Genetic Correlation and Genome Wide Association Study of Pulmonary Arterial Pressure and Post Weaning Growth Traits in Angus Heifers from a High Altitude Breeding Program

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ABSTRACT: Elevated pulmonary arterial pressure (PAP) is an indicator trait for bovine pulmonary hypertension. The objective of this study was to determine the genetic relationship between yearling PAP (YPAP), yearling weight (YW) and post-weaning gain (PWG). Heritability and genetic correlations were estimated with data from Angus heifers at Colorado State University Beef Improvement Center (CSU-BIC) using a multivariate animal model. A genome-wide association study was performed for each trait using univariate models. The estimated heritabilities of YPAP, YW and PWG were 0.22 ± 0.04, 0.43 ± 0.04 and 0.28 ± 0.04, respectively. Genetic correlations between YPAP and YW or PWG were low and positive (0.22 ± 0.04 and 0.04 ± 0.12, respectively). There were no genome windows associated with both YPAP and either weight trait. Selection for post-weaning growth should not lead to increased risk of high PAP in Angus heifers.

Keywords: Pulmonary arterial pressure; Growth traits; Genetic relationship

Introduction

Pulmonary hypertension is a major cause of calf morbidity in beef cattle ranches and feedyards above 1500 m (Hecht et al. (1962); Jensen et al. (1976)). In response to alveolar hypoxia, the pulmonary artery constricts resulting in hypertension, right heart ventricular hypertrophy, vascular remodeling, and death from congestive hear failure (Holt and Callan, (2007)). Pulmonary arterial pressure (PAP) is a measure indicative of hypertension that has been shown to be moderately heritable in cattle (0.34 to 0.46; Enns et al. (1992); Shirley et al. (2007)). Genetic correlations between PAP and birth weight (BW) and weaning weight (WW) were reported to be moderate (0.49 to 0.51; Shirley et al. (2007)), suggesting selection for high growth rate may lead to cattle with increased risk of developing high PAP and Pulmonary hypertension. Estimates of genetic correlations between sexes of less than unity indicate that PAP measurements in heifers and bulls are potentially different traits (Cockrum et al. (unpublished data)). There is limited information as to the genetic correlation between PAP and post weaning traits in females. The objective of the study was therefore to determine the genetic relationships between YPAP and YW or PWG in Angus heifers.

Materials and Methods

Data. Records of YPAP (n = 2,962), YW (n = 2,498) and PWG (n = 2,483) from Angus heifers were used to estimate genetic parameters. This data was collected from 1993 to 2012 at the John E. Rouse Colorado State University Beef Improvement Center (CSU-BIC; 2,340m elevation). The same licensed veterinarian measured PAP in mmHg for every heifer over a 1 to 2 day period each year (Holt et al. (2007)). Yearling PAP was not normally distributed; therefore, log10 transformation was performed. Yearling weight (YW) was adjusted to 365 days of age according to guidelines of Beef Improvement Federation (2002). Post weaning gain (PWG) was the difference between 205-Day adjusted weaning weight and 365-Day adjusted YW. Heifers (n = 3,048) in the data file were AI or natural-mated progeny of 238 sires and 1,243 dams, and had at least one phenotype of the three traits. Subsets of heifers were genotyped using the Illumina Bovine SNP50 BeadChip for genome wide association study of YPAP (n = 1060), YW (n = 987) and PWG (n = 980). Descriptive statistics of yearling PAP and growth traits of heifers for full and subset data are provided in Table 1.

Table 1. Descriptive statistics of untransformed yearling pulmonary pressure (YPAP), yearling weight (YW), post-weaning gain (PWG) and age of YPAP (AOP) for all heifers and that subset used in genetic evaluation and Genome-wide association study (GWAS)

Item	No.	Min	Mean	Max	SD
Genetic evaluation					
YPAP[1]	2,962	22.00	41.36	135.00	8.67
YW[2]	2,498	225.50	324.26	430.45	33.26
PWG[3]	2,483	21.19	88.11	155.52	19.55
AOP[4]	2,962	261.00	352.59	420.00	25.45
GWAS					
YPAP	1,060	26.00	41.06	116.00	7.71
YW	987	231.11	317.31	430.45	31.84
PWG	980	21.19	83.67	155.52	18.25
AOP	1,060	280.00	348.24	420.00	24.39

1Unit is millimeter of mercury (mmHg)
[2]YW = post-weaning ADG * 160 + 205-Day adjusted WW; Unit is kilogram
[3]PWG = 365-Day adjusted YW – 205-Day adjusted WW; Unit is kilogram
[4]Unit is day

Genetic Evaluation. ASReml (2009) was used to fit a multivariate animal model to estimate the genetic corre-

lations between YPAP, YW and PWG. The model included three equations accounting for YPAP, YW and PWG. The fixed effects for YPAP included PAP date, age of dam (AOD), and covariate variables included linear and quadratic terms for age at PAP (Table 1). The fixed effects for YW and PWG included classes for year of birth, weaning date and AOD, with day of birth as covariate. Animals were random effects in the model.

Genome Wide Association Study (GWAS). The BayesC method and GenSel software (http://big.ansci.iastate.edu) were used for GWAS. The analytical model equation was $y=Xb+\sum_{i=1}^{n} x_i\alpha_i\delta_i+e$, where y was the vector of phenotype date (i.e., YPAP, YW or PWG), X was the incidence matrix for fixed effects, n was the number of SNP loci, x_i was the column vector representing the covariate at SNP locus i, α_i was the random effect for locus i, δ_i was the random indicator value (i.e. 0 or 1) indicating the absence (with probability π) or presence (with probability 1 - π) of effect of locus i, and e denotes the random residual effect which was assumed to be normally distributed as $N(0, \sigma_e^2)$. BayesC fitted about $1 - \pi$ SNP simultaneously and assumed a common variance for SNP loci (σ_α^2). The prior distributions for variances (σ_α^2 and σ_e^2) were assumed as scaled inverse Chi-square distribution with 4 or 10 degrees of freedom. The parameter $\pi = 0.999$ was assumed in the study in order to detect high variation SNP. In the GenSel program, after 1,000 burn-in samples, 40,000 samples were accumulated to obtain the posterior mean of each SNP effect. Genetic variance was computed every 100th iteration for every 1 Mb genome fragment and expressed as a percentage of the total genetic variance explained by the whole genome in that iteration.

Results and Discussion

Genetic Parameters. Table 2 presents the estimated genetic parameters from the multivariate animal model. Heritability for YPAP was estimated as 0.22 ± 0.04, which was lower than previous reports of PAP collected in Angus calves at weaning and from both sexes (i.e., 34 to 0.46; Enns et al. (1992); Shirley et al. (2007)). However, the estimated heritability was similar to previous estimates in cows (0.13 to 0.23; Schimmel et al. (1981)). Low positive genetic correlations between YPAP and YW or PWG were observed in Angus heifers (Table 2). These results suggest that selection for YW or PWG should have minimal impact on PAP scores in heifers within this historic Angus breeding program at high altitude. Previous studies reported genetic correlations of 0.49 ± 0.12 and 0.51 ± 0.18 between weaning PAP and birth weight, and weaning PAP and weaning weight (Shirley et al. (2007)) and -0.75 ± 0.65 between bull PAP and YW (Schimmel (1981)). The varied estimates of genetic correlations may be explained by genetic difference observed among PAP collected at different age (weaning versus yearling) or different sex (bulls versus heifers; Cockrum et al. (unpublished data)). The estimated heritability for YW and PWG reported in the Table 2 are consistent with prior estimates (Winder et al. (1990)).

Table 2. Heritability ± S.E. (on diagonal) and genetic correlation ± S.E. (above diagonal) between yearling pulmonary pressure (YPAP), yearling weight (YW) and post-weaning gain (PWG)

Traits	YPAP	YW	PWG
YPAP	**0.22 ± 0.04**	0.22 ± 0.11	0.04 ± 0.12
YW		**0.43 ± 0.04**	0.73 ± 0.05
PWG			**0.28 ± 0.04**

Genome Wide Association Analysis. Manhattan plots for YPAP, YW and PWG in heifers are presented in Figure 1. Windows that account for ≥ 1.0% total variance were considered as QTL associated with target traits (Peters et al. (2013)). The number of detected SNP windows for YPAP, YW and PWG were 5, 11 and 9, respectively. The top 3 detected windows were distributed across chromosomes 7, 21 and 28 for YPAP, chromosomes 20, 21 and 15 for YW, and chromosomes 21 and 20 for PWG. All of the three traits had QTL associated windows on chromosome 21, but window positions varied on this chromosome. Two SNP windows were in concordance for YW and PWG (Figure 2), which suggest that QTL for YW are also associated with PWG. This result is consistent with the estimated high genetic correlation (0.73 ± 0.05) between YW and PWG. There were no concordant QTL with YPAP and YW or PWG. The GWAS results appeared to be consistent with the weak genetic correlations of YPAP with YW and PWG in Angus heifers selected for tolerance to high elevation. These results suggest that post-weaning growth in heifer is genetically independent of YPAP in this population.

Conclusion

Selection for lower YPAP in Angus heifers in a high altitude breeding program should reduce risk of pulmonary hypertension with minimal effects on post weaning growth performance. In the future, a similar study should be executed for growing bulls in this environment.

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Shirley, K. L., Beckman, D. W., and Garrick, D. J. (2008). *J. Anim. Sci*., 86:815-819.

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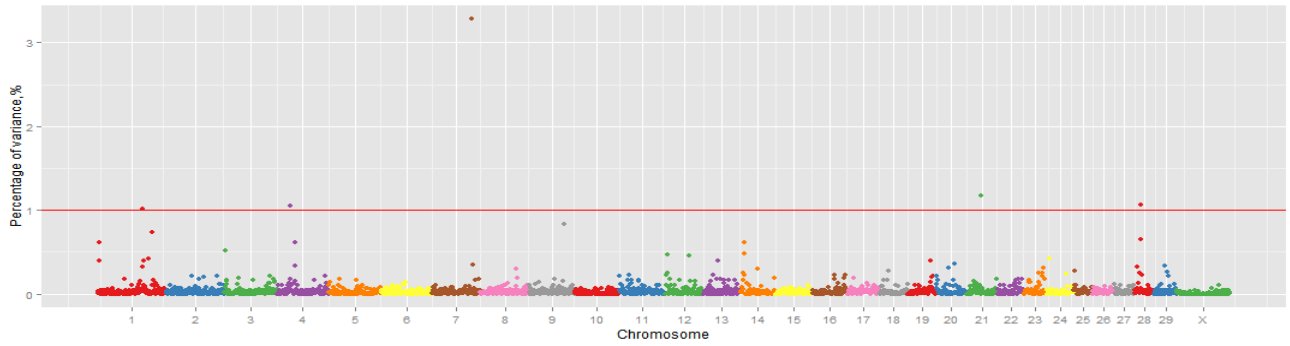
A.



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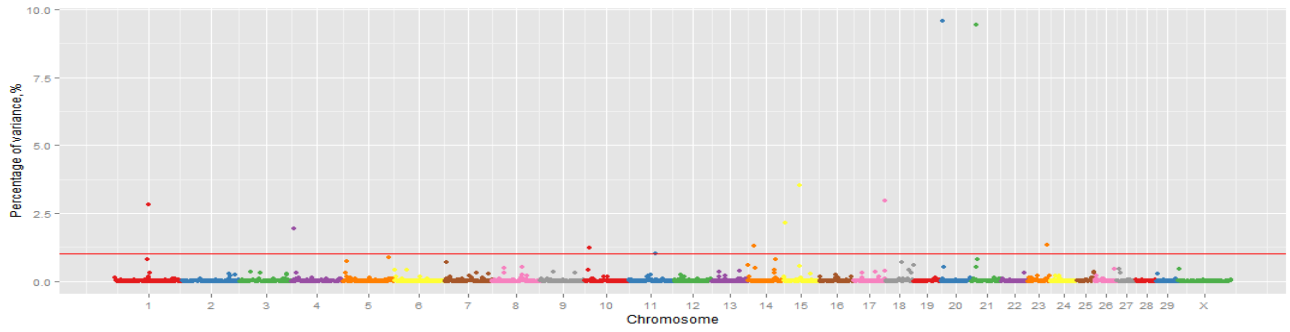

C.

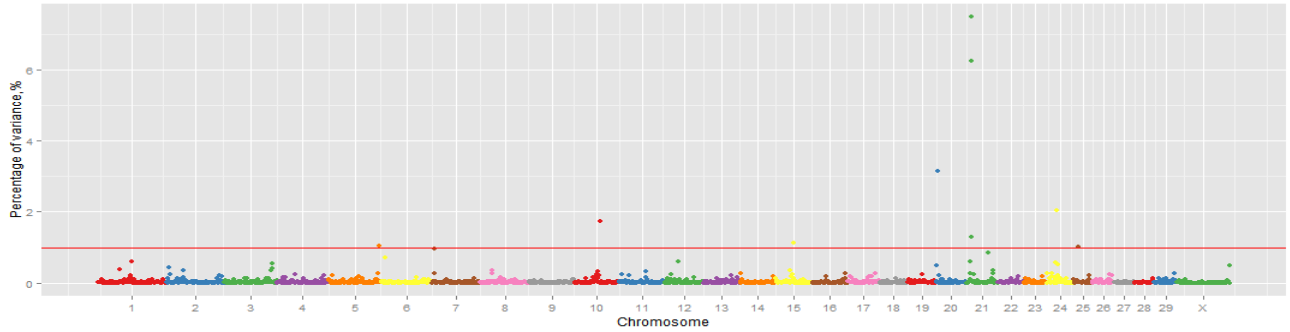

Figure 1. Genome-wide association study (GWAS) results for A) yearling pulmonary arterial pressure; B) yearling weight; C) post-weaning gain in Angus heifers genotyped with the Illumina BovineSNP50 BeadChip. The x-axis is genomic position of SNP window. The y-axis represents the percentage of genetic variance explained by SNP window. The red line denotes the 1.0% genetic variance level.

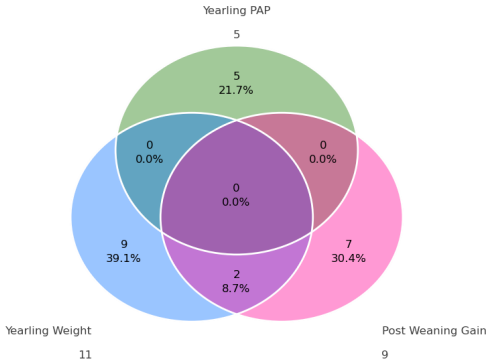

Figure 2. Proportional Venn diagram of SNP windows of yearling pulmonary arterial pressure (YPAP), yearling weight (YW) and post-weaning gain (PWG) of Angus heifers. The percentage indicates the proportion of SNP windows concordant across the traits.