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Genome-wide association study for ketosis in US Jerseys using producer-recorded data

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ABSTRACT

Ketosis is one of the most frequently reported metabolic health events in dairy herds. Several genetic analyses of ketosis in dairy cattle have been conducted; however, few have focused specifically on Jersey cattle. The objectives of this research included estimating variance components for susceptibility to ketosis and identification of genomic regions associated with ketosis in Jersey cattle. Voluntary producer-recorded health event data related to ketosis were available from Dairy Records Management Systems (Raleigh, NC). Standardization was implemented to account for the various acronyms used by producers to designate an incidence of ketosis. Events were restricted to the first reported incidence within 60 d after calving in first through fifth parities. After editing, there were a total of 42,233 records from 23,865 cows. A total of 1,750 genotyped animals were used for genomic analyses using 60,671 markers. Because of the binary nature of the trait, a threshold animal model was fitted using THRGIBBS1F90 (version 2.110) using only pedigree information, and genomic information was incorporated using a single-step genomic BLUP approach. Individual single nucleotide polymorphism (SNP) effects and the proportion of variance explained by 10-SNP windows were calculated using postGSf90 (version 1.38). Heritability of susceptibility to ketosis was 0.083 [standard deviation (SD) = 0.021] and 0.078 (SD = 0.018) in pedigree-based and genomic analyses, respectively. The marker with the largest associated effect was located on chromosome 10 at 66.3 Mbp. The 10-SNP window explaining the largest proportion of variance (0.70%) was located on chromosome 6 beginning at 56.1 Mbp. Gene Ontology (GO) and Medical Subject Heading (MeSH) enrichment analyses identified several overrepresented processes and terms related to immune function. Our results indicate that there is a genetic component related to ketosis susceptibility in Jersey cattle and, as such, genetic selection for improved resistance to ketosis is feasible.

Key words: genetic parameter, genome-wide association study, Jersey, ketosis

INTRODUCTION

An unfavorable association between production and health has become clear with the significant progress made in the dairy industry for traits related to yield throughout recent decades (e.g., Pryce et al., 1998; Esposito et al., 2014). Declining health of dairy cows is an important concern for producers because it can result in decreased profitability due to increased veterinary costs, replacement rates, and labor, among other factors. Concurrently, the public increasingly wants assurances that the dairy products they consume are from healthy animals raised in a humane environment (Boichard and Brochard, 2012).

Metabolic diseases are common among high-producing dairy cows, especially in early lactation (Pryce et al., 2016). At that time, the cow is transitioning from a pregnant, nonlactating state through parturition to lactation. During this period, the cow typically enters a state of negative energy balance, in which it is unable to consume enough energy to wholly support the requirements of lactation, and must rely on stored body reserves. One metabolic disease that can arise during this period is ketosis, which is one of the most important metabolic diseases in US dairy herds (Oetzel, 2007). Total cost per incidence is estimated to be $77 in first parity and $181 in later parities (Liang et al., 2017). Costs associated with ketosis include treatment, increased risk of other diseases, risk of decreased reproductive performance, decreased milk production, and higher risk of culling in early lactation (Gordon et al., 2013). Ketosis is thought to occur most often due to an imbalance in the supply and demand of glucose typical-

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ly occurring early in lactation (Baird, 1982). Symptoms can include decreased appetite, decreased milk production, weight loss, hypoglycemia, and hyperketonemia (Baird, 1982). Risk factors for ketosis include milk fever (Bigras-Poulin et al., 1990), later parity (Bigras-Poulin et al., 1990; Gröhn et al., 1984), high production (Gröhn et al., 1989), displaced abomasum (Curtis et al., 1985), and prior incidence of metritis (Dohoo and Martin, 1984). Additional risk factors include over-conditioning before parturition, season of calving, prolonged previous lactation length, extended dry period length, and amount of colostrum produced (Vanholder et al., 2015). Herds with an increased incidence of ketosis in early lactation tend to have increased incidences of displaced abomasum and increased culling in the first 60 d in milk (Oetzel, 2007). All of the above impacts of ketosis will have a negative effect on profitability for producers and are detrimental to animal well-being.

Incidence estimates of ketosis have been reported in several different dairy populations, though few specific to the Jersey breed. Based on 18 large-scale studies, median incidence of ketosis was 3.3% (Pryce et al., 2016) with values ranging from 0.24% in first-parity animals (Kadarmideen et al., 2000) to 17.2% in third-parity animals (Heringstad et al., 2005). Genetic variability, albeit small, has been identified to play a role in resistance to ketosis. Because ketosis has been shown to have a genetic component (e.g., Heringstad et al., 2005; Koeck et al., 2012; Parker Gaddis et al., 2014), one method for improving ketosis resistance would be through genetic selection. Heritability estimates for ketosis in US Holsteins range from 0.04 to 0.14 (Zwald et al., 2004; Parker Gaddis et al., 2014), although corresponding values specific to Jerseys are not available.

The objectives of this study were to estimate variance components for ketosis in Jerseys from available producer-recorded data. Given a significant genetic component, we also sought to identify regions of the genome associated with ketosis and investigate these regions for genes and biological pathways that could play a role in ketosis susceptibility in Jerseys.

MATERIALS AND METHODS

Data

Voluntary producer-recorded health event data related to ketosis were available from Dairy Records Management Systems (North Carolina State University, Raleigh) from US farms. Data editing was performed similarly to that described in Parker Gaddis et al. (2012). Standardization of ketosis codes was implemented to account for the numerous different acronyms used in herds to represent ketosis. General editing of ketosis data included selecting records from Jersey animals with an acceptable ID located within US herds. Ketosis events were restricted to occurring within 60 d after calving. Cows were considered healthy if they did not have a reported ketosis event within this period. If multiple ketosis events were recorded during a single lactation, only the first event was retained for analysis. Ketosis event data were merged with lactation data available from the Council on Dairy Cattle Breeding (**CDCB**; Bowie, MD). Only completed lactation records from cows within parities 1 through 5 were retained for analysis. We detected no significant difference in incidence rate between first-lactation and later-lactation animals. Minimum and maximum constraints on the occurrence of ketosis were implemented on a herd-year basis in an attempt to exclude information from herds that either did not report ketosis or over-reported ketosis events (a possible indication of using the acronym for management of ketosis as opposed to diagnosis). As a minimum constraint, herd-years were required to have at least 5 cows with lactation records and at least 1 reported incidence. The maximum constraint required that a herd-year's incidence not be greater than 3 standard deviations beyond the overall average incidence. Pedigree information spanned 3 generations, including 49,382 animals. A summary of the data set is provided in Table 1.

Genotypes were obtained from CDCB and included the 60,671 markers used for national routine genomic evaluations in the United States. These SNP were previously selected based on criteria including minor allele frequency, parent-progeny conflicts, call rate, and correlation between SNP (Wiggans et al., 2010, 2016). A total of 1,750 genotyped animals were used for the analyses. These included cows in the data set that were genotyped as well as genotyped sires. The majority of these animals (n = 1,497) were genotyped with either version 1 or 2 of the Illumina BovineSNP50 BeadChip (Illumina Inc., San Diego, CA), with the remaining animals genotyped on other platforms. All animals were imputed to the common set of 60,671 markers using Findhap version 3 (VanRaden et al., 2011).

Table 1. Summary statistics

Number of records	42,233
Number of animals	23,865
Number of herd-years	272
Mean incidence of ketosis (%)	2.81
Number of genotyped individuals	1,750
Number of SNP after editing	60,671