

QTLs associated with resistance to MAP infection in Holstein-Friesian cattle



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INTRODUCTION

- Johne's disease (JD) is a chronic enteritis of ruminants caused by infection with the Gram-positive bacteria *Mycobacterium avium* subsp. *paratuberculosis* (MAP)
- Absence of treatment options and lack of availability of vaccines with high efficacy has hindered JD control. As resistance to JD is shown to be heritable in nature, employing genetic selection to breed for increased resistance is one potential way to control JD.
- JD is polygenic in nature as reported by several Genome-wide Association (GWA) studies. Previously, a 50k GWA study conducted by our lab identified QTLs associated with resistance to MAP infection. However, there is a need to perform JD GWA studies using high density (HD) SNP panels. The hypothesis behind the current study is that the use of imputed HD SNP genotypes leads to identification of additional QTL associations, especially in the regions with low coverage on the 50k panel used in the previous study.
- New QTLs identified could be used in marker-assisted selection to breed for resistance to JD in cattle.

OBJECTIVES

- 1) To impute previously analysed LD genotype (50k) data to HD (777k) panel;
- 2) To perform GWA analysis of HD imputed genotype data by principle component regression analysis

MATERIALS AND METHODS

- **Dataset:** 50k (Illumina BovineSNP50) genotype data of 232 cows comprised of MAP-negative cohort (n=142) and MAP-positive cohort (n=90). Phenotype classification of cows as "case" and "control" was based on plasma and milk ELISA test results.
- **Imputation:** 50k genotype data of 232 animals was imputed to HD bovine illumina 777k SNP panel using FImpute software (Sargolzaei *et al.*, 2014).
- **Statistical analysis:** HD imputed data was analysed using principle component regression analysis model as follows:

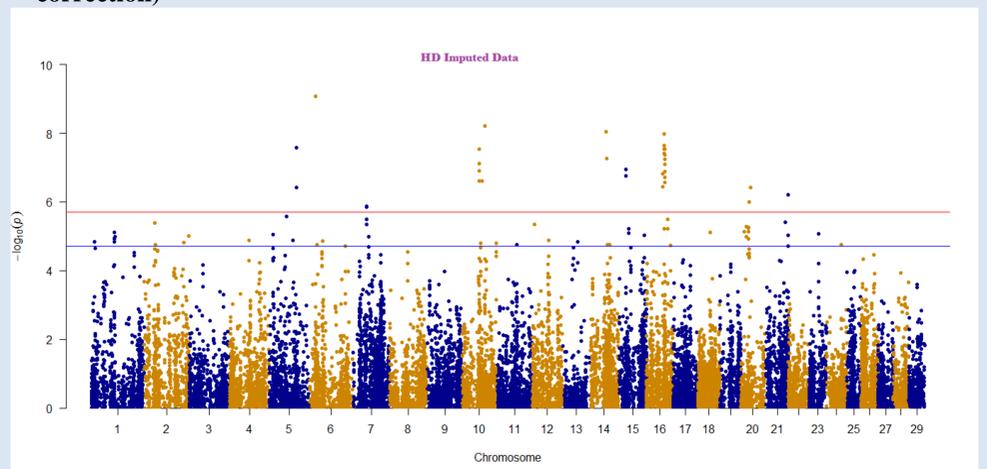
$$\text{Logit}(Y_i) = \mu + \beta_t \alpha_t + \sum_{j=1}^k \beta_j P_j + e_i$$

where:

Y_i=binomial response phenotype of the ith animal (coded as 0 or 1); μ=overall mean; β_t=regression coefficient for the additive effect(α_t) of the SNP_t; β_j=multiple regression coefficients for the PC terms(P_j); e_i=random error.

RESULTS

Figure 1: Manhattan plot for chromosome-wise principal component regression analysis of imputed genotype data. A total of 41 SNPs across 8 chromosomes (Bta 5,6,7,10,14,15,16,20,21) were found to be significant at p= 1.99E⁻⁶ (Sidak correction)



- This is the first study to carry out Johne's disease GWA analysis using HD (777k) imputed genotype data.
- Seven novel QTLs on Bta 15, 16, 20 and 21 were identified in addition to previously reported QTLs on Bta 1, 5, 7, 10, 11 and 14 that were identified using the same resource population but a lower density marker panel.
- Post-GWA analysis, bioinformatic analysis revealed several candidate genes with pro-inflammatory immune function that are relevant to the host defense against MAP infection: *NLRP3*, *IFI47*, *TRIM41*, *TNFRSF18* and *TNFRSF4*. Further functional validation (using CRISPR) will be used to confirm the relevance of these genes.
- With the current availability of bovine sequence data, future work should consider imputation of low density marker genotypes to sequence data to add to the knowledge of marker-QTL associations concerned with JD in cattle.

REFERENCES

Sargolzaei *et al.*, (2014). BMC Genomics 2014 15:478
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