Opportunities for Understanding Bovine Respiratory Disease Mechanisms through Genetic Studies

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Abstract

Bovine respiratory disease (BRD) continues to challenge the beef and dairy cattle industries in spite of improved husbandry practices, implementation of immunization protocols for BRD pathogens, and the recent use of genomic selection to choose cattle less susceptible to infection. Barriers of overcoming challenges in reducing BRD incidence include difficulties in: identifying animals suffering from BRD without showing clinical signs, identifying and understanding the complexity of multiple pathogens effecting the animal, accounting for differences in frequencies of pathogens in different climates and management schemes, and an understanding for the interaction of these factors with the animal's genome. As BRD susceptibility has been identified as having a genetic component, genomic selection is an attractive approach to reducing cattle that are susceptible to BRD. Genome-wide association analyses have identified genomic regions associated with BRD susceptibility for use in genomic selection. Genomic selection using DNA variants that capture most of the genetic variation for BRD susceptibility enables identifying cattle susceptible to BRD as calves to increase the rate of genetic change for BRD resistance. Gene set enrichment analysis and gene expression analyses have also been investigated to understand the genes and gene pathways utilized in resistance to BRD. These studies provide an opportunity to better

understand BRD disease mechanisms and to develop therapies that are more effective by targeting the gene pathways utilized by BRD pathogens.

Keywords: bovine respiratory disease, genetics, disease mechanisms

Bovine respiratory disease (BRD) remains a health issue in feedlots, particularly with the trend for cattle to arrive lighter and have more days on feed before harvest. Since 2010, cattle weights at arrival are lower by 43 pounds than in 2023, yet final cattle weights average 140 pounds higher than in 2010 (Peel 2023; USDA, National Agricultural Statistics Service). Cattle are averaging 187 days on feed, which is 39 days more in 2023 than in 2010. This extended time in the feedlot reduces the number of cattle in the feedlot over a year's time, increasing the financial impact of cattle getting sick or dying (Peel 2023). The financial loss from sick and dying cattle has increased as the average steer death loss rate increased 56% from 2010 to 1.93% in 2023, making disease prevention a high priority in the feedlot (Peel 2023). Cattle that become sick later in the feeding period are costlier to the feedlot than cattle that are sick shortly after arrival due to the increased cost of treatment and the increasing cumulative investment made in the animal. In a study conducted in two feedlots, 45% and 39% of BRD pulls occurred after 100 days on feed (Neibergs personal communication). Even for cattle that recovered from BRD, they remained on feed an average of 10 days longer and averaged 20 pounds lighter at harvest than non-BRD calves. The economic impact of BRD morbidity has been suggested to be as great as carcass and production traits during the finishing period (Buchanan et al., 2016).

In addition to the economic losses that face feedlots, BRD also remains economically important for dairy producers. Economic losses occur from treatment costs, but also from the lifetime decrease in production and higher rate of culling of cows that experienced BRD as calves. BRD remains a leading cause of preweaned mortality in dairy calves with an estimated cost of $252 per incident or $395.49 per death attributed to BRD (Dubrovsky et al., 2020; Overton 2020). Depending on the study and how BRD is detected, BRD is found in 12% to 64% of calves prior to weaning and 6 to 11% in weaned calves (Guterbock 2014; Cuevas-Gomez et al., 2021; Cantor & Costa, 2022).

A genetic component for BRD has been reported and ranges from 0.04 to 0.24 (Snowder et al., 2006; Neibergs et al. 2014; Quick et al., 2020). Genome-wide association studies have identified genomic regions that are predictive of BRD infection using different approaches to identifying BRD susceptibility (Neibergs et al 2014; Van Eenennaam et al., 2014; Keele et al., 2015; Kiser et al., 2017). Some studies have used one or more detection method which may improve sensitivity and specificity, while others have used more general phenotypes such as "treated for BRD". Some commonly used methods for BRD detection are the Wisconsin Health Scoring System (sensitivity 46% - 77.9%, specificity 74.1 to 94.2%), the California System (sensitivity 46.8 -72.6%, specificity 79.1-84.4%), thoracic ultrasound (sensitivity 76.5%, specificity 92.9%) and thoracic auscultation (sensitivity 53, specificity 72.9%) (Buczinski et al, 2015; Buczinski et al., 2016; Love et al., 2016; Decaris et al., 2022). The use of detection systems that rely solely on clinical symptoms of BRD will underestimate the true proportion of cattle with disease as a large number of cattle will appear healthy but have subclinical disease (Gulliksen et al., 2009; Kiser et al., 2017).

While there are justifications for the use of all these methods, it will influence the loci identified as associated with BRD and ultimately the accuracy of selection of animals based on those loci. Loci that are robust and consistently associated with BRD susceptibility are important to identify and use in prediction for selection against disease susceptibility. Accuracies for selection range from 0.23 in Angus cattle in the feedlot to 0.12 to 0.30 in Holstein dairy calves (Quick et al., 2020; Hayes et al., 2024).

A second consideration when assessing the validation and importance of the loci identified that are associated with BRD is pathogen identification that are common in the population that is being studied. Assessing the pathogen(s) that initiated the disease is challenging as the pathogens present when clinical

77 symptoms are noted, may differ from those that initiated the onset of disease. Profiling BRD pathogens is
78 challenging in the timing and collection of specimens for diagnostic tests, and few genetic studies have
79 this information to inform the loci associated with disease. Summary diagnostic results for BRD pathogens
80 across the US are not readily available for cattle newly diagnosed, and so the frequency of these
81 pathogens in BRD cases is unknown. The distribution of pathogens is further complicated by differences
82 in management practices, vaccines and the environment. Efforts are underway to collect diagnostic data
83 on approximately 5500 cattle in different regions of the US to tease apart the important role of pathogen
84 specific susceptibility in cattle and to begin to identify if there are specific pathogens that are more
85 prevalent in certain areas of the US (Neibergs personal communication).

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87 In addition to genome-wide association studies, gene expression and gene set enrichment analyses are
88 identifying gene pathways that are critical to BRD (Tizioto et al., 2015; Neupane et al., 2018; Sun et al.,
89 2020; Hasankhani et al., 2021; Lebedev et al., 2021; Cao et al. 2023). A better understanding of these gene
90 pathways provides opportunities for targeted therapies to decrease morbidity and mortality rates
91 associated with BRD in cattle and to better understand the mechanisms of bovine respiratory disease.

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93 In summary, efforts to reduce the frequency of BRD and the impact it has on beef and dairy cattle have
94 not been fully effective. The continued exploration of loci associated with BRD provides the foundation
95 for genomic selection to enhance disease resistance in cattle. The identification of the pathways and genes
96 that are utilized for BRD resistance hold promise for identifying the mechanisms of the disease that can
97 be used to treat cattle with disease. The use of these genetic approaches provides a management tool to
98 reduce the frequency of BRD and the economic losses associated with it.

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