A Genome-Wide Association Study of Immune Response in Holstein Bulls

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ABSTRACT: Selection for enhanced immune responsiveness using the High Immune Response Technology is a genetic approach to improve animal health. Previous genomic research has shown promise for the inclusion of immune response in genomic breeding objectives; however the research was based on a small number of cows or bulls that were selectively genotyped (n=140-168). The objective of this study was to confirm previous results on a larger sample of bulls, not selectively genotyped, with known immune response phenotypes. Immune response and 50k SNP panel genotypes for 631 Holstein bulls were included in the association study. A significant peak on chromosome 23 was found confirming previous results from the association studies using cows or bulls with extreme phenotypes for immune response. This study provides strength for the inclusion of immune response traits in genomic breeding indices to improve animal health.
Keywords: dairy cattle; health; genomics; immune; response

Introduction

Selection for improved immune response is a feasible and sustainable genetic tool to improve animal health. Dairy cattle with enhanced or High Immune Responses are known to have a lower occurrence of many diseases of economic importance including mastitis, metritis, ketosis and retained placenta (Thompson-Crispi et al. 2012a 2013; Wagter et al. 2000). Immune response has also been associated with increased longevity and some reproductive traits (Thompson-Crispi et al. 2012b), because healthier cows will remain in the herd longer. The High Immune Response Technology measures the ability of cows to mount adaptive immune responses to test antigens that stimulate the antibody-mediated immune response (AMIR) and the cell-mediated immune response (CMIR). These branches of the adaptive immune system are essential to provide protection for extracellular and intracellular pathogens respectively. Selecting animals on these two traits may help to achieve broad-based disease resistance. The immune response traits AMIR and CMIR are heritable, indicating it is possible to make genetic gain (Thompson-Crispi et al. 2012b). In collaboration with the University of Guelph, a Canadian AI company has released an exclusive line of commercial bulls based on the High Immune Response Technology. This has made it possible for producers worldwide to breed, on the sire side, for enhanced immune response and health.

Genomics has allowed for increased accuracy in prediction of the genetic merit of dairy cattle for routinely evaluated traits. It has also allowed for the potential to include new traits in breeding objectives. Utilizing genomics to improve immune response traits would be of significant benefit to the dairy industry. Previous genomic research selectively genotyped cows classified as High and Low immune responders and found unique genetic profiles associated with AMIR and CMIR. A significant peak on Chromosome 23, which contains the bovine major histocompatability complex, was associated with AMIR (Thompson-Crispi et al. 2012c). The results of this potential QTL were confirmed in an independent population of selectively genotyped Holstein bulls that had been immune response typed. These studies provide insight into the genetic regulation of immune response traits, and provide promise for their inclusion in genomic breeding indices. This will allow producers to make genetic improvement for immune response and health on both the dam and sire side.

Initial genomics and immune response studies were performed by selective genotyping. This approach increases the power to detect QTL given a sample size of genotyped individuals (Darvasi and Soller 1992). The objective of this research was to confirm results of these previous genome-wide association studies in a larger sample of Holstein bulls by including all the available immune response typed bulls.

Materials and Methods

Animals. A total of 631 Holstein bulls were immune response phenotyped and breeding values estimated for AMIR and CMIR.

Statistical Analysis. ASReml was used to estimate heritability and breeding values for AMIR and CMIR independently (Ronnengard et al. 2013). The pedigree was obtained from the Canadian Dairy Network and included 20,615 animals. The model included the fixed effects of testing facility, test group and their interaction, a random animal effect, covariates age in months at immune response testing, and a control for each immune response test. The 50K genotypes were provided by the Semex Alliance. A total of 45,187 SNPs were considered for association analysis and SNPs with a minor allele frequency < 0.05 were excluded. A generalized quasi-likelihood score method (Feng et al. 2011) was used to determine SNP markers associated with the immune response traits. This method accounts for the population structure by means of

the pedigree-based relationships among animals. In order to account for multiple comparisons, a chromosome-wise false discovery rate (FDR) of 0.05 was applied (Benjamini and Hochberg 1995).

Results and Discussion

The heritability of AMIR was 0.46 (±0.08) and for CMIR was 0.22 (±0.08) in Holstein bulls, similar to previous results for Holstein cows (Thompson-Crispi et al. 2012b).

After applying quality control measures, 39,888 SNP were included for the analysis. A total of 2,864 SNP were significantly (chromosome-wise $P < 0.05$) associated with AMIR, and after accounting for multiple comparisons, 266 SNP remained significant at FDR 0.05. After applying the FDR, the majority (67%) of the SNP were found on chromosome 23 (Figure 1). For CMIR, a total of 2,828 SNP were significant and after applying an FDR of 0.05, 46 SNP remained significant (Figure 2).

After accounting for multiple comparisons, comparatively few markers remained significant for CMIR as was found for AMIR. The proportion of significant SNP on chromosome 23 associated with AMIR in previous studies was higher than what is reported here when the entire sample of bulls was genotyped. In the previous study, over 90% of significant markers fell within chromosome 23 compared to 67% found here. However, the number of markers significant after accounting for multiple comparisons was similar, 186 with selective genotyping (Thompson-Crispi et al 2012c), and 266 found here. This confirms that chromosome 23 is a highly important gene region regulating antibody responses in dairy cattle. Chromosome 23 contains the bovine major histocompatability complex, BoLA, a polymorphic, complex gene region that is important in the initiation and regulation of adaptive immune responses. Previous research identified candidate genes and biological pathways associated with AMIR, and found multiple BoLA genes within 250kbp of markers associated with this immune response trait. When mapped to biological pathways, the antigen processing and presentation pathway was identified, mediated by BoLA (Thompson-Crispi et al. 2012c).

Results found here are similar and confirm what has been found in previous genome-wide association studies for immune response in Canadian Holstein cows. Initial genomic and immune response studies were performed by selectively genotyping cows or bulls with High or Low immune responses. This approach is economical, and increases the power that associations will be found with a trait of interest given a sample size, which is why it was chosen for the initial studies. The current study, using a large sample of genotyped bulls, confirms the previous finding and, therefore, provides strength for the inclusion of immune response traits in genomic breeding indices to improve animal health.

Conclusions

This study confirms that chromosome 23 and the major histocompatability complex play a significant role in the genetic regulation of adaptive immune responses in cattle. These results provide additional evidence for the potential to include immune response traits in breeding objectives to improve animal health. The establishment of a large reference population with known immune response phenotypes and genotypes is currently underway and is the next critical step for genomic selection for immune response.

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Figure 1. Manhattan plot for antibody mediated immune response for 631 Holstein bulls. The x-axis is the position of each SNP on the bovine chromosome and the y-axis is the –log10*P*. The bottom red line is a comparison-wise *P* < 0.05 and top blue line is *P* < 0.001.

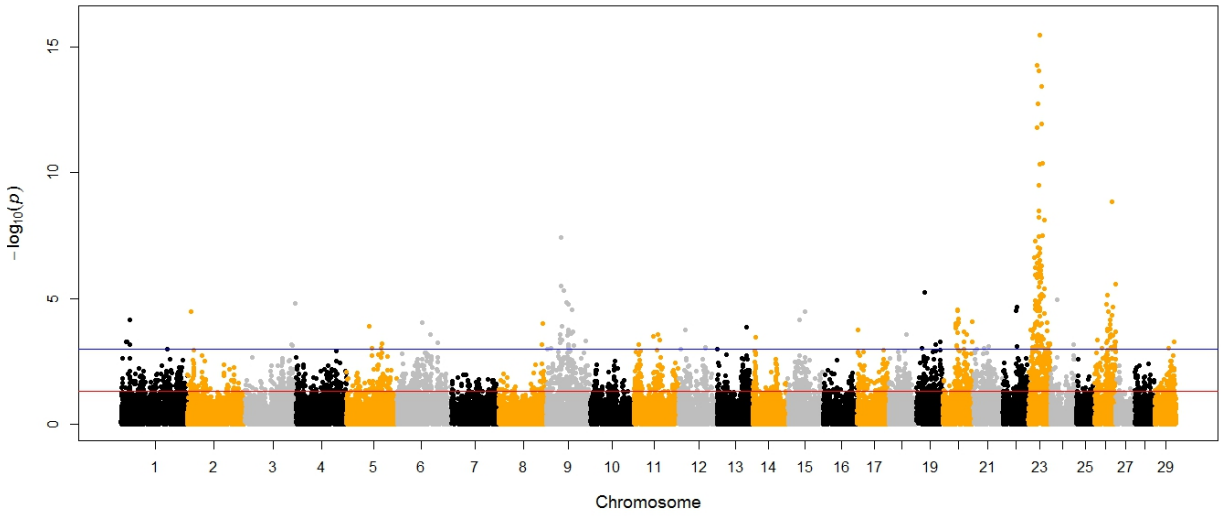

Figure 2. Manhattan plot for the cell mediated immune response for 631 Holstein bulls. The x-axis is the position of each SNP on the bovine chromosome and the y-axis is the –log10*P*. The bottom red line is a comparison-wise *P* < 0.05 and top blue line is *P* < 0.001.