Identification of Genetic Regions Associated with Tolerance and Infection to Johne’s Disease in Cattle Using a Fine-Mapping Approach

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ABSTRACT

Johne’s disease is an incurable illness of ruminants, caused by Mycobacterium avium subspecies paratuberculosis (Map). Once an animal is exposed to Map it can become infected or resist infection. Susceptible animals may develop Johne’s disease with different severity levels or exhibit different levels of tolerance. Selection of animals that are resistant or tolerant to Johne’s disease would reduce economic losses and reduce disease prevalence. Tolerance was measured by the relationship between fitness (Map fecal shedding) and infection intensity (Map tissue infection); infection was determined by the presence of Map in four tissues. We previously identified associations with a region on BTA 3 and Map tissue infection and on BTA 15 with tolerance to Johne’s disease using a whole-genome analysis. The objective of this study was to confirm the association on BTA 3 and BTA 15. On BTA 15, 54 SNPs were used to interrogate a 193kb region and on BTA 3, 42 SNPs were chosen for a 235kb region. Sixteen SNPs on BTA 15 and 18 SNPs on BTA 3 were removed due to low minor allele frequencies (< 0.01) or genotyping failure (>10%). Association analyses were conducted with the Wald test (tolerance) and the Chi-square test (Map tissue infection). A region of 32kb was associated with tolerance (P<0.03), and an 86kb region was associated with Map tissue infection (P<0.05). These results support our previous findings and suggest the existence of a gene or regulatory element associated with tolerance and infection on BTA 15 and BTA 3, respectively.

RESULTS

A candidate gene was found localized on BTA 15, Guanine nucleotide-binding proteins (GNA12). This gene is involved as a modulator in various trans-membrane signaling systems. On BTA 3, three candidates genes were found (EDN2, HIVEP3, and LOC521287). Endothelin-2 (EDN2) is associated with initiation of intracellular signaling events and cytokines activities as an endothelium vasoconstrictor peptide. Human immunodeficiency virus type I enhancer binding protein 3 (HIVEP3) has been described in regulating patterns of gene activation in response to pro-inflammatory stimul. LOC521287 is an important regulator of DNA replication and mitosis in a variety of cell types.

DISCUSSION

Host can evolve to two types of defense mechanism against pathogenic infection. Resistance and tolerance. A candidate gene was found localized on BTA 15, Guanine nucleotide-binding proteins (GNA12). This gene is involved as a modulator in various trans-membrane signaling systems. On BTA 3, three candidates genes were found (EDN2, HIVEP3, and LOC521287). Endothelin-2 (EDN2) is associated with initiation of intracellular signaling events and cytokines activities as an endothelium vasoconstrictor peptide. Human immunodeficiency virus type I enhancer binding protein 3 (HIVEP3) has been described in regulating patterns of gene activation in response to pro-inflammatory stimul. LOC521287 is an important regulator of DNA replication and mitosis in a variety of cell types.

CONCLUSION

Our findings confirmed the previous results of association between BTA 3 and Map tissue infection and BTA 15 and Map tolerance. The identification of the candidate genes with possible association with tolerance and resistance to Johne’s disease may lead us to the discovery of the genetic component responsible for those mechanisms of defense against pathogenic infection. Future research will focus on sequencing GNA12 and EDN2.

MATERIALS AND METHODS

- 87 Holstein cows were genotyped for the quantitative trait of tolerance
- BTA 15, 54 SNPs were used to interrogate a 193kb region.
  - 19 SNP were excluded due to minor allele frequency (< 0.01) /genotyping failure (>10%)
- 205 Holstein cows were genotyped (89 cases and 118 controls) for the trait of Map tissue infection
- BTA 3, 42 SNPs were chosen for a 235kb region.
  - 10 SNPs were excluded due to low minor allele frequencies (< 0.01).

Association analyses were conducted with the Wald statistical test (tolerance) and the Chi-square test (Map tissue infection).

INTRODUCTION

The incidence of Johne’s disease continues to increase in the United States. It is estimated to be present in 67% of US dairy herds (APHIS, 2008), resulting in annual losses exceeding $200 million US dollars (Olt et al. 1999). The disease results in lowered milk production, intermittent diarrhea, weight loss and death. Impediments to lowering the incidence of Johne’s disease are dairies with large animal numbers, low sensitivity of current diagnostic techniques and a long incubation period prior to the appearance of clinical signs (Chiodini & Merkal 1984, Collins et al. 2006). Oral-fecal transmission is the most common mode of infection between animals. The association between Johne’s disease in cattle and Crohn’s disease in humans is not well known. However, Map was found in more than 42% of patients with Crohn’s disease and was not observed in healthy individuals (Rudoler, 2004).

=> If Johne’s disease is found to be zoonotic, selection of animals that will be resistant to Johne’s could be used to reduce the spreading of the disease to humans.

=> If Johne’s disease is not a zoonotic disease, selection of animals that will be tolerant to Johne’s could be used to reduce the economic losses caused by the disease.

OBJECTIVE

The objective of this study was to confirm the association of Map Tissue Infection on BTA 3 and with Tolerance on BTA15, using a fine mapping approach.