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QUANTITATIVE TRAIT LOCI FOR RESISTANCE TO FLAVOBACTERIUM PSYCHROPHILUM IDENTIFIED USING HIGH-DENSITY GENOTYPING IN RAINBOW TROUT FRENCH SELECTED LINES

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Introduction

Bacterial cold-water disease (BCWD) and rainbow trout fry syndrome, caused by *Flavobacterium psychrophilum* (Fp), are among the most problematic diseases in rainbow trout (*Oncorhynchus mykiss*) farming. Trout farming often suffers substantial economic loss due to problems associated with BCWD outbreaks, including high mortality, increased susceptibility to other diseases and skeletal deformities resulting in quality reduction in recovering fish. The management of this disease is a significant cause of antibiotic use in rainbow trout farming which raises environmental concerns and issues about the emergence of antibiotic resistance. Therefore, there is a crucial need for other methods to control the disease. Selective breeding of resistance to BCWD is a promising approach to reducing the frequency and severity of BCWD outbreaks. Several Quantitative Trait Loci (QTLs) for BCWD resistance have been identified in previous studies (e.g., Fraslin et al., 2018, Vallejo et al., 2022). With the development of a new high-density Axiom™ Trout HD genotyping array (Bernard et al., 2022), the detection and mapping of QTLs can now be more precise. This work refines the description of genetic architecture of BCWD resistance in rainbow trout using waterborne experimental infection model and genome-wide association studies (GWAS) with high-density genotyping and imputation.

Materials and Methods

Fish used in this experiment were from two French commercial breeding programs (pop. A and pop. B) and derived from partial factorial mating design plans from approx. 100 dams and 100 sires for each line. “Eyed” eggs were disinfected before entering the INRAE-IERP experimental unit (Jouy-en-Josas, France). After 4 months of breeding in flow water at 10°C, at an average weight of 3.9 g for pop. A and 3.3 g for pop. B, 1200 fish for each population were challenged with the virulent strain FRGDSA 1882/11 isolated in France from diseased rainbow trout. Briefly, bacteria were maintained in contact with fish at a concentration of 10⁶ CFU mL⁻¹ by stopping the water flow for 24 h. Water was maintained at 10°C with vigorous aeration and physical parameters (NH₄⁺, O₂, ...) were monitored. Over a 29-d period, mortality was monitored twice a day, and live and dead fish were fin-clipped for DNA extraction and genotyping.

Challenged offspring and their sires were genotyped with the 57K Axiom™ Trout Genotyping array (Palti et al., 2015) at the INRAE genotyping Platform Gentyane. Their dams (96 for pop. A and 90 for pop. B) were genotyped with the high-density 675K Axiom™ Trout HD array. Offspring's 57K genotypes were imputed to HD thanks to the dams reference HD genotypes using FIMPUTE3 software (Sargolzaei et al., 2014). After quality controls, 1148 individuals genotyped for 403,863 SNPs and 1038 individuals genotyped for 402,750 SNPs were kept for analysis in pop. A and pop. B, respectively. Variance components analysis was performed for each line considering a binary survival

trait (dead or alive at 29 days) in a threshold mixed animal model using genomic relationship matrices with THRGIBBS1F90 from the BLUPF90 family of programs (Misztal et al., 2014). GWAS was then performed using the Bayesian sparse linear mixed model (BSLMM) implemented in the GEMMA software (Zhou et al., 2013). This model allows partitioning the genetic variance into two components: a polygenic small effect for all SNPs and a QTL large effect for a limited set of SNPs. GWAS have been performed either on each line or the two of them combined using phenotypes corrected for the line effect to capture shared QTL. The Bayes factor (BF) was calculated to quantify the degree of association between a SNP and the phenotype. Evidence for a QTL was provided by a value $2\ln(\text{BF}) \geq 14$ at a SNP position. A credibility interval for the QTL was computed around the peak SNP including all SNPs for which $2\ln(\text{BF}) \geq 6$ in a sliding window of 250 kb.

Results and Discussion

Survival rate post immersion challenge was 49% and 29% and heritability of Fp resistance was estimated to be 0.57 (CI: 0.47-0.68) and 0.39 (CI: 0.25-0.53) for the pop. A and B, respectively, which is consistent with estimates in the literature. Overall, for the two lines, only 10 to 20 SNPs were jointly selected in the BSLMM model, but they explained ~60% and ~75% of the genetic variance of Fp resistance in pop. A and B, respectively. Such results suggest that Fp resistance is a polygenic trait but with a few genes having very large effects. In pop. A, we found 4 QTLs located in chromosomes (chr) 3, 17, 29 and 31 (Figure 1A), while 10 QTLs on chr 1, 2, 11, 13, 15, 16 and 24 were identified in pop. B (Figure 1B). The GWAS combining the two lines revealed only a few shared QTLs, suggesting distinct molecular pathways underlying host resistance. Some of the detected QTL have been reported in Troutlodge, Inc., May-spawning line (Vallejo et al., 2022) or French INRAE lines (Fraslin et al., 2018). Investigations are in progress to identify candidate genes.

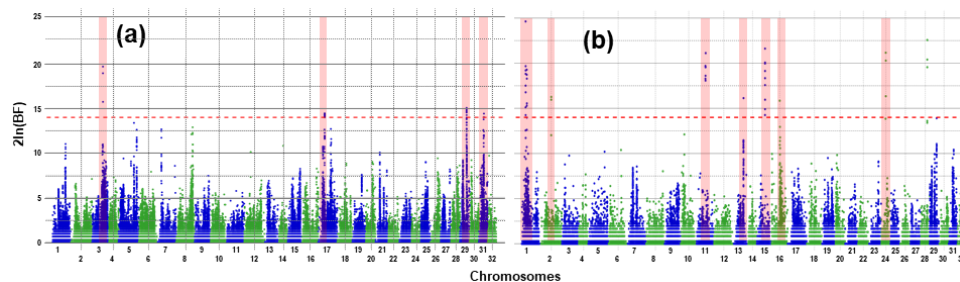


Figure 1. Manhattan plot of QTL detected for Fp resistance trait (A) in pop A and (B) in pop B. The red line corresponds to the QTL evidence threshold ($2\ln(\text{BF}) \geq 14$).

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