Association of ARRDC3 and NFIA Genes with Bovine Congestive Heart Failure

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Abstract

Background: Bovine congestive heart failure (BCHF) has become increasingly prevalent in feedlot cattle in the Western Great Plains of North America with up to 7% mortality in disease outbreaks. BCHF is an untreatable complex condition involving pulmonary hypertension that culminates in right ventricular failure and death. No candidate genes are presently associated with BCHF, and thus, our aim was to search genome-wide for genetic risk factors in feedlot cattle.

Methods: Samples of 102 clinical BCHF cases and 102 unaffected matched penmates were used in a genome-wide association study (GWAS) with 777,962 single nucleotide polymorphisms (SNPs). The paired nominal data were analyzed with McNeNer's test with association.

Results: Analyses of 633,042 filtered SNPs revealed more than 15 genomic regions highly associated with BCHF. Regions with the strongest association included the arresting domain-containing 3 protein (ARRDC3) and nuclear factor IA (NFIA) genes. A missense mutation in exon 4 of ARRDC3 (C182Y), and SNPs in intron 5 of NFIA had the best statistical support for association (McHeam's Chi-square > 20). Animals with either or both the ARRDC3 or NFIA risk factors were approximately 7- and 15-fold more likely to have BCHF compared to those without (p-value < 10^-10 for both), respectively. A two-SNP genotyping test for ARRDC3 and NFIA risk factors was used to test an independent cohort of feedlot cattle with end stage heart failure and similar associations with disease were observed.

Conclusions: A matched case-control GWAS identified major genetic risk factors associated with BCHF in feedlot cattle. Although the roles of these genes in disease pathogenesis are unknown, their discovery facilitates classifying animals by genetic risk for heart failure and will allow producers to make informed decisions for selective breeding and animal health management.

Matched case-control pair

Figure 1. Example of a pen matched case-control pair. Panel A: Steer with end-stage congestive heart failure (left); unaffected penmate (right). Panel B: Heart from an affected steer (primary view), and an unaffected matched Angus steer (stare view). The view of the sectioned hearts is bowing away from the apex and into the valves. The McNeNer's Chi-square test: L,L: left ventricle; PA: pulmonary artery.

Genetic distance within pairs

Figure 2. Manhattan and q-q plots of SNP genotypes for 563,042 genome-wide SNPs. SNP genotypes on the BovineHD BovineGenome array were filtered with PLINK software v1.9 (URL), and imported into custom software for McNemar test analyses. For each SNP, both alleles were tested in a genome-wide association study (GWAS) with 777,962 single nucleotide polymorphisms (SNPs).

Power to detect association

Figure 3. McNemar's odds ratio. Colored dots show results for a “2-copy” model, where disease risk is conferred by having either 1 or 2 copies of the SNP alleles (i.e., additive or dominance). The horizontal red line is the Bonferroni correction at 0.05 alpha.

Table 1. SNP genotypes on the BovineHD array. McNemar test analyses of 563,042 filtered SNPs revealed more than 15 genomic regions highly associated with BCHF. Regions with the strongest association included the arresting domain-containing 3 protein (ARRDC3) and nuclear factor IA (NFIA) genes. A missense mutation in exon 4 of ARRDC3 (C182Y), and SNPs in intron 5 of NFIA had the best statistical support for association (McHeam's Chi-square > 20). Animals with either or both the ARRDC3 or NFIA risk factors were approximately 7- and 15-fold more likely to have BCHF compared to those without (p-value < 10^-10 for both, respectively). A two-SNP genotyping test for ARRDC3 and NFIA risk factors was used to test an independent cohort of feedlot cattle with end stage heart failure and similar associations with disease were observed.

Table 1. Feedlot sites and sources for case-control matching.

Table 2. SNPs associated with the highest risk of BCHF in feedlot cattle.

Table 3. Survival analysis of ARRDCC3 and NFIA genotypes on the C267T position in the juxta-keratin.

Acknowledgements

This work was supported by S. Grotelueschen and E. Vander Ley for oversight and administrative support. S. Johnson and A. Oommen for technical assistance. D. George, D. Ridgway, and S. Schmidt for secretarial and administrative support. R. Workman AM and G. Krafsur, J. Pollak, and M. Boggess for leadership and support during the design and execution of the project. Dr. D. George, D. Ridgway, and S. Schmidt for identifying clinical cases, assisting with sample acquisition, and sharing their knowledge of animal genetics.

Outcomes

➢ ARRDC3 and NFIA variants are major risk factors for heart failure in feedlot cattle.
➢ A 2-SNP test sorts animals by risk group
➢ Other loci were also significantly associated

Conclusion

Congestive heart failure in feedlot cattle has major underlying genetic factors.

Testing for risk with two SNPs

Figure 4. Relationship between effect size of the top 21 associated loci and the power for their detection with 102 matched pairs. SNPs ranked in Table 2 are plotted against two power curves for thresholds of detection. SNPs ranked by disease were fitted by proportion of discordant pairs (p < 0.04) and McNeNer's p < 0.04.

Top 21 SNP associations

Table 2. SNPs associated with the highest risk of BCHF in feedlot cattle.

Table 3. Survival analysis of ARRDCC3 and NFIA genotypes on the C267T position in the juxta-keratin.

C182 conservation in ARRDC3

Figure 5. C182 conservation in ARRDC3. The targeted SNPs were BovineHD0700027239 (ARRDC3, BCHF) and BovineHD0300024366 (NFIA, RV). Both SNPs are associated with heart failure and similar associations with disease were observed.

Figure 6. Survival analysis of ARRDCC3 and NFIA genotypes on the C267T position in the juxta-keratin.

Figure 7. Relationship between effect size of the top 21 associated loci and the power for their detection with 102 matched pairs. SNPs (562 k) associated with disease were fitted by proportion of discordant pairs (p < 0.04) and McNeNer's p < 0.04.

Figure 8. McNemar's odds ratio. Colored dots show results for a “2-copy” model, where disease risk is conferred by having either 1 or 2 copies of the SNP alleles (i.e., additive or dominance). The horizontal red line is the Bonferroni correction at 0.05 alpha.

Figure 9. Relationship between effect size of the top 21 associated loci and the power for their detection with 102 matched pairs. SNPs (562 k) associated with disease were fitted by proportion of discordant pairs (p < 0.04) and McNeNer's p < 0.04.

Figure 10. McNemar's odds ratio. Colored dots show results for a “2-copy” model, where disease risk is conferred by having either 1 or 2 copies of the SNP alleles (i.e., additive or dominance). The horizontal red line is the Bonferroni correction at 0.05 alpha.