Genetic Resistance to Johne's Disease in Cattle: Three Candidate Genes

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Introduction

Paratuberculosis (Johne's disease) is an economically significant, infectious disease of ruminants caused by *Mycobacterium avium* subsp *paratuberculosis*, and characterized by progressive weight loss and nonresponsive diarrhea. Genetic factors have been associated with differences in host susceptibility to bovine paratuberculosis. Research has been aimed at detecting associations between susceptibility and polymorphisms at candidate genes with no definitive results. Several gene products are candidates for this association. Interferon gamma is an inducible cytokine with a crucial role in the innate host response to intracellular bacteria. Toll-like receptors are trans-membrane structures responsible for coordination of innate and adaptive immune responses. The SLC11A1 gene plays an important role in innate immunity, preventing bacterial growth in macrophages during the initial stages of infection. The objective of this candidate gene case-control study was to characterize the distribution of polymorphisms in three candidate genes related to the immune function; interferon gamma (BoIFNG), toll-like receptor 4 (TLR4), and solute carrier family 11 member1 (SLC11A1) genes, and test their association with paratuberculosis infection in cattle.

Materials and Methods

The study population consisted of 431 adult cows, including of 299 Holstein, 50 Jersey and 82 Brahman-Angus crosses. The population was recruited from three Holstein and one Jersey dairy herds, and one Brahman-Angus cow-calf herd near Gainesville, Florida, USA. A case-control design was used based on the infection status of the animals following multiple tests to reduce misclassification of individuals. Paratuberculosis infection was determined by parallel interpretation of five diagnostic tests (serum ELISA, milk/blood/fecal PCR and fecal culture) or by necropsy examination. Two (SNP1 and SNP2) and three (SNP3, SNP4, and SNP5) previously reported single nucleotide polymorphisms (SNP) within IFNG and TLR4 gene were tested. A region corresponding to 275 base pairs, targeting SLC11A1 gene and containing different numbers of the microsatellite repeat (GT) was PCR amplified to determine different alleles. The statistical analysis, which consisted of Chi square and Fisher exact tests, were used to test significant differences in allele frequencies between cases and control populations. Logistic regression models were proposed to estimate odds of infection related to the presence of singular alleles. Our hypothesis was that infected and non-infected cows will present different alleles for our candidate genes that could represent resistance alleles.

Results

The ratio of cases to controls was 1:2.4 (126 cases vs. 305 controls) with an average age for cases and controls of 64 and 65 months, respectively. The statistical analysis demonstrated significant differences in allelic frequencies between cases and controls for BoIFNG SNP1 and SLC11A1 microsatellites, indicating a significant association between infection and variant alleles. In the analysis of genotypes, a significant association was also found between infection status and BoIFNG SNP1 and SLC11A1-275-279-281 microsatellites. Although some of the analyses in this study suggest a potential connection between polymorphisms in BoIFNG and SLC11A1 genes and paratuberculosis, subsequent examination in the multivariate logistic regression analysis, controlling for potential confounding such as age and breed, dismissed this association, leaving in question the role of these candidate genes in host susceptibility to paratuberculosis.

Significance

Further analysis including a larger population and new polymorphisms in these candidate genes would provide a greater clarity as to the potential role of IFNG and SLC11A1 genes in paratuberculosis susceptibility. Subsequent results could provide the basis for further research to create a rapid method to select for more resistant individuals, genetically contributing to the control of Johne's disease.