* and *atp5mc1*). The gene

592 *atp5mc1* is a crucial gene for mitochondrial cristae morphology, and plays important roles in

593 metabolic processes associated to growth (Table 6; Palmer et al., 2011; Miller et al., 2019;

594 Wang et al., 2020). In zebrafish, a morpholino knockdown of *chn1* reveals its crucial role in

595 early development, revealing severe abnormalities (development of round somites, lack of yolf

596 extension, and kinkled posterior notochord) (Leskow et al., 2006).

597 Three genes located in close vicinity in region chr16_a (between 46.42 and 46.53 Mb;

598 Supplementary information S11), *samd10* (sterile alpha motif domain-containing protein 10-

599   like*)*, d*najc5* (dnaJ homolog subfamily C member 5-like*)*, and *tpd54* (tumor protein D54) were

600   also detected in close chromosomal vicinity and under positive selection in ten modern goat

601   breeds and one wild Bezoar goat (Signer-Hasler et al., 2022). This cluster of genes has a

602   significant role in survival and cellular processes (Table 6). In addition, in this region chr16_a,

603   the protein of the gene *magi2* (membrane-associated guanylate kinase, WW and PDZ domain-

604   containing protein 2, Table 6) plays a vital role in embryogenesis in zebrafish (Borah et al.,

605   2016). The gene *magi2* was also identified under positive selection in a domesticated sheep

606   breed compared to the wild Asiatic mouflon (Cumer et al., 2021).

607

608   4.3.2.2 | Regions and genes involved in neural and brain development, and behaviour

609   In total, we identified 7 genes as primarily associated to neural and brain development in both

610   regions detected under positive selection (*tsnare1, cdk14, brsk2a, auts2, brd2,*

611   *znf135,* and *grxcr1*). Some genes (*brsk2a, znf135, grxcr1, auts2; Table 6*), related to brain

612   development may induce behavior modifications in farmed animals, that may be related to

613   domestication processes (Pasquet, 2018; Milla et al., 2021; Deng et al., 2022; Liu et al., 2022).

614   This is in line with Żarski et al. (2020) study showing that domestication modulates gene

615   expression involved in neurogenesis.

616   In particular, the gene *auts2* gene was previously identified under positive selection both in

617   cattle (Consortium, bovine Hapmap, 2009) and in domesticated Atlantic salmon populations

618   from Canada and Scotland compared to their wild Atlantic salmon counterpart (López et al.,

619   2018). The gene *znf135* was also detected under positive selection in a farmed population of

620   Atlantic salmon compared to a wild-type population (Gutierrez et al., 2016). The gene *grxcr1*

621   was detected under positive selection in the Tharparkar cattle (Saravanan et al., 2021). It

622   strongly suggests that all these genes play a key role in domestication processes and may act on

623   essential behaviours in both terrestrial and aquatic farmed animals.

624

625   4.3.2.3 | Regions and genes involved in growth metabolism

626   Genes related to growth metabolism were only identified in four regions under positive

627   selection, none of them were detected in high heterozygosity regions.

628   In the homozygous region chr2_a (Table 6), the protein *mrap2* (melanocortin-2 receptor

629   accessory protein 2A) is associated to growth. A lack of this gene exhibit severe obesity in

630   many species (human, zebrafish, rodent: Liu et al., 2013; sea lamprey: Zhu et al., 2019;

631   snakehead: Wang et al., 2021). Yoshida et al. (2017) detected a growth-QTL in Atlantic salmon

632   and considered *mrap2* as a candidate gene for growth up to 25 months. In addition, *mrap2* was

633   identified in the Chilean farmed rainbow trout population as under positive selection (Cádiz et

634   al., 2021). A QTL related to sea lice resistance in rainbow trout (Cáceres et al., 2021) was also

635   detected in the region chr2_a (located from 10.43 Mb to 11.81 Mb of the Swanson reference

636   genome, which corresponds to 26.69 Mb – 28.07 Mb of the Arlee reference genome). Cáceres

637   et al. (2021) explained that having a high potential for growth seem essential for sea lice

638   resistance. Indeed, proteomic investigations allow to establish a link between growth and

639   immune function in salmonids (Causey, 2018).

640   In homozygous region chr2_b (Table 6), the *col9a2* (collagen alpha-2(IX) chain) gene is a

641   component of cartilage and seems also related to growth (Xu et al., 2022).-This gene is detected

642   under positive selection in a Scottish farmed population of Atlantic salmon (López et al.,

643   2018). In addition, the gene *scap* (sterol regulatory element-binding protein cleavage-activating

644 protein) was already identified under positive selection in six farmed Pacific white Shrimp

645 populations (Wang et al., 2022).

646 In the homozygous region chr2_d (Table 6), the gene *igf-1α* (insuline like growth factor receptor

647 1a) plays an important role in growth and transformation events. In salmonids, expressions of

648 *igf-1α* and growth hormone were demonstrated to be modified between domesticated and wild

649 populations of rainbow trout and coho salmon (Tymchuk et al., 2009). The same observation

650 was made with a higher expression of *igf-1α* between larvae from domesticated spawners than

651 larvae from wild spawners of the Eurasian perch (Palińska-Żarska et al., 2021). In addition, *igf-*

652 *1* was also observed as a marker of domestication in dogs (Wayne & vonHoldt, 2012).

653 In the homozygous region chr16_a, the *emilin-3a* gene (elastin microfibril interfacer 3a, Table

654 6) plays a role in extracellular matrix organization and elastic fiber formation. Its gene

655 expression is related to embryonic development and involved in muscle fiber development in

656 zebrafish (Milanetto et al., 2008). *Emilin-3a* had already been identified as under positive

657 selection in one population of F2 Australian snapper farmed population compared to the first

658 generation (F1) of domestication of a wild population (Baesjou & Wellenreuther, 2021). Thus,

659 this signature of selection can be considered as a result of the domestication process.

660 All identified growth-related genes seem associated with domestication. This assertion is

661 confirmed for five genes (*mrap2*, *col9a2*, *scap*, *igf-1α, emilin-3*) that were also identified under

662 positive selection in various farmed populations with favorable alleles linked to better growth

663 phenotypes (Table 6).

664

665 <u>4.3.2.4 | Regions and genes involved in reproduction</u>

666 Very few genes directly related to reproduction traits were only identified in highly

667 homozygous regions.

668 In the homozygous region chr2_b, the *brd2* (bromodomain-containing protein 2, Table 6) gene

669 is implicated in several biological process (see section 4.4.1.). It seems related to oogenesis and

670 egg-to-embryo transition in zebrafish (DiBenedetto et al., 2008), which is consistent with a

671 QTL detected for egg size in this region in rainbow trout (D'Ambrosio et al., 2020). Moreover,

672 it seems that *brd2* is involved in spermatogenesis or folliculogenesis, as demonstrated in situ

673 on mice cells (Rhee et al., 1998). Khendek et al. (2017) compared the reproductive

674 performances (egg size, gonadal histology, hormonal levels) between domesticated and F1 with

675 wild broodstock of Eurasian perch populations. They showed that domestication may have

676 increased the oocyte diameter and the level of 17β-Estradiol, but decreased the embryo survival

677 of domesticated fish. This gene was also identified under positive selection in a selected

678 Canadian population of Atlantic salmon (López et al., 2018).

679 In the homozygous region chr15_a (Table 6), the gene *zp4* has already been identified under

680 positive selection in a farmed Scottish population of Atlantic salmon compared to a wild

681 population (López et al., 2018), and may be related to domestication process.

682

683 4.3.2.5 | Regions and genes involved in immunity

684 Magris et al. (2022) observed that regions under positive selection revealed an enrichment of

685 KEGG terms related to viral infection in farmed brown trout. However, it should be noticed

686 that in our study, few genes related to immune function were identified and no enrichment in

687 immune terms was observed in GO analysis.

688   Genes related to immune function were mainly identified in three different regions detected as

689   putatively under positive selection for two of them and under balancing selection for the last

690   one.

691   In the homozygous region chr2_b (Table 6), genes *tnfaip8l2b* (tumor necrosis factor, alpha-

692   induced protein 8-like protein 2 B) and *atg5* (autophagy protein 5) are related to immune

693   functions. Note that atg5 is well conserved across vertebrates (> 80%).

694   In the region chr15_a, the gene *zc3h15* (Table 6) seems to have an inhibitory effect on HIV-1

695   replication and then on HIV infection in vitro (mice cells) (Capalbo et al., 2010).

696   A last gene in the region chr16_a, the gene *atp1b3* (sodium/potassium-transporting ATPase

697   subunit beta-1-interacting protein 3) was also identified under positive selection in farmed

698   Atlantic Salmon (Naval-Sanchez et al., 2020). In the Senegalese sole, atp1b3a and atp1b3b

699   paralogs have been hypothesized to be involved in response to low salinity (Armesto et al.,

700   2015). In addition, this gene is involved in some immune responses. It was shown in cell culture

701   study, that *atp1b3* inhibits hepatitis B virus replication via inducing NF-kappa B activation

702   (human: Zhang et al., 2021) and is involved in numerous viral propagation such as HIV and

703   EV71 (Zheng et al., 2020) in cell culture experiments.

704

705   4.4. Conclusion

706   To sum up, we identified 13 regions under selection with numerous genes strongly involved in

707   essential biological functions. By identifying signatures of selection shared by our four studied

708   populations, we have focused our detection on regions related to ancient evolutionary processes

709   that are essentially important for species survival. We only identified nine homozygous regions

710   presumably under positive selection and four heterozygous regions putatively under balancing

711   selection in four different rainbow populations. While common homozygous regions may be

712   associated with important biological functions underlying both fish fitness and domestication,

713   the heterozygous regions seem mainly linked to fitness functions (cell organization, embryonic

714   development, and immunity) which are involved at different developmental stages or to cope

715   with various pathogens or abiotic stressors. Maintaining genetic diversity in these regions could

716   be essential for the species survival.

717   This study allows us to confirm the importance of a large set of 17 genes already detected as

718   under positive selection in previous studies, among which 10 genes were identified in fishes

719   (*auts2, atp1b3, zp4, znf135, igf-1α brd2, col9a2, mrap2, pbx1* and *emilin-3*). We also identify

720   new promising candidate genes as important for rainbow trout fitness. In our opinion, this study

721   substantially increases knowledge of evolutionary processes and helps to determine the

722   genomic location and the nature of the genetic variation that must be maintained in rainbow

723   trout populations for domestication and selection purposes**.**

724

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730

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732
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Data Accessibility and Benefit-Sharing

Restrictions applied to the availability of the data that support the findings of this study, which were used under license and so are not publicly available. The data can be made available for reproduction of the results from Florence Phocas (florence.phocas@inrae.fr) on request via a material transfer agreement and with permission of the two breeding companies "Viviers de Sarrance" (Sarrance, France) and "Milin Nevez" (Plouigneau, France).

Author contributions

Katy Paul: Investigations, Methodology, Formal analysis, Writing - Original Draft;

Gwendal Restoux: Conceptualization, Methodology, Draft Reviewing;

Florence Phocas: Supervision, Conceptualization, Methodology, Investigation, Formal analysis, Resources, Writing - Original Draft.

Tables and Figures (with captions)

TABLE 1. Data information used to phase the HD genotypes of the study females that belong to the parental cohorts. Number of individuals and SNPs available after quality control

Line	Status of individuals	Number of individuals	Number of SNP used
LB	parents	288	571,319
	offsprings	1,297	29,091
LC	parents	173	569,03
	offsprings	1,350	30,379
SY	parents (dams + 1 sire)	16	569,03
	offsprings (+ 8 sires)	866	32,725

TABLE 2. ROH statistics and inbreeding coefficients of the four studied populations (Standard deviations are indicated in brackets).

Population	Average number of ROH	Average size of ROH (in kb)	Average F_{ROH}
LB	168 (14.6)	2,770 (270.8)	0.20 (0.02)
LC	157 (15.9)	2,485 (326.8)	0.17 (0.03)
SY	141 (33.5)	1,860 (291.2)	0.12 (0.05)
HA	167 (65.6)	1,433 (145.6)	0.04 (0.03)

TABLE 3. Genome-wide Fst statistics derived two-by-two between the four populations.

	LC	LB	HA
SY	0.104	0.122	0.275
LC		0.122	0.275
LB			0.289

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1580 **TABLE 4.** Homozygous regions under positive selection in the four studied populations.

Region	CHR	Start (Mb)	End (Mb)	Size (kb)
chr2_a	2	25.40	26.30	900
chr2_b	2	31.60	34.20	2600
chr2_c	2	46.00	46.66	664
chr2_d	2	69.70	71.20	1500
chr2_e	2	88.46	89.34	878
chr12_a	12	57.97	59.10	1138
chr15_a	15	38.96	39.57	610
chr16_a	16	45.80	47.00	1200
chr20_a	20	19.10	19.83	726

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1582 **TABLE 5.** Highly heterozygous regions shared by the four studied populations.

Region	CHR	Start (Mb)	End (Mb)	Size (kb)	SNP number	SNP density per Mb
chr10_a	10	56.314	56.366	53	20	379
chr13_a	13	46.959	48.071	1,112	446	401
chr19_a	19	10.753	10.823	70	24	342
chr19_b	19	11.354	11.517	163	52	319

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1598 **TABLE 6.** List and functions of the 17 genes annotated in three homozygous regions (chr2_a,
1599 chr2_c and chr15_a) shared by the four rainbow trout populations, and the 15 genes in the six
1600 other regions already identified as signatures of selection in the literature. *SS : Identify by*
1601 *signature of selection in that study*

Region	Gene name	Protein name		General functions	References
chr2_a	mrap2	melanocortin-2 receptor accessory protein 2A	Cellular organization and growth	May regulate both receptor trafficking and activation in response to ligands. Link to energy homeostasis control and body weight regulation. Linked to severe obesity in many species	Liu et al., 2013 (human, zebrafish, rodent); Zhu et al., 2019 (sea lamprey); Wang et al., 2021 (snakehead); **SS** : Cadiz et al., 2021 (rainbow trout), Cumer et al., 2021 (goat)
	cep162	centrosomal protein of 162 kDa	Cellular and nuclear organization	Involved in cilium assembly (promote transition at the cilia base). Acts by specifically recognizing and binding the axonemal microtubule.	Wang et al., 2013
	uncharacterized LOC110539089				
	adgrb1	adhesion G protein-coupled receptor B1	Neuronal and embryonic development	Essential for growth and metastasis of solid tumors (zebrafish). Plays a role during brain/neuron development, associated with autism in mice and human (BAI1 synonymous of adgrb1).	Purcell, 2017 (human); Cazorla-Vázquez & Engel, 2018 (from zebrafish to human); Shiu et al., 2022 (mice)
	tsnare1	t-SNARE domain-containing protein 1	Cellular organization and neuronal developement	Predicted to be involved in intracellular protein transport; vesicle docking; vesicle fusion ; and integral component of membrane. Neurodevelopment function.	Fromer et al., 2016 (zebrafish and human)
	pttg1ip	pituitary tumor-transforming gene 1 protein-interacting protein	Cellular organization and growth	Participates in metaphase-anaphase transition of the cell cycle and facilitates translocation of pttg1 into the nucleus + allow to predict breast cancer survival + induced transcriptional activation of transcriptional basic fibroblast growth factor (when coexpressing with pttg1).	Repo et al., 2017 (human)
	Cdk14	cyclin-dependent kinase 14	Neuronal and embryonic development	Regulator of cell cycle progression and proliferation + role in meiosis, neuron differentiation/craniofacial development (Wnt signaling pathway)	Margarit et al., 2014 (zebrafish); Yin et al., 2021 (human)
chr2_b	pbx1	pre-B-cell leukemia transcription factor 1	Neuronal and embryonic development	Related to early development in zebrafish. Mutations in this gene generally cause major malformations, which seem to play an essential role in survival in various species.	Teoh et al., 2010 (zebrafish); Selleri et al., 2001 (mouse); Le Tanno et al., 2017 (human); **SS:** Cadiz et al., 2021 (rainbow trout)
	col9a2	collagen alpha-2(IX) chain	Neuronal and embryonic development	Component of cartilage, implicated in human intervertebral disc degeneration (IVDD) and seems also related to growth. Mutations in this gene may cause diverse syndromes, such as multiple epiphyseal dysplasias and ocular, skeletal, orofacial, and auditory abnormalities in humans.	Muragaki et al., 1996; Baker et al., 2011; Xu et al., 2022 (human); **SS:** Lopez et al., 2018 (atlantic salmon)
	brd2	bromodomain containing 2	Nuclear and cellular organization, neuronal and embryonic development	Associated with transcription complexes and acetylated chromatin during mitosis. Potential role in oogenesis, egg-to-embryo transition, and proper development of the digestive and central nervous systems (zebrafish). And involved in spermatogenesis or folliculogenesis, as demonstrated in situ on mice cells.	DiBenedetto et al., 2008 (zebrafish); Rhee et al., 1998 (mouse); **SS:** Lopez et al., 2018 (atlantic salmon)
	scap	sterol regulatory element-binding protein cleavage-activating protein	Cellular organization	Binds to sterol regulatory element binding proteins (SREBPs) and transports them from the ER to the Golgi.	Howarth et al., 2013 (zebrafish); **SS:** Wang et al., 2022 (Pacific White Shrimp)

Table 6 (continued)

Region	Gene name	Protein name		General functions	References
chr2_c	*tnf-α - ip8l2b*	tumor necrosis factor, alpha-induced protein 8-like protein 2 B	Immunity	Predicted to be involved in the negative regulation of T-cell activation, inflammatory response, innate and adaptative immunity by maintaining immune homeostasis.	Umasuthan et al., 2014 (Oplegnathus fasciatus); Sullivan et al., 2017 (vertebrates)
	atg5	autophagy protein 5	Immunity	Involved in several cellular processes linked to the immune response, such as autophagic vesicle formation, innate antiviral immune response, lymphocyte development and prolifération in mice.	Miller et al., 2008; Ye et al., 2018 (mouse)
	brsk2a	serine/threonine-protein kinase BRSK2	cellular organization, neuronal and embryonic development	Enable in several functions: ATP/ATPase binding activity, proteine kinase activity. Key role in polarization of neurons and axonogenesis, cell cycle progress (apoptotic signaling pathway) and insulin secretion (metabolic process). This gene is related to autism spectrum disorder (social deficit) and locomotor defects (larval phase and adulthood) in zebrafish	Hiatt et al., 2019 (human); Deng et al., 2022 (human); Liu et al., 2022 (zebrafish)
	abtb2b	Ankyrin Repeat And BTB Domain Containing 2b	Cellular organization	Predicted to be involved in SMAD protein signal transduction., heterodimerization activity. Act upstream of or within cellular response to toxic substance.	
	b4galnt4a	N-acetyl-beta-glucosaminyl-glycoprotein 4-beta-N-acetylgalactosaminyltransferase 1	Cellular organization	Enables acetylgalactosaminyltransferase activity. Predicted to be located in Golgi cisterna membrane. Predicted to be integral component of membrane.	
chr2_d	*igf-1α*	insulin-like growth factor 1a receptor	Growth	Plays a critical role in transformation events. Cleavage of the precursor generates alpha and beta subunits. It is highly overexpressed in most malignant tissues where it functions as an anti-apoptotic agent by enhancing cell survival.	**SS :** Wayne & vonHoldt, 2012 (dog); Lopez et al., 2019 (atlantic salmon)
chr2_e	*znf135*	gastrula zinc finger protein XlCGF26.1	Neuronal development and cellular organization	Involved in cytoskeleton organization, regulation of cell morphogenesis, and RNA-binding. A mutation of znf135 is related to neurological symptoms in humans.	Raghuram et al., 2017 (human); **SS** : Gutierrez et al., 2016 (atlantic salmon)
chr12_a	*grxcr1*	glutaredoxin domain-containing cysteine-rich protein 1-like	Neuronal development and cellular organization	Involved in actin organization in hair cells and is associated with a non-syndromic hearing impairment and the regulation of hair bundle morphogenesis in mouse. A mutant for this gene was identified in mice and linked to hyperactivity (modifies behaviour).	Liu et al., 2021, Lorente-Cánovas et al., 2022 (mouse); **SS:** Saravanan et al., 2021 (cattle)
chr15_a	*chn1*	N-chimaerin	Embryonic development	Encodes GTPase-activating protein. Plays an important role in neuronal signal-transduction mechanisms. Implication during embryonic development: cell polarity and lack of yolk extension. In zebrafish, a morpholino knockdown of chn1 reveals its crucial role in early development, revealing severe abnormalities (development of round somites, lack of yolf extension, and kinkled posterior notochord).	Leskow et al., 2006 (zebrafish); Miyake et al., 2008; Ip et al., 2012 (human)
	atp5mc1	ATP synthase lipid-binding protein, mitochondrial	Energetic function	Loss of ATP synthase -> aberrant mitochondria cristae morphology + energy metabolism correlated to immune system	Palmer et al., 2011; Miller et al., 2019 (human); Wang et al., 2020 (chicken)

Table 6 (continued)

Region	Gene name	Protein name		General functions	References
	zc3h15	zinc finger CCCH domain-containing protein 15	Embryonic development and cellular organization	Embryonic development (positive regulation of GTPase activity) / Elongation processivity (high tumor progression in melanoma). In addition, in vitro (mice cells) that zc3h15 knockdown had an inhibitory effect on HIV-1 replication and then on HIV infection.	Capalbo et al., 2010 (mice); Li et al 2021 (human)
	zp4	zona pellucida sperm-binding protein 4-like	Reproduction	Extracellular matrix that surrounds the oocytes and early embryo. Plays vital roles during oogenesis, gamete development, fertilization and preimplantation development. Mutation in this gene induces infertility in both males and females in mammals.	Wassarman & Litscher, 2018 (fish); Li et al., 2021 (zebrafish); SS : Lopez et al., 2019 (atlantic salmon)
	uncharacterized protein LOC110490841				
	nid2	nidogen-2-like	Cellular and nuclear organization	Cell-adhesion protein that binds collagens I and IV and laminin and may be involved in maintaining the structure of the basement membrane. Linked to ovarian cancer	Torky et al., 2018 (human); Zhang et al., 2022 (zebrafish, mouse)
	brca2	breast cancer type 2 susceptibility protein	Genome stability and cellular organization	Essential for efficient homology-directed ADN repair. Impaired homology-directed repair caused by brca2 deficiency leads to chromosomal instability and tumorigenesis through lack of repair or misrepair of DNA damage. plays an essential role in ovarian development and tumorigenesis of reproductive tissues	Shive et al., 2010 (zebrafish); Rodriguez-Mari et al., 2011 (zebrafish); Moynahan et al., 2001; Chen et al., 2018 (human)
chr16_a	*atp1b3*	sodium/potassium-transporting ATPase subunit beta-1-interacting protein 3	Cellular and nuclear organization	ATPase responsible for establishing and maintaining the electrochemical gradient of Na+ and K+ ions across the plasma membrane, essential for osmoregulation.	Zhang et al., 2019 (human); SS: Naval-Sanchez et al., 2020 (atlantic salmon)
	Dnajc5	dnaJ homolog subfamily C member 5-like	Cellular and nuclear organization	Regulated the ATPase activity of 70kDa heat shock proteins and plays a role in membrane trafficking and protein folding. This protein has been shown to have also anti-neurodegenerative properties in human with a gene expression study.	Nosková et al., 2011 (human); SS: Signer-Hasler et al., 2022 (goat)
	samD10	sterile alpha motif domain-containing protein 10-like	Cellular and nuclear organization	Linked to binding activity and transmembranaire pathway	SS: Signer-Hasler et al., 2022 (goat)
	nol4	nucleolar protein 4-like	Cellular and nuclear organization	Predicted to enable RNA binding activity	SS: Signer-Hasler et al., 2022 (goat)
	tpd54 (=TPD52L2)	tumor protein D54	Cellular and nuclear organization	Related to cellular organization, are characterized by an N-terminal coiled-coil motif that forms homo and heteromeric complexes and affects cell proliferation, adhesion, and invasion.	Mukudai et al., 2013; Zhuang et al., 2019 (human); SS: Signer-Hasler et al., 2022 (goat)
	magi2	membrane-associated guanylate kinase, WW and PDZ domain-containing protein 2	Neuronal and embryonic development	Plays a role in regulating activin-mediated signaling in neuronal cells. In zebrafish, the protein of this gene plays a vital role in embryogenesis.	Borah et al., 2016 (zebrafish); SS: Cumer et al., 2021 (sheep); Hou et al., 2012 (cattle)
	emilin3 (=emilin-2)	EMILIN-3	Embryonic development and growth	Played a role in extracellular matrix organization and elastic fiber formation. Its gene expression was related to embryonic development and involved in muscle fiber development in zebrafish.	Milanetto et al., 2008 (zebrafish); SS: Baesjou & Wellenreuther, 2021 (australasian snapper)
chr20_a	*auts2*	autism susceptibility gene 2 protein homolog	Neuronal development	Related to central nervous system development and is associated with autism in humans.	Oksenberg et al., 2013; Hori et al., 2021 (human); SS: Lopez et al., 2018 (atlantic salmon); Consortium, bovine hapmap, 2009 (cattle)

TABLE 7. Percentage of protein identity between rainbow trout and nine other vertebrate species for all genes annotated in homozygous regions chr2_a, chr2_c and chr15_a.

Region	gene_ID	Human	Mouse	Goat	Cattle	Pig	Chicken	Zebrafish	Medaka	Atlantic salmon
chr2_a	mrap2a	45.71	43.52	43.87	44.98	45.45	42.20	56.22	50.45	87.55
	cep162	36.61	37.50	40.95	40.95	50.00	53.73	38.61	62.50	80.66
	adgrb1	62.37	63.44	62.12	61.95	61.74	67.72	84.02	80.94	98.16
	tsnare1	54.78	31.50	56.99	55.79	56.02	60.74	85.62	78.55	98.29
	pttg1IP	60.00	57.89	57.04	57.04	58.82	59.74	70.92	66.03	93.89
	cdk14	87.05	87.05	86.44	86.02	85.99	87.24	88.96	91.08	99.58
chr2_c	brsk2a	92.12	92.50	92.66	92.19	92.66	93.82	96.14	92.05	96.26
	abtb2b	71.54	70.76	71.93	71.74	71.74	72.46	81.05	61.68	97.35
	b4galnt4a	63.35	65.38	57.14	64.63	64.95	66.37	66.06	79.96	96.55
chr15_a	chn1	88.80	86.59	88.04	87.32	88.04	88.10	85.29	85.01	98.04
	atp5mc1	97.37	87.10	91.76	94.44	93.33	86.17	91.30	97.87	94.12
	zc3h15	69.35	68.57	67.55	67.55	67.55	66.90	74.33	71.57	97.30
	zp4	29.67	29.61	31.87	37.47	30.21	31.46	45.60	49.74	74.74
	nid2	52.00	51.16	51.11	51.11	51.22	55.00	58.14	52.78	97.87
	brca2	46.24	43.72	37.12	32.42	45.61	45.85	38.68	54.08	92.05

TABLE 8. List and functions of the 4 genes annotated in three heterozygous regions (chr10_a, chr19_a, and chr19_b) shared by the four rainbow trout populations.

| Region	Gene name	Protein name	General function	References
chr10_a	*ctnna2*	catenin alpha 2	Enables actin filament binding activity, and involved in negative regulation of Arp2/3 complex-mediated actin nucleation. Regulation of neuron migration and of neuron projection development. Implicated in brain malformations. Seems implicated in vertebral development(/deformities) in Yunlong grouper.	Uvarov et al., 2014 (vertebrates) ; Li et al., 2022 (Yunlong grouper)
chr19_a	*smarca5*	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 5	The protein encoded by this gene is a member of the SWI/SNF family of proteins. Members of this family have helicase and ATPase activities and are thought to regulate transcription of certain genes by altering the chromatin structure around those genes. The protein encoded by this gene is a component of the chromatin remodeling and spacing factor RSF, a facilitator of the transcription of class II genes by RNA polymerase II	Ding et al., 2021 (zebrafish); Limi et al., 2018 (mice) : Armas et al., 2013 (zebrafish)
	frem2	FRAS1-related extracellular matrix protein 2	Plays a role in epidermal-dermal interactions -> important for the integrity of skin and renal epithelia.	Gautier et al., 2008 (zebrafish)
chr19_b	*pou4f2*	POU domain, class 4, transcription factor 2-like	May be involved in maintaining visual system neurons in the retina, and in the lateral line. The level of the encoded protein is also elevated in a majority of breast cancers, resulting in accelerated tumor growth. Seems link to cardiac development in zebrafish	DeCarvalho et al., 2004 (zebrafish); Maskell et al. 2017 (zebrafish)

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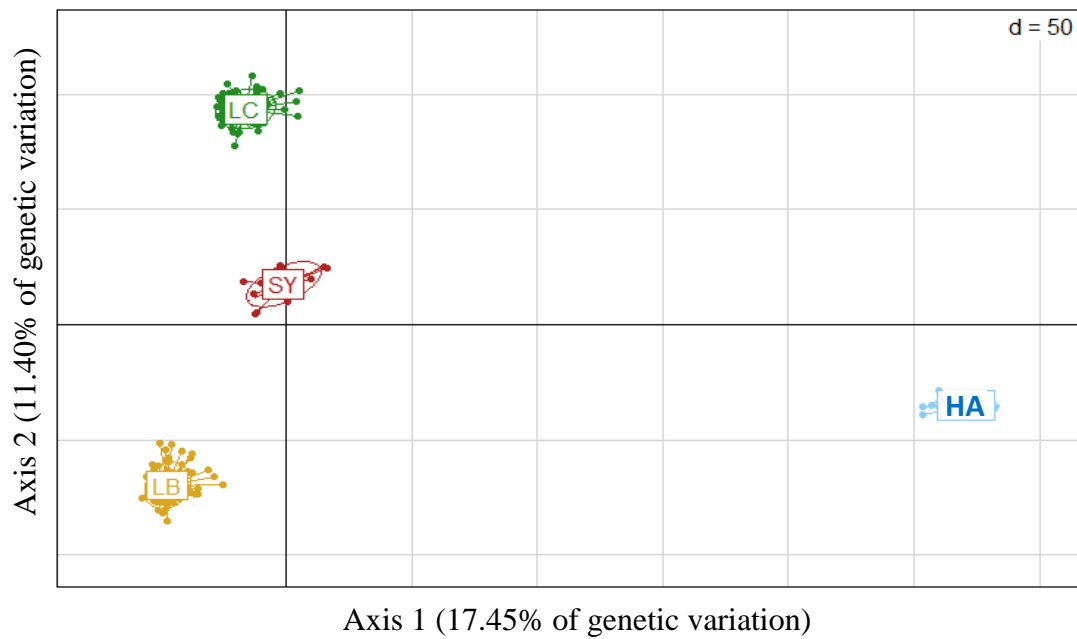
FIGURE 1. Principal component analysis (PCA) of the genetic diversity of the four rainbow trout populations (LB, LC, SY, and HA) based on 546,903 SNPs.
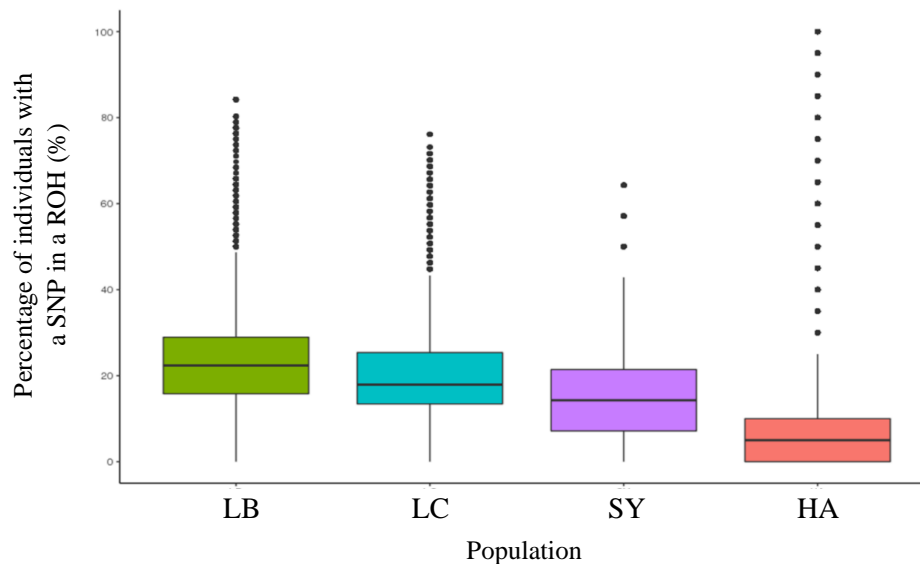

FIGURE 2. Box-plots of the occurrence of ROH (number of individuals having this ROH) per SNP for each rainbow trout population LB, LC, SY, and HA.
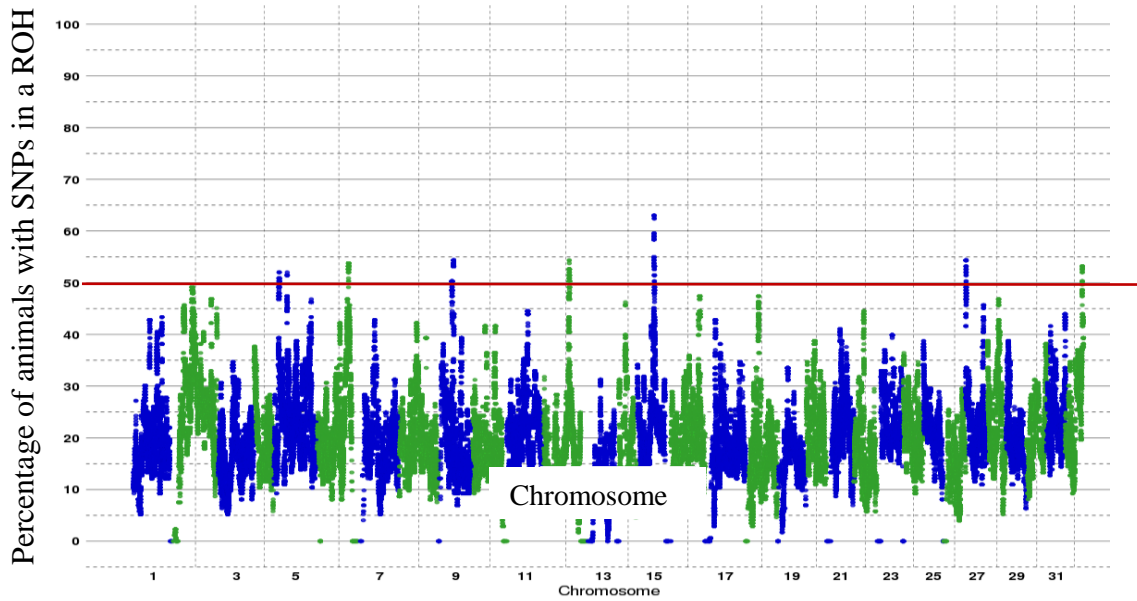
FIGURE 3. Manhattan plot of the occurrence of ROH per SNP across chromosomes (gathering all rainbow trout populations). The red line highlights the ROH islands.
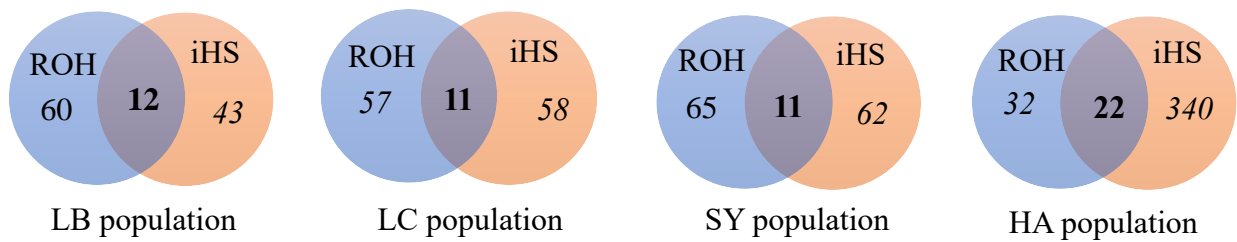

FIGURE 5. Venn Diagram of the number of regions identified as ROH island or iHS signature of selection for each rainbow trout population.

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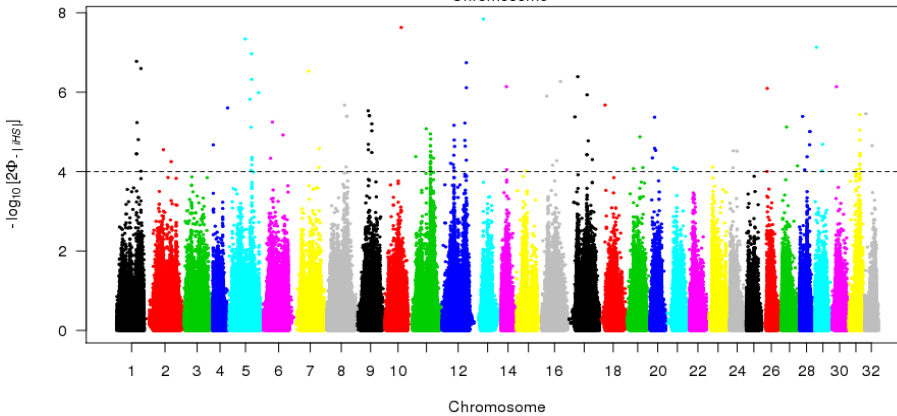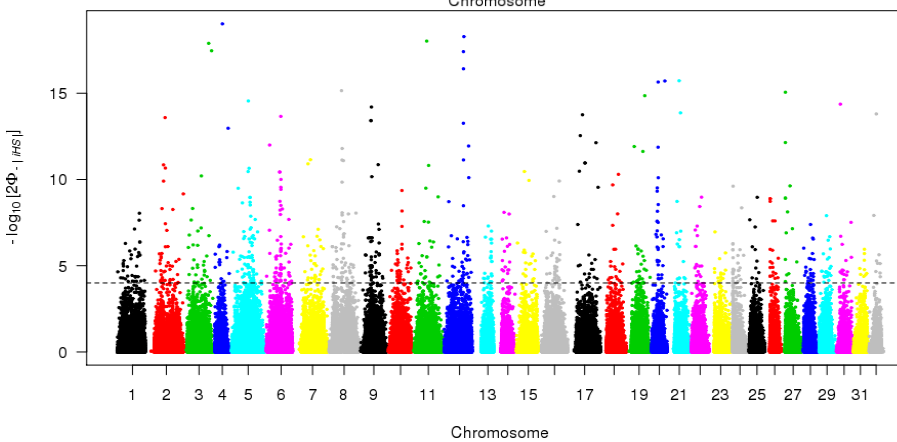1687
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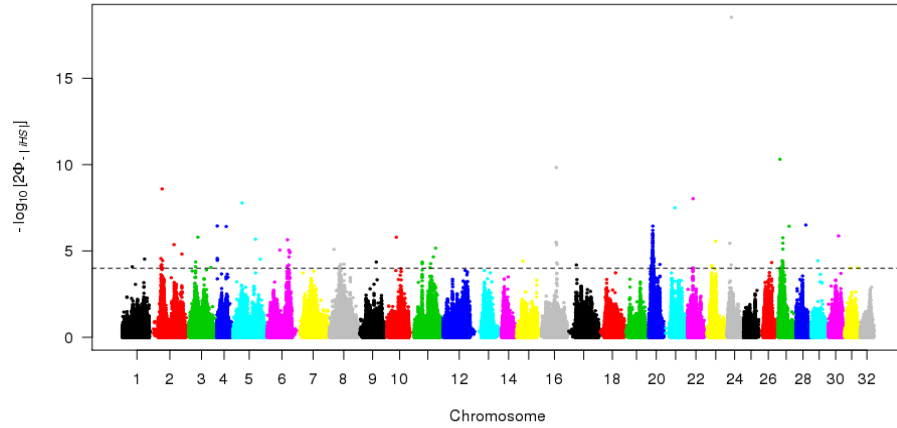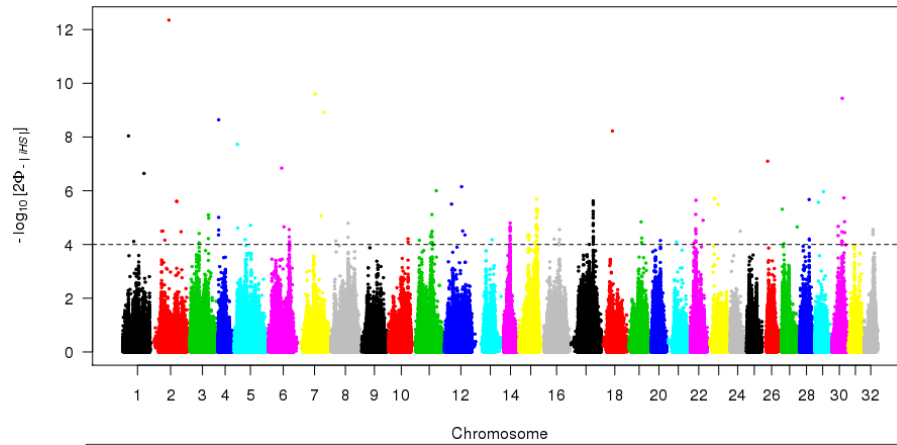
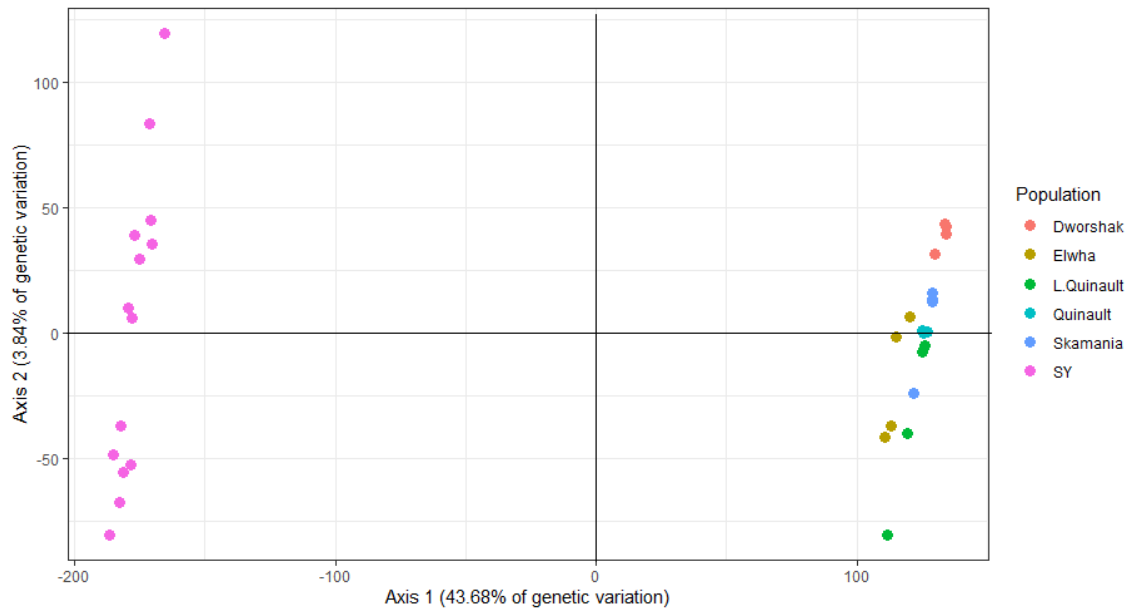**FIGURE 4.** Genome-wide distribution of log(p-value) for standardized iHS for each population (LB, LC, SY, HA). The dashed line indicates the log(p-value) significance threshold set to 4 to identify regions under positive selection

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1700 **Appendices**

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1715 **Supplementary figure 1.** Principal component analysis (PCA) of the genetic diversity of SY,
1716 and HA sub-populations based on 546,903 SNPs.

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1718 File: *Supplementary_Tables.xlsx*

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