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Yann Guiguen, Edwige Quillet

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FOURTEEN CANDIDATE GENES GOVERNING SPONTANEOUS SEX-REVERSAL IN XX-RAINBOW TROUT

F. Phocas^{*}, A. Dehaullon, C. Fraslin, A. Bestin, Y. Guiguen, and E. Quillet
Université Paris-Saclay, INRAE, AgroParisTech, GABI, 78350 Jouy-en-Josas, France
florence.phocas@inrae.fr

Introduction. Revealing the molecular mechanisms of sex determination and differentiation may have important implications for research on reproductive development, sex-ratio control, and selective breeding in fish. Although phenotypic sex in rainbow trout is primarily controlled by a XX/XY male heterogametic sex determination system, spontaneous masculinization of XX fish is a phenomenon repeatedly observed at low frequencies. This spontaneous sex-reversal is a highly heritable trait and several QTL were detected (Fraslin et al., 2020), highlighting the existence of minor sex-determining genes that are independent of the major determinant carried by the sex chromosome (Omy29). In particular, two QTLs were located on Omy1 with a strong evidence while two other QTL were identified on Omy12 and Omy20. Variants from these four QTL regions were kept for further investigations in the present study using the new reference genome USDA_OmykA_1.1.

Material and methods. Sequenced samples. The initial data set was produced by Fraslin et al. (2020), and the 4 QTL detected in the previous study were further investigated in the current work, using realignment against the new reference genome USDA_OmykA_1.1. Here we only considered the sequence data of 23 dams with at least 10 progenies evaluated for phenotypical sex and extreme proportions of sex-reversed offspring, either $\geq 25\%$ or $\leq 6\%$ of neomales among their XX daughters. **Genotyped Samples.** A set of 192 SNP located within the 4 QTL were selected to design two 96 SNP genotyping arrays using microfluidic real-time PCR Fluidigm Kasp chemistry. These arrays were used to genotype 315 fish from 6 diverse French populations of rainbow trout with at least 30 XX fish and a minimum of 8 neomales per line. **Statistical analysis.** An exact Fisher test was run for the discovery population as well as for each of the 6 validation populations using the R ‘fisher.test’ function to test the independence of genotypes at each SNP and phenotypic sex. SNPs were considered as significant when $p_value < 0.005$. To deal both with “large p, small n” issue and correlations among SNPs, we applied a machine learning method on the discovery data set using haplotypes of 80 subsequent SNPs using the R package ‘RandomForest’.

Results and discussion. We confirmed on several commercial lines, the importance of several genomic regions as containing minor sex-determining genes involved in spontaneous sex-reversal in rainbow trout. The candidate genes based on positional and functional information are SYNDIG1, TLX1, HELLS and GBF1 on Omy1, HCN1 on Omy12, and ARFGF3, AKT3, KHDRSB2, DST, CILK1, CSMD1, RPS6KA2, LRRC59 and CASKIN2 on Omy20. These results are consistent with a model of sex determination in which spontaneous female-to-male sex-reversal in rainbow trout is associated with genetic factors able to reduce germ cell proliferation and arrest oogenesis, as suggested by works in zebrafish and medaka (Siegfried et al., 2008; Nishimura et al., 2018). This study paves the way for identifying the main causal mutations responsible for sex-reversal of XX rainbow trout.

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