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GENOME-WIDE ASSOCIATION ANALYSIS OF BIRTH AND WEANING WEIGHTS IN AUSTRALIAN TAURINE BEEF CATTLE

W.M.S.P. Weerasinghe[1], B.J. Crook[1], and N. Moghaddar[2]

[1]Agricultural Business Research Institute, UNE, Armidale, NSW, 2350 Australia
[2]School of Environmental and Rural Science, UNE, Armidale, NSW, 2350 Australia

SUMMARY

Birth and weaning weights are two traits which ultimately influence traits of economic relevance in the beef cattle industry. In this study, multi-breed genomic analysis was performed using three Australian beef cattle breeds to detect genomic regions that influence birth and weaning weights. Principal component analysis revealed a clear genetic separation between the Hereford, Simmental and Charolais breeds. A genome-wide association study based on 29k density SNP genotypes revealed significant SNPs associated with birth and weaning weights on chromosomes 5, 6, 7 and 20 in a multi-breed dataset after correction for genetic relationship between animals and population stratification. GREML results suggested a top marker present on chromosome 6 accounted for 11% and 5% of the additive genetic variance for BW and WW respectively. Results of this study may indicate a role for weighted GBLUP evaluations when very large effect QTL for production traits are evident in beef cattle.

INTRODUCTION

Quantitative trait loci (QTL) mapping is an important step to identify genetic variants associated with economically important traits in livestock industries. Traits such as birth weight (BW) and weaning weight (WW) contribute significantly to the profitability of beef breeding enterprises by way of impact on calving outcomes and post-birth growth potential, as well as influencing reproductive and nutritional management decisions. There are several biological events and associated genes involved with these two traits, with both having a moderate to high pedigree-based heritability that is favourable for the detection of genomic regions. Several genome-wide association studies (GWAS) have been conducted for *Bos taurus*, *Bos indicus* and crossbred cattle types, with specific chromosomes and genomic regions being identified for BW and WW (Akanno *et al.*, 2018; Saatchi *et al.*, 2014; Utsunomiya *et al.*, 2013).

The aim of the present study was to investigate the presence of significant genomic regions in association with BW and WW in each of three Australian beef breeds, as well as in a combined (multi-breed) context. Total genetic variation explained by such informative SNPs was quantified.

MATERIALS AND METHODS

The BW and WW data for Australian Hereford, Simmental and Charolais used in this study were derived from data extracts as used in the BREEDPLAN analysis undertaken for each breed (Graser *et al.*, 2005). Single-animal contemporary groups were excluded from further analysis as were contemporary groups for animals born prior to 2000. Breed-specific variance components were estimated for BW and WW using WOMBAT (Meyer, 2011). Records were pre-adjusted for age of dam (BW and WW) and age of calf (WW only) effects, with each model including random effects for direct genetic, maternal genetic and dam permanent environment (PE) and with contemporary group as a fixed effect. Variance components were used to perform within-breed BLUP analyses for BW and WW to obtain the direct genetic and residual solutions. Both solutions were combined to give phenotypes (corrected for maternal genetic, dam PE and contemporary group effects) for use in the subsequent GWAS.

Genomic data for animals with BW and WW records were subjected to quality control (QC) and imputation. Several different platforms were used for genotyping, predominantly different versions of the GGP-LD product, with 14,904 animals genotyped with the 50k SNP panel (BovineSNP50 BeadChip, Illumina Inc., San Diego, CA.) used for the analysis. QC of genomic data was conducted using PLINK software (Chang *et al.*, 2015), with SNPs removed at a minor allele frequency of <0.01 and a deviation from Hardy–Weinberg equilibrium of $p<1E^{-6}$ as exclusion cut-off. SNPs with a call rate less than 90% and SNPs located on sex chromosomes were excluded. Animals with a call rate lower than 85% for all loci were excluded. Sporadic missing SNPs were imputed by FImpute (Sargolzaei *et al.*, 2014). For the multi-breed GWAS, a total of 29,101 combined genotypes were used. Principal component analysis (PCA) was carried out to determine the genetic structure of the three breeds and was performed on the genomic relationship matrix (GRM) based on the method of VanRaden (2008). Although some crossbred genotypes were represented in the combined extract, only those animals regarded as "registered purebreds" and separated by PCA results were selected for further analysis.

GWAS analysis of SNP effects and significance was conducted for each trait using the program GCTA (Yang *et al.*, 2011), following a linear mixed model as below:

$$\boldsymbol{y} = \boldsymbol{Xb} + \boldsymbol{Za} + \boldsymbol{e}$$

where $\boldsymbol{y}$ is a vector of corrected phenotypes, $\boldsymbol{b}$ is a vector of overall mean, SNP effect and the first and second principal components as linear covariates, $\boldsymbol{a}$ is a vector of random additive genetic effects and $\boldsymbol{e}$ is a vector of random residual effects. $\boldsymbol{X}$ and $\boldsymbol{Z}$ are incidence matrices that relate fixed effects to phenotypes and additive genetic effects to each animal respectively.

Additive genetic effects in the GWAS were assumed to be normally distributed as: $a \sim N(0, \boldsymbol{G}\sigma_a^2)$, where $\boldsymbol{G}$ is a genomic relationship matrix based on the 29k SNP genotypes, and σ_a^2 is the additive genetic variance. Significant SNPs were identified using a Bonferroni correction with α=0.05 and –log10 (p)=5.76 as well as with P<0.001. Significant SNPs (based on the P<0.001) present in the same genomic regions were subjected to joint multivariate regression analysis using GCTA with P<1.712e-06 to identify the most informative SNPs for the particular trait.

Restricted maximum likelihood analysis with GTCA including the genomic relationship matrix (GREML) was used to estimate trait heritability and the proportion of additive genetic variation explained by the most informative SNPs. Individual SNP variances were calculated as $2pq\alpha^2$ where *p* and *q* are allele frequencies and α is the SNP effect.

RESULTS AND DISCUSSION

PCA revealed clear genetic separation between the three Australian beef breeds. The first principal component (PC1) separated Hereford from the other two, whereas the second principal component (PC2) separated Simmental and Charolais. PC1 explained 79% of total variation between animals, with PC2 explaining a further 5%.

Data structure and variance components for BW and WW in each breed are presented in Table 1. Hereford gave higher additive genetic variance and heritability for BW, whereas Simmental gave higher additive genetic variance and heritability for WW. The descriptive statistics for the data used for GWAS are also shown in Table 1. A greater number of Hereford animals with both phenotype and genotypes were available for GWAS compared to other two breeds.

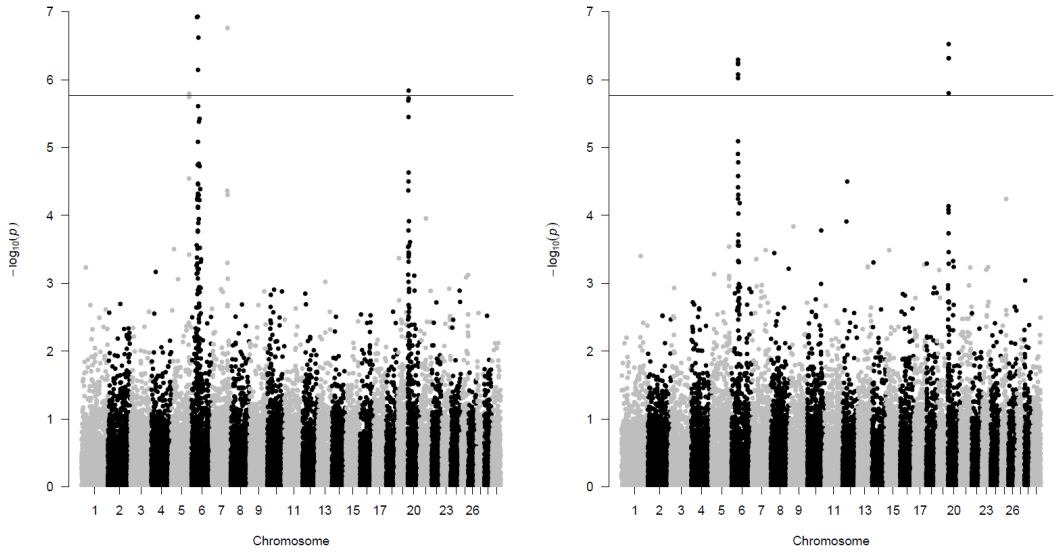
There were 124, 59 and 57 SNPs of significant (P<0.001) association with BW, with 48, 2 and 12 SNPs remaining after Bonferroni correction for Hereford, Simmental and Charolais respectively in single breed GWAS. For WW, there were 74, 32 and 27 SNPs showing a significant (P<0.001) association in Hereford, Simmental and Charolais respectively. After Bonferroni correction, however, only 14 significant SNPs were evident and for Hereford only.

Figure 1 gives the Manhattan plots derived from the multi-breed GWAS results of BW and WW.

Both traits have highly significant SNPs present on chromosomes 6 and 20, with BW also showing some significant genomic associations on chromosome 5. There were 106 significant SNPs present on chromosome 6, 20, 7, 5, 25 (in descending number of SNPs) with chromosomes 1, 4, 13, 19 and 21 also having a significant SNP associated with BW. Only 34 SNPs remained after Bonferroni correction. Multivariate regression of these SNPs resulted in 5 significant SNPs remaining. Initially there were 62 significant SNPs associated with WW, 13 remained after Bonferroni correction and only 2 significant SNPs remaining after multiple regression, present on chromosomes 6 and 20.

Table 1. Additive genetic variance (VG) and heritability (h^2) estimated for BW and WW using BLUP within breed and descriptive statistics for data used for GWAS

	BLUP			GWAS				
Breed	No.	V(G)	h^2±SE	No.	Mean	SD	Min	Max
BW(kg)								
Hereford	265,406	6.97	0.37±0.006	7,398	40.53	5.59	16.40	65.40
Simmental	48,557	5.10	0.31±0.014	1,325	40.96	5.73	24.00	63.00
Charolais	68,457	4.86	0.32±0.012	1,211	43.23	5.49	24.80	70.20
WW(kg)								
Hereford	333,800	120.99	0.16±0.004	8,363	259.70	52.54	105.10	512.70
Simmental	30,442	206.36	0.26±0.017	1,011	309.60	52.63	138.60	487.90
Charolais	68,953	158.20	0.20±0.011	1,249	285.30	45.11	161.10	484.90



(– log10 (1.718154e-06)) for Bonferroni correction

Saatchi *et al.* (2014) identified significant SNPs for BW and WW in *Bos taurus* breeds, present on chromosomes 2, 4, 5, 6, 7, 14, 20, 21 and 29. Genomic regions significant for BW and WW include chromosome 5 (106Mb), 6 (38Mb), 7 (93Mb) and 20 (4Mb), these being associated with genes responsible for tissue development, ossification, adipose tissue development and regulation

of transport activities (Saatchi *et al.*, 2014). In the present multi-breed GWAS, the final significant SNPs identified for BW (Table 2) explained 19% of additive genetic variance, with a major contribution (11%) coming from SNPs on chromosome 6 (39Mb region). This appears to be a well-known QTL region affecting body weight in other beef breeds (Snelling *et al*., 2010) and animal species (Metzger *et al*., 2013). For WW, the final significant SNPs explained 9% of additive genetic variance (Table 2), with a major contribution coming from the same SNP on chromosome 6 (39Mb region) as for BW.

Table 2. Significant SNPs associated, variance and heritability of the BW and WW of multi-breed GWAS*

Trait	Chr	Mb	P-values	V(G)	V(snp)/V(G)	h^2
BW	5	106	1.610E-06	4.56 ± 0.25	0.01	0.32 ± 0.01
	6	39	1.17E-35		0.11	
	7	93	5.80E-11		0.03	
	20	4.6	8.03E-17		0.04	
WW	6	39	3.08E-12	82.67±6.57	0.05	0.18 ± 0.01
	20	6.3	5.25E-11		0.04	

* Chr = Chromosome; Mb = Mega base pairs position according to UMD3.1 resemble; V(G) = total genetic variance =; V(snp)/V(G) = total genetic variance explained by significant SNP, h^2= heritability.

CONCLUSIONS

This study detected several SNPs as having a significant association with birth and weaning weight, with these SNPs being located on chromosomes 5, 6, 7 and 20. Of the final significant SNPs identified, they accounted for 19% and 9% of the total genetic variance for BW and WW respectively. Results of this study may have application for genetic evaluations where specific SNPs are included to improve the accuracy of prediction for birth and weaning weight in beef cattle.

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