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Genome-wide association study of growth in crossbred beef cattle[1,2]

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ABSTRACT: Chromosomal regions harboring variation affecting cattle birth weight and BW gain to 1 yr of age were identified by marker association using the highly parallel BovineSNP50 BeadChip (50K) assay composed of 54,001 individual SNP. Genotypes were obtained from progeny (F_1; 590 steers) and 2-, 3-, and 4-breed cross grandprogeny ($F_1^2 = F_1 \times F_1$; 1,306 steers and 707 females) of 150 AI sires representing 7 breeds (22 sires per breed; Angus, Charolais, Gelbvieh, Hereford, Limousin, Red Angus, and Simmental). Genotypes and birth, weaning, and yearling BW records were used in whole-genome association analyses to estimate effects of individual SNP on growth. Traits analyzed included growth component traits: birth weight (BWT), 205-d adjusted birth to weaning BW gain (WG), 160-d adjusted postweaning BW gain (PWG); cumulative traits: 205-d adjusted weaning weight (WW = BWT + WG) and 365-d adjusted yearling weight (YW = BWT + WG + PWG); and indexes of relative differences between postnatal growth and birth weight. Modeled fixed effects included additive effects of calf and dam SNP genotype, year-sex-management contemporary groups, and covariates for calf and dam breed composition and heterosis. Direct and maternal additive polygenic effects and maternal permanent environment effects were random. Missing genotypes, including 50K genotypes of most dams, were approximated with a single-locus BLUP procedure from pedigree relationships and known 50K genotypes. Various association criteria were applied: stringent tests to account for multiple testing but with limited power to detect associations with small effects, and relaxed nominal *P* that may detect SNP associated with small effects but include excessive false positive associations. Genomic locations of the 231 SNP meeting stringent criteria generally coincided with described previously QTL affecting growth traits. The 12,425 SNP satisfying relaxed tests were located throughout the genome. Most SNP associated with BWT and postnatal growth affected components in the same direction, although detection of SNP associated with one component independent of others presents a possible opportunity for SNP-assisted selection to increase postnatal growth relative to BWT.

Key words: beef cattle, genome-wide association study, growth, single nucleotide polymorphism

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INTRODUCTION

Beef producers may select for greater growth to increase market weight and income received from calves sold, although selection solely for increased growth may not be profitable. In response to selection for weaning and yearling weight, cow size, nutrient requirements, and feed costs can rise along with calf birth weight, calving difficulty, and calf death loss. Selection toward intermediate optima for birth weight, milk production, and mature size, and increasing growth rate relative to birth weight and mature size may improve production efficiency more than selection focused on fast growth and larger calves (Bourdon, 1988). Phenotypic selection over multiple generations to increase postnatal growth relative to birth weight has been effective (MacNeil et al., 1998; MacNeil 2003; Bennett et al., 2008), but might be accelerated if DNA polymorphisms responsible for birth weight and postnatal growth differentials can be determined.

Chromosomal regions, genes, and specific polymorphisms associated with relatively large effects on different measures of growth have been described (Casas et al., 2003; Allan et al., 2007; Gutierrez-Gil et al., 2009).

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[2]Mention of a trade name, proprietary product, or specified equipment does not constitute a guarantee or warranty by the USDA and does not imply approval to the exclusion of other products that may be suitable.

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Overlapping regions containing QTL for birth weight and later measures of growth were reported, as well as regions that may independently affect birth weight, pre- or postweaning BW gain (Kneeland et al., 2004). Further insight into DNA variation affecting cattle growth, including variants with independent or opposite effects on birth and postnatal measures, may be revealed by genome-wide association studies enabled by the 54,001 SNP BovineSNP50 BeadChip (**50K**; Illumina Inc., San Diego, CA; Van Tassell et al., 2008). Following human genome-wide association studies, which have individually analyzed each SNP on high-density arrays to find variants strongly associated with quantitative traits (Lee et al., 2008), objectives of this study are to describe associations between measures of growth to yearling age and the 50K SNP in a population of crossbred cattle and to identify SNP differentially affecting birth and postnatal weights.

MATERIALS AND METHODS

The US Meat Animal Research Center (**USMARC**) Animal Care and Use Committee approved the procedures used in this experiment.

Population and Genotypes

In Cycle VII of the USMARC Germplasm Evaluation (**GPE**) Project, purebred Angus (**AN**), Hereford (**HH**), Simmental (**SM**), Limousin (**LI**), Charolais (**CH**), Gelbvieh (**GV**), and Red Angus (**AR**) sires were mated by AI to composite MARC III [1/4 AN, 1/4 HH, 1/4 Pinzgauer (**PZ**), 1/4 Red Poll (**RP**)], AN- and HH-base cows to produce progeny designated as (but not strictly) F_1, born in 1999, 2000, and 2001. The 1999- and 2000-born male calves were castrated and fed for slaughter. Female F_1 and the 2001-born F_1 males were kept for breeding, and mated in multiple-sire pastures to produce 2-, 3-, and 4-breed cross progeny designated F_1^2. The F_1^2 calves were born in March through May of 2003 to 2007, from 3-yr-old and older dams. Male calves were castrated within 24 h after birth. Calves were weaned in September at approximately 165 d of age. After weaning, steers were managed and fed for slaughter, and heifers were developed for breeding starting the following May.

BovineSNP50 genotypes of Cycle VII AI sires, F_1 and F_1^2 progeny were obtained following manufacturer's protocols (Illumina, 2008). BeadStudio software with the genotyping module (Illumina, 2006) was used to determine genotypes of the 150 purebred sires, 745 F_1 (73 bulls, 517 steers, 155 heifers), and 2,013 F_1^2 animals (1,306 steers, 707 heifers). Only 52 of the 592 F_1 heifers that became dams of F_1^2 calves had BovineSNP50 genotypes, so genotypes of the remaining F_1 dams were approximated with a mixed model method (Gengler et al., 2007) that used 50K genotypes of the sire of each dam, progeny, and other known relatives to predict probable genotypes. The equations to approximate missing genotypes included covariates of proportion AN, HH, SM, LI, CH, GV, AR, PZ, and RP to account for allele frequency differences in the contributing breeds.

Phenotypes and Analyses

Body weights observed at birth, weaning, and approximately 12 mo of age were utilized. Phenotypes analyzed included birth weight (**BWT**), BW gain from birth to weaning, adjusted to 205 d (**WG**), 205-d adjusted weaning weight (**WW**), 160-d adjusted postweaning BW gain (**PWG**), and 365-d adjusted yearling weight (**YW**), with age-adjusted traits defined as

$$\text{WG} = 205 \times (\text{weaning weight} - \text{BWT})/(\text{weaning age, d}),$$

$$\text{WW} = \text{BWT} + \text{WG},$$

$$\text{PWG} = 160 \times (\text{yearling weight} - \text{weaning weight})/(\text{yearling age} - \text{weaning age, d}), \text{ and}$$

$$\text{YW} = \text{WW} + \text{PWG}.$$

Observations for biological index traits favoring decreased birth weight and increased postnatal growth were computed from component traits, BW, WG, and PWG. Three index traits were analyzed, standardized BW gain to weaning less birth weight (**WmB**), postweaning BW gain minus birth weight (**PWmB**), and BW gain to yearling minus birth weight (**YmB**), computed from raw phenotypic means ($\hat{\boldsymbol{\mu}}$) and SD ($\hat{\boldsymbol{\sigma}}$) as

$$\text{WmB} = \left(\text{WG} - \hat{\mu}_{\text{WG}}\right)/\hat{\sigma}_{\text{WG}} - \left(\text{BWT} - \hat{\mu}_{\text{BWT}}\right)/\hat{\sigma}_{\text{BWT}},$$

$$\text{PWmB} = \left(\text{PWG} - \hat{\mu}_{\text{PWG}}\right)/\hat{\sigma}_{\text{WG}} - \left(\text{BWT} - \hat{\mu}_{\text{BWT}}\right)/\hat{\sigma}_{\text{BWT}}, \text{ and}$$

$$\text{YmB} = \left(\text{WG} - \hat{\mu}_{\text{WG}}\right)/\hat{\sigma}_{\text{WG}} + \left(\text{PWG} - \hat{\mu}_{\text{PWG}}\right)/\hat{\sigma}_{\text{WG}} - \left(\text{BWT} - \hat{\mu}_{\text{BWT}}\right)/\hat{\sigma}_{\text{BWT}}.$$

Effects of both calf and dam genotypes on each of the traits were simultaneously estimated from single-trait analysis, repeated for each SNP, with the model:

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}_{\mathbf{d}}\mathbf{u}_{\mathbf{d}} + \mathbf{Z}_{\mathbf{m}}\mathbf{u}_{\mathbf{m}} + \mathbf{Z}_{\mathbf{p}}\mathbf{u}_{\mathbf{p}} + \mathbf{e},$$

with random effects distributed as multivariate normal having mean equal to zero and covariance equal to

$$\mathbf{V}\begin{bmatrix}\mathbf{u}_{\mathbf{d}}\\ \mathbf{u}_{\mathbf{m}}\\ \mathbf{u}_{\mathbf{p}}\\ \mathbf{e}\end{bmatrix} = \begin{bmatrix}\mathbf{A}\sigma^2_{\mathbf{d}} & \mathbf{A}\sigma_{\mathbf{dm}} & \mathbf{0} & \mathbf{0}\\ \mathbf{A}\sigma_{\mathbf{dm}} & \mathbf{A}\sigma^2_{\mathbf{m}} & \mathbf{0} & \mathbf{0}\\ \mathbf{0} & \mathbf{0} & \mathbf{I}_{\mathbf{p}}\sigma^2_{\mathbf{p}} & \mathbf{0}\\ \mathbf{0} & \mathbf{0} & 0 & \mathbf{I}_{\mathbf{e}}\sigma^2_{\mathbf{e}}\end{bmatrix},$$

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where $\mathbf{y}$ was the vector of observations for a trait, $\boldsymbol{\beta}$ a vector of fixed effects, $\mathbf{u_d}$ and $\mathbf{u_m}$ vectors of random direct and maternal additive polygenic effects, $\mathbf{u_p}$ a vector of random maternal permanent environmental effects, and $\mathbf{e}$ a vector of random residual effects; $\mathbf{X}$ was an incidence matrix relating observations to fixed effects, which included calf and dam genotype, contemporary group, age of dam (years), ordinal birth date, calf and dam breed composition, and breed heterozygosity; $\mathbf{Z_d}$, $\mathbf{Z_m}$, and $\mathbf{Z_p}$ were incidence matrices relating individuals to random additive direct, additive maternal, and maternal permanent environmental effects; $\mathbf{A}$ was the additive numerator relationship matrix among all animals; $\mathbf{I_{p(e)}}$ were identity matrices, $\boldsymbol{\sigma}^2_{\mathbf{d}}$ was the additive direct genetic variance, $\boldsymbol{\sigma}^2_{\mathbf{m}}$ was the additive maternal variance, and $\boldsymbol{\sigma}_{\mathbf{dm}}$ the additive direct-maternal covariance; $\boldsymbol{\sigma}^2_{\mathbf{p}}$ and $\boldsymbol{\sigma}^2_{\mathbf{e}}$ were maternal permanent environmental and residual variances.

Calf and dam genotypes were simultaneously evaluated as fixed effect covariates. Values of each covariate were 0, 1, or 2 copies of the minor allele for individuals with 50K genotypes, or predicted number of copies, continuous between 0 and 2 (Gengler et al., 2007), for animals without 50K genotypes (most dams). Approximate genotypes were also substituted when the observation of a genotyped individual for a particular SNP was missing. Contemporary groups for BWT were defined by year, calf sex at birth (bull or heifer), and dam management group. For WW and WG, the BWT contemporary groups were divided by sex at weaning (bull, steer, or heifer), and the PWG and YW contemporary groups were defined by weaning group and yearling weigh date. Weaning contemporary groups were used for the WmB index, and yearling groups for the PWmB and YmB indices. Calf and dam breed compositions were modeled with covariates for proportions AN, HH, SM, LI, CH, GV, AR, PZ, and RP. Covariates for expected calf and dam heterozygosity were computed from parental breed composition. Polygenic and breed effects were included to reduce the effects of family structure on breed- and family-specific alleles (Kuehn et al., 2007; Goddard and Hayes, 2009).

Twin calves and calves raised by foster dams were excluded. The data set used for association analysis consisted of 2,578 BWT; 2,569 WG and WW; and 2,540 PWG and YW observations of genotyped animals with a 7,941-animal pedigree, which included ancestors of the GPE Cycle VII purebred sires and base cows. For each trait, an MTDFREML (Boldman et al., 1995) evaluation to simultaneously estimate effects of calf and dam genotype was repeated for each of the 50K SNP with minor allele frequency (**MAF**) > 0.05 in the F_1[2] generation. Additional analyses that considered calf and dam genotype independently were conducted to investigate separation between direct and maternal SNP effects attempted by simultaneous analysis of both genotypes.

Because preliminary analyses indicated meaningful changes in variance components due to individual SNP would not be detectable, variance components were held constant for the association analyses. Assumed (co)variances were estimated with the same univariate model described for association analysis, without calf and dam genotypes. Body weights of ungenotyped animals in the pedigree were added to the data set, so 5,530 BWT, 5,427 WG and WW, and 5,355 PWG and YW records were available to estimate variance components for this population.

Significance of associations between genotype and calf performance were determined from the 2-tailed t, with SE obtained from diagonal blocks of the inverse coefficient matrix (Boldman et al., 1995). Polymorphisms were evaluated for association with direct and maternal components using nominal P ($\boldsymbol{P_n}$), Bonferroni-corrected P ($\boldsymbol{P_b}$), and false discovery rate (**FDR**; Benjamini and Hochberg, 1995; Weller et al., 1998). Correspondence between SNP associations and QTL described in literature was ascertained via Web-accessible cattle QTL databases (Polineni et al., 2006; Hu et al., 2007), with SNP and QTL-defining markers mapped according to the *Bos taurus* 4.0 draft genome assembly (Btau4.0; Bovine Genome Sequencing and Analysis Consortium, 2009).

Variance components were estimated with REML algorithms implemented in the WOMBAT package (Meyer, 2006). The 5/22/2002 version of MTDFREML (Boldman et al., 1995) was used to estimate SNP allele effects, and the mixed model equations to approximate genotypes were assembled and solved with Animal Breeder's Toolkit software (Golden et al., 1992). Perl scripts were developed to control MTDFREML and Animal Breeder's Toolkit analyses repeated for each of the 50K SNP.

RESULTS AND DISCUSSION

Polygenic Variation

Measures of growth to yearling age were lowly to moderately heritable in the GPE Cycle VII population (Table 1). Estimated using genotyped calves and observations using ancestors, direct heritability of BWT was approximately twice that of other BW or BW gains, and the relative difference between PWG and BWT was estimated to be more heritable than differences including WG. Maternal influences on WW and WG were greater than for other traits, with the proportion of variance due to additive maternal or maternal permanent environment effects at least as great as direct additive variance. There was some additive maternal influence on all traits except PWG. Direct heritability of PWG, reestimated without maternal effects in the model, was almost 50% greater than the estimate from the model including maternal effects. Direct-maternal genetic correlations were negative for birth and weaning traits and positive for PWG and YW, but with

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Table 1. Phenotypic means of genotyped animals and estimated parameters applied to genome-wide association studies of growth traits[1,2]

Trait	Mean	SD	n	h^2_d	SE	h^2_m	SE	r_g	SE	c^2	SE
Genotyped GPE Cycle VII calves and ancestor observations											
BWT, kg	40.0	6.1	5,530	0.44	0.05	0.10	0.03	−0.09	0.13	0.00	0.02
WG, kg	200.8	31.6	5,427	0.17	0.04	0.18	0.05	−0.41	0.11	0.27	0.03
PWG, kg	162.8	49.3	5,355	0.22	0.04	0.01	0.03	0.46	0.77	0.00	0.02
WW, kg	240.8	34.5	5,427	0.22	0.04	0.21	0.05	−0.41	0.10	0.22	0.03
YW, kg	403.7	70.0	5,355	0.27	0.04	0.06	0.04	0.13	0.23	0.07	0.03
WmB	0.0	1.1	5,427	0.18	0.04	0.10	0.04	−0.02	0.20	0.16	0.03
PWmB	0.0	1.1	5,355	0.27	0.05	0.10	0.04	−0.14	0.15	0.02	0.03
YmB	0.0	1.4	5,355	0.17	0.04	0.05	0.04	0.18	0.35	0.15	0.03
Genotyped GPE Cycle VII calf observations											
BWT, kg	42.2	5.9	2,578	0.45	0.08	0.06	0.06	−0.11	0.26	0.03	0.04
WG, kg	214.2	29.1	2,569	0.12	0.04	0.22	0.08	−0.32	0.24	0.29	0.06
PWG, kg	190.6	46.7	2,540	0.28	0.06	0.03	0.05	0.03	0.50	0.00	0.04
WW, kg	256.5	31.3	2,569	0.17	0.04	0.23	0.08	−0.37	0.20	0.25	0.06
YW, kg	447.0	60.3	2,540	0.26	0.06	0.04	0.06	0.23	0.57	0.11	0.05
WmB	0.1	1.1	2,569	0.24	0.06	0.09	0.08	0.04	0.44	0.18	0.06
PWmB	0.2	1.1	2,540	0.38	0.08	0.08	0.07	−0.46	0.25	0.07	0.05
YmB	0.6	1.3	2,540	0.19	0.06	0.07	0.07	0.40	0.66	0.14	0.05

[1]Direct heritability (h^2_d), maternal heritability (h^2_m), direct-maternal genetic correlation (r_g), maternal permanent environment (c^2).
[2]Birth weight (BWT); 205-d adjusted preweaning BW gain (WG); 160-d adjusted postweaning BW gain (PWG), 205-d adjusted weaning weight (WW); 365-d yearling weight (YW); weaning less birth weight (WmB); postweaning BW gain minus birth weight (PWmB); yearling minus birth weight (YmB).

large SE. The only direct-maternal correlations different than zero were for WG and WW.

Genotyped F_1 and F_1^2 calves were somewhat heavier and grew faster than their observed ancestors (Table 1). Although within SE of estimates from full data, estimates for WG and WW direct heritability were less using only genotyped records of calves, and the PWG heritability estimates were greater. Drought during the period F_1^2 calves were raised may provide a partial explanation, as annual precipitation during 4 (2003 to 2006) of the 5 yr F_1^2 calves were born was 12 to 24 cm below recorded means, and rainfall from April through August in those years was 6 to 24 cm less than average (High Plains Regional Climate Center, 2009). Partly in response to dry conditions, the F_1^2 calves were weaned and placed in the feedlot approximately 3 wk earlier than previous GPE cycles. Limited grazed forage and early weaning may have masked genetic differences in growth to weaning, whereas extending the postweaning phase when calves were provided a controlled ration may have increased opportunity to express differences postweaning.

Single SNP Associations

With expected FDR limited to 5%, calf (dam) genotypes for 866 (652) SNP may be associated with at least one component of growth from conception to yearling (Table 2). Numbers of SNP having significant direct (maternal) associations with individual components at FDR <0.05 are 524 (1) for BWT, 14 (124) for WG, and 478 (532) for PWG. For cumulative traits representing sums of birth weight and postnatal BW gains, numbers of SNP meeting FDR < 0.05 for direct (maternal) associations are in the same range, 116 (75) for WW, and 478 (579) for YW. Many SNP associated with growth are located on BTA 6 and 11, although every chromosome is represented (Figure 1). Fewer SNP appear significant at FDR < 0.05 for association with the indexes for relative differences between BWT and postnatal BW gains, with 135 (23) SNP associated with direct (maternal) WmB, 139 (8) with PWmB, and 14 (627) with YmB.

At more conservative Bonferroni-corrected significance criteria, fewer associations are detected, but smaller FDR ($\leq$0.0085 at $P_b < 0.05$) offers increased confidence that the detected SNP mark real effects. Lenient nominal significance criteria suggest many SNP may be associated with small effects throughout the genome (Supplemental Figure 1; http://jas.fass.org/content/vol88/issue3/) even if one- to two-thirds of the SNP meeting $P_n < 0.05$ may be false positives. The infinitesimal polygenic model, commonly assumed in studies of quantitative traits, may closely approximate these numerous small effects throughout the genome.

There appears to be some correspondence between heritability estimates and counts of significant associations. In general, more associations were detected for traits having greater heritability estimates, suggesting a relationship between detectable additive genetic variation and SNP associations. This observation does not imply that heritability and number of loci affecting a trait are related, just that identifying SNP that account for a portion of heritable variation may be easier in traits that are at least moderately heritable. Low heritable traits may be controlled by many genes, but detecting DNA variants linked to those genes to explain a meaningful fraction of the heritable variation may require substantially more data.

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Table 2. Summary of BovineSNP50 BeadChip SNP associated with growth traits at various significance levels

		Significance criterion[1]						
Item		$P_b < 0.01$	$P_b < 0.05$	FDR <0.01	FDR <0.05	FDR <0.1	$P_n < 0.01$	$P_n < 0.05$
Component trait[2] (direct)								
BWT	n	113	140	267	524	786	1,845	5,008
	Nominal P	2.26E-7	1.13E-6	5.94E-5	5.87E-4	1.77E-3	0.010	0.050
	FDR	8.14E-5	3.51E-4	0.010	0.049	0.100	0.239	0.441
	|b|,[3] kg	1.50	1.46	1.24	1.04	0.95	0.77	0.60
WG	n	3	4	4	14	37	902	3,302
	Nominal P	2.26E-7	1.13E-6	7.69E-7	1.51E-5	8.28E-5	0.010	0.050
	FDR	1.42E-3	8.49E-3	8.49E-3	0.048	0.099	0.489	0.668
	|b|, kg	4.46	4.30	4.30	4.55	4.15	2.80	2.27
PWG	n	25	46	124	478	898	2,217	5,751
	Nominal P	2.26E-7	1.13E-6	2.80E-5	5.40E-4	2.03E-3	0.010	0.050
	FDR	3.74E-4	1.01E-3	0.010	0.050	0.100	0.199	0.384
	|b|, kg	6.08	5.72	5.36	4.50	4.12	3.53	2.89
Any component	n	121	160	329	866	1,508	4,348	11,695
All components	n	3	4	4	9	11	80	315
Cumulative trait[4] (direct)								
WW	n	11	18	40	116	172	1,197	3,817
	Nominal P	2.26E-7	1.13E-6	7.46E-6	1.30E-4	3.87E-4	0.010	0.050
	FDR	8.47E-4	2.09E-3	8.23E-3	0.049	0.099	0.369	0.578
	|b|, kg	6.58	5.79	5.15	4.38	4.19	3.15	2.54
YW	n	61	91	221	478	902	2065	5511
	Nominal P	2.26E-7	1.13E-6	4.98E-5	5.33E-4	2.04E-3	0.010	0.050
	FDR	1.63E-4	5.32E-4	0.010	0.049	0.100	0.214	0.401
	|b|, kg	9.53	9.06	7.99	7.05	6.27	5.38	4.33
Relative index[5] (direct)								
WmB	n	24	35	51	135	252	1,251	4,067
	Nominal P	2.26E-7	1.13E-6	9.55E-6	1.53E-4	5.68E-4	0.01	0.05
	FDR	4.04E-4	9.66E-4	8.27E-3	0.050	0.100	0.35	0.54
	|b|	0.26	0.23	0.22	0.18	0.17	0.13	0.10
PWmB	n	17	25	43	139	244	1,458	4,505
	Nominal P	2.26E-7	1.13E-6	9.47E-6	1.54E-4	5.50E-4	0.01	0.05
	FDR	5.32E-4	1.81E-3	0.010	0.049	0.100	0.302	0.490
	|b|	0.23	0.22	0.20	0.17	0.16	0.12	0.10
YmB	n	1	6	1	14	32	1,186	3,954
	Nominal P	2.26E-7	1.13E-6	1.58E-7	1.25E-5	7.12E-5	0.01	0.05
	FDR	6.99E-3	7.20E-3	6.99E-3	0.040	0.098	0.370	0.558
	|b|	0.25	0.23	0.25	0.20	0.19	0.13	0.11
Component trait (maternal)								
BWT	n	1	1	1	1	2	930	3,580
	Nominal P	2.26E-7	1.13E-6	6.39E-8	6.39E-8	2.80E-6	0.010	0.050
	FDR	2.82E-3	2.82E-3	2.82E-3	2.82E-3	0.062	0.475	0.616
	|b|, kg	1.45	1.45	1.45	1.45	1.42	0.95	0.76

Continued

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Table 2 (Continued). Summary of BovineSNP50 BeadChip SNP associated with growth traits at various significance levels

		Significance criterion[1]						
Item		$P_b < 0.01$	$P_b < 0.05$	FDR <0.01	FDR <0.05	FDR <0.1	$P_n < 0.01$	$P_n < 0.05$
WG	n	2	9	16	124	358	1,948	5,660
	Nominal P	2.26E-7	1.13E-6	3.22E-6	1.36E-4	8.05E-4	0.010	0.050
	FDR	3.49E-3	5.36E-3	8.88E-3	0.049	0.099	0.226	0.390
	|b|, kg	11.05	8.72	8.32	6.66	5.91	4.78	3.94
PWG	n	5	12	88	532	1,357	2,744	6,876
	Nominal P	2.26E-7	1.13E-6	1.99E-5	6.02E-4	3.07E-3	0.010	0.050
	FDR	1.58E-3	3.54E-3	0.010	0.050	0.100	0.161	0.321
	|b|, kg	7.90	6.91	6.25	5.39	4.81	4.36	3.63
Any component	n	8	22	105	652	1,694	5,308	13,972
All components	n	0	0	0	0	0	7	130
Cumulative trait (maternal)								
WW	n	2	8	11	75	266	1,762	5,344
	Nominal P	2.26E-7	1.13E-6	2.46E-6	8.41E-5	5.95E-4	0.010	0.050
	FDR	3.98E-3	5.84E-3	0.010	0.050	0.099	0.250	0.413
	|b|, kg	8.86	9.90	10.18	7.31	6.44	5.10	4.18
YW	n	6	10	39	579	1,370	2,730	6,955
	Nominal P	2.26E-7	1.13E-6	8.71E-6	6.54E-4	3.10E-3	0.010	0.050
	FDR	1.58E-3	4.88E-3	0.010	0.050	0.100	0.162	0.317
	|b|, kg	12.30	11.26	11.00	8.72	7.86	7.07	5.90
Relative index (maternal)								
WmB	n	0	3	0	23	208	1,646	5,134
	Nominal P		1.13E-6		2.53E-5	4.71E-4	0.01	0.05
	FDR		0.013		0.049	0.100	0.268	0.430
	|b|		0.29		0.27	0.24	0.19	0.16
PWmB	n	0	4	0	8	62	1,426	4,717
	Nominal P		1.13E-6		8.72E-6	1.35E-4	0.01	0.05
	FDR		0.011		0.048	0.096	0.310	0.468
	|b|		0.32		0.29	0.21	0.16	0.13
YmB	n	6	14	60	627	1,657	2,906	7,198
	Nominal P	2.26E-7	1.13E-6	1.27E-5	7.03E-4	3.75E-3	0.01	0.05
	FDR	1.61E-3	3.55E-3	0.009	0.050	0.100	0.152	0.307
	|b|	0.33	0.30	0.29	0.24	0.21	0.20	0.16

[1]Bonferroni-corrected P (P_b); false discovery rate (FDR); nominal P (P_n).
[2]Birth weight (BWT); 205-d adjusted preweaning BW gain (WG); 160-d adjusted postweaning BW gain (PWG).
[3]Mean absolute value of minor allele effect.
[4]205-d adjusted weaning weight (WW); 365-d yearling weight (YW).

[5]WmB (standardized BW gain to weaning minus birth weight) $= (\mathrm{WG} - \hat{\mu}_{\mathrm{WG}}) / \hat{\sigma}_{\mathrm{WG}} - (\mathrm{BWT} - \hat{\mu}_{\mathrm{BWT}}) / \hat{\sigma}_{\mathrm{BWT}}$; PWmB (postweaning BW gain minus birth weight) $= \left(\mathrm{PWG} - \hat{\mu}_{\mathrm{PWG}}\right) / \hat{\sigma}_{\mathrm{WG}} - \left(\mathrm{BWT} - \hat{\mu}_{\mathrm{BWT}}\right) / \hat{\sigma}_{\mathrm{BWT}}$; YmB (BW gain to yearling minus birth weight) $= \left(\mathrm{WG} - \hat{\mu}_{\mathrm{WG}}\right) / \hat{\sigma}_{\mathrm{WG}} + \left(\mathrm{PWG} - \hat{\mu}_{\mathrm{PWG}}\right) / \hat{\sigma}_{\mathrm{WG}} - \left(\mathrm{BWT} - \hat{\mu}_{\mathrm{BWT}}\right) / \hat{\sigma}_{\mathrm{BWT}}$. $\hat{\mu}$ = raw phenotypic mean; $\hat{\sigma}$ = SD.

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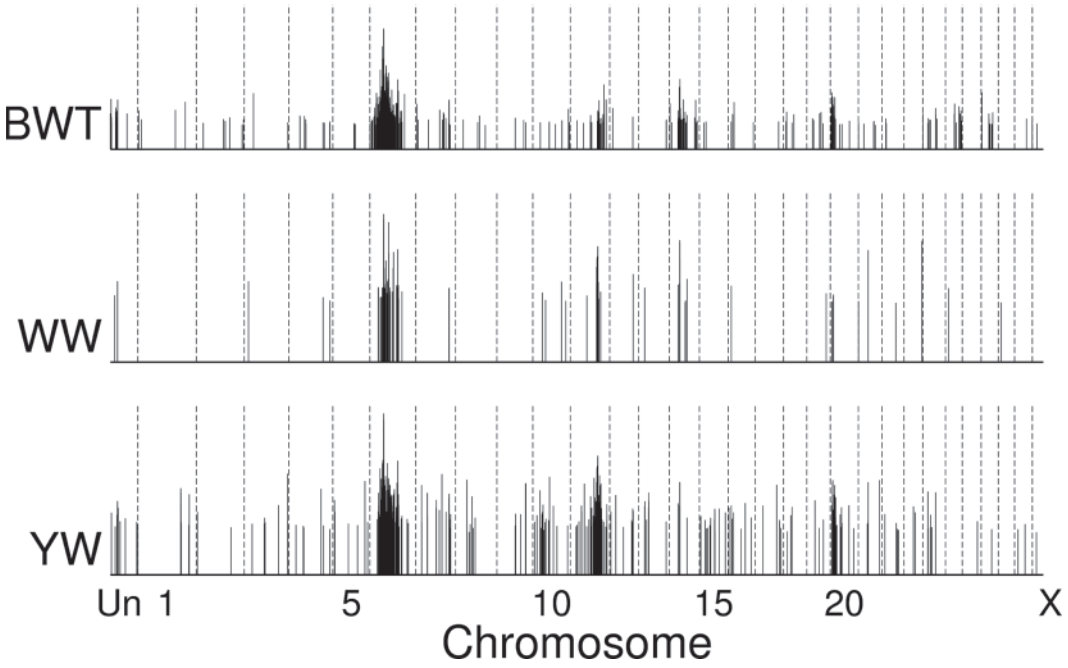

Figure 1. Genomic map of SNP associated with calf genotype effects on birth (BWT), weaning (WW), and yearling weight (YW) that meet false discovery rate <0.05. Mapping to unassigned scaffolds (Un), autosomes (1 to 29), and X is based on *Bos taurus* 4.0 draft genome assembly. Chromosome boundaries are indicated by dashed vertical lines. Height indicates relative magnitude of estimated effects.

The number of SNP significantly associated with dam genotype effects on PWG appears to be excessive, given the near-zero maternal heritability estimate. The attempt to separate calf and dam genotype effects, by simultaneously analyzing both effects in a data set that includes few observations on genotyped dams, may exaggerate effect estimates. Examination of direct and maternal SNP effects shows that when both effects are included in the analysis, correlations between estimates are near −1 among SNP having significant associations with calf and dam genotypes, and the correlations among all SNP are about −0.5 (Table 3). Independently reestimating calf and dam genotype effects in analyses that included only calf or only dam genotypes provided little separation between estimates and reflected the contribution of the dam to the genotypes of the calves. Among SNP significantly associated with calf and dam genotypes in separate analyses, correlations between estimated effects approached +1, and correlations between estimated direct and maternal effects among all SNP were near +0.5. Correlations between simultaneously estimated direct (maternal) and the corresponding independently estimated direct (maternal) effects were high. Significance of the simultaneous estimates is more conservative than the independent estimates. Except for maternal WG, fewer SNP were identified as significant from the simultaneous direct-maternal analyses than from the separate analyses of direct and maternal effects. Data including multiple generations of genotyped and phenotyped dams and calves may be needed to provide clearer separation and more reliable estimates of direct and maternal SNP effects.

Available pedigree records were used to correct for admixture. Breed composition coefficients computed from pedigree records were used to account for breed-specific effects, and the polygenic term with pedigree relationships accounted for family-specific effects to reduce false positive associations due to SNP whose frequencies differ across breeds and families (Goddard and Hayes, 2009). Whole-genome association studies of human conditions have shown the need to account for stratification within studies (Helgason et al., 2005; Seldin and Price, 2008; Tian et al., 2008). Rather than relying on multiple generations of pedigree information, human ancestry is often inferred from DNA marker genotypes (Pritchard et al., 2000; Price et al., 2006). Applied to admixed cattle, these genomic approaches may more accurately account for breeds sharing common ancestry (Bovine HapMap Consortium, 2009) and allow for variation in ancestry among individuals sharing identical pedigree-based breed composition. Further examination of these data utilizing inferred ancestry based on genotypes may provide additional insight into structure of this population and contributing breeds and allow assessment of pedigree- and genotype-based approaches to correcting for stratification in association analyses.

Association results for each of the 44,163 SNP with MAF > 0.05 in the F_1^2 generation, including estimated minor allele effects, SE, P_n, MAF, and mapping to Btau4.0 are listed in the supplemental table (available at http://jas.fass.org/content/vol88/issue3/) to allow further examination and combining with results from other data for meta-analysis that may contribute to development of selection tools based on BovineSNP50 genotypes. Values in the supplement are most pertinent for the GPE Cycle VII population under USMARC management and environmental conditions. Significant

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Table 3. Summary of BovineSNP50 BeadChip SNP associated with direct or maternal effects on growth, estimated simultaneously or in separate analyses of calf and dam genotypes[1]

				Simultaneous		Separate	
Trait[2]	Criterion[3]	Analysis[4]	Effect	Direct	Maternal	Direct	Maternal
BWT							
	$P_b < 0.05$	Simultaneous	Direct	140	—	0.995	0.988
			Maternal	1/1	1	—	—
		Separate	Direct	0/123	1/1	149	0.993
			Maternal	0/5	0/0	0/5	5
	$P_n < 0.05$	Simultaneous	Direct	5,008	−0.928	0.985	0.531
			Maternal	1,186/1,191	3,580	−0.488	0.965
		Separate	Direct	0/3,101	342/481	5,051	0.927
			Maternal	154/505	11/1,469	3/1,124	3,753
	All	Simultaneous	Direct	n[5]	−0.553	0.874	0.095
			Maternal	30,561/n	n	−0.080	0.708
		Separate	Direct	7,638/n	22,923/n	n	0.524
			Maternal	21,256/n	10,827/n	14,300/n	n
WG							
	$P_b < 0.05$	Simultaneous	Direct	4	—	0.934	—
			Maternal	0/0	9	—	—
		Separate	Direct	0/3	0/0	7	—
			Maternal	0/0	0/1	0/0	7
	$P_n < 0.05$	Simultaneous	Direct	3,302	−0.956	0.984	−0.220
			Maternal	967/971	5,660	0.415	0.983
		Separate	Direct	0/1,750	141/487	3,549	0.962
			Maternal	216/341	0/3,203	4/984	5,060
	All	Simultaneous	Direct	n	−0.487	0.823	−0.068
			Maternal	29,329/n	n	0.092	0.868
		Separate	Direct	8,620/n	20,709/n	n	0.483
			Maternal	23,122/n	7,245/n	14,874/n	n
PWG							
	$P_b < 0.05$	Simultaneous	Direct	46	−1.000	0.995	—
			Maternal	2/2	12	—	—
		Separate	Direct	0/28	0/0	65	0.990
			Maternal	0/1	0/1	0/7	25
	$P_n < 0.05$	Simultaneous	Direct	5,751	−0.950	0.973	−0.016
			Maternal	2,175/2,185	6,876	0.066	0.972
		Separate	Direct	0/2,962	424/938	5,978	0.949
			Maternal	552/1,016	1/3,711	11/2,191	7,555
	All	Simultaneous	Direct	n	−0.593	0.778	−0.047
			Maternal	31,020/n	n	0.042	0.782
		Separate	Direct	9,844/n	21,176/n	n	0.551
			Maternal	23,166/n	9,186/n	14,014/n	n

[1]Number of SNP meeting significance criteria for association with effect on diagonal, correlations between estimated effects among SNP meeting criteria for both effects above diagonal, number of SNP with estimated effects in opposite directions/number of SNP meeting criteria for both effects below diagonal.

[2]Birth weight (BWT), 205-d adjusted preweaning BW gain (WG), 160-d adjusted postweaning BW gain (PWG).

[3]Bonferroni-corrected P (P_b), nominal P (P_n).

[4]Direct and maternal SNP effects estimated simultaneously with calf and dam genotypes included in analysis, or with calf and dam genotypes analyzed separately.

[5]n = 44,163.

associations of the same or neighboring SNP obtained from unrelated cattle, representing other breeds and crosses under different production environments, will add support to determine SNP that may be closely linked to causative mutations. Bioinformatic approaches to integrate associations determined in this study with functional annotation of the genome (Bovine Genome Sequencing and Analysis Consortium, 2009), gene expression (Lehnert et al., 2007; Harhay et al., 2008), QTL (Polineni et al., 2006; Hu et al., 2007), and other databases may reveal interesting loci with biological evidence to support effects on growth.

QTL Regions

Most SNP (140/181) associated with direct growth at $P_b < 0.05$ were located on BTA 6. Six or more were placed on BTA 7, 11, 14, and 20, and BTA 10 and 23 each had a single SNP. The greatest concentration of SNP strongly associated with direct growth is between 25 and 53 Mbp on BTA 6. This region overlaps QTL described for birth weight (Casas et al., 2000; Kneeland et al., 2004; Gutierrez-Gil et al., 2009), pre- and postweaning BW gain (Yeo et al., 2003; Kneeland et al., 2004), and yearling weight (Casas et al., 2000) in

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Table 4. Summary of BovineSNP50 BeadChip SNP associated with pairs of growth traits at various significance levels

		Direct association[3]					Maternal association[3]				
Criterion[1]	Trait[2]	BWT	WG	PWG	WW	YW	BWT	WG	PWG	WW	YW
$P_b < 0.05$	BWT		0.982	0.979	0.989	0.990		—	—	—	—
	WG	0/4		0.978	0.997	1.000	0/0		—	0.998	—
	PWG	0/26	0/4		0.995	0.996	0/0	0/0		—	—
	WW	0/15	0/4	0/11		0.990	0/0	0/7	0/0		—
	YW	0/59	0/4	0/39	0/15		0/0	0/1	0/1	0/1	
FDR <0.05	BWT		0.822	0.963	0.960	0.975		—	—	—	—
	WG	0/12		0.900	0.979	0.932	0/0		0.996	0.999	0.984
	PWG	0/137	0/10		0.989	0.991	0/0	0/5		0.996	0.988
	WW	0/80	0/14	0/57		0.986	0/0	0/72	0/4		0.983
	YW	0/197	0/14	0/271	0/98		0/0	0/54	0/167	0/36	
$P_n < 0.01$	BWT		0.893	0.943	0.955	0.967		0.871	0.864	0.980	0.973
	WG	3/159		0.935	0.992	0.964	4/59		0.876	0.998	0.981
	PWG	1/381	3/156		0.967	0.985	6/98	9/164		0.913	0.970
	WW	0/399	0/744	1/270		0.980	0/112	0/1,525	6/164		0.982
	YW	0/558	0/421	0/1,129	0/641		1/174	0/945	0/1,085	0/947	
$P_n < 0.05$	BWT		0.850	0.904	0.941	0.949		0.715	0.792	0.918	0.914
	WG	40/767		0.845	0.992	0.961	83/526		0.670	0.997	0.972
	PWG	35/1,233	51/681		0.900	0.980	69/702	159/1,046		0.746	0.970
	WW	4/1,334	0/2,796	47/908		0.970	24/740	0/4,731	116/1,031		0.974
	YW	7/1,672	0/1,590	0/3,341	0/2,039		29/964	0/3,173	1/3,370	0/3,244	
All SNP	BWT		0.347	0.378	0.555	0.558		0.188	0.229	0.350	0.373
	WG	17,499/n[4]		0.254	0.971	0.694	19,593/n		0.216	0.985	0.784
	PWG	17,301/n	18,740/n		0.320	0.845	18,966/n	18,625/n		0.241	0.750
	WW	14,384/n	3,167/n	17,923/n		0.756	17,219/n	2,430/n	18,349/n		0.810
	YW	14,526/n	11,391/n	8,103/n	10,310/n		16,830/n	9,241/n	9,944/n	8,757/n	

[1]Bonferroni-corrected P (P_b), false discovery rate (FDR), nominal P (P_n).

[2]Birth weight (BWT), 205-d adjusted preweaning BW gain (WG), 160-d adjusted postweaning BW gain (PWG), 205-d adjusted weaning weight (WW), 365-d yearling weight (YW).

[3]Correlations between estimated SNP effects above diagonal, number of SNP with estimated effects in opposite direction/number of SNP meeting significance criteria for both traits below diagonal.

[4]n = 44,163.

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beef cattle. Interestingly, QTL for stillbirth (Kuhn et al., 2003) and calving difficulty (Schrooten et al., 2000) in Holstein Friesian dairy cattle also fall within this region. Annotation of Btau4.0 (Ensembl, 2009) shows 77 genes in the region, including secreted phosphoprotein 1 (SPP1) at 37.5 Mbp, which has been implicated to affect growth traits (Allan et al., 2007; White et al., 2007). Among the most significant associations between calf genotype and all phenotypes are those within a block of 5 SNP, all in strong linkage disequilibrium ($D' \geq 0.997$, $r^2 \geq 0.98$), located from 38.1 to 38.3 Mbp on BTA 6. This block encompasses a single annotated gene, non-SMC condensin I complex, subunit G (**NCAPG**), which functions in protein binding and cell division. The segment surrounding NCAPG on the mouse genome corresponds to Noq1, a QTL related to 12- and 22-wk BW at 22-wk fat content of mice (Kluge et al., 2000). Human QTL for body mass index (Stone et al., 2002; Arya et al., 2004), fat percentage (Norman et al., 1997), and subcutaneous abdominal fat (Perusse et al., 2001) are within the region of HSA4 syntenic to this segment of BTA 6.

Other regions containing SNP associated with calf genotype at $P_b < 0.05$ correspond to previously described QTL for cattle growth or correlated carcass traits. A yield grade QTL (Casas et al., 2003) overlaps SNP associated with WG, WW, PWG, and YW on BTA 11. Markers defining pre- and postweaning BW gain (Kneeland et al., 2004) and LM area (Stone et al., 1999) QTL surround the SNP on BTA 14 associated with BWT, WW, PWG, or YW. The SNP associated with BWT, PWG, and YW on BTA 20 are under a BWT QTL near the centromere (Casas et al., 2003). A HCW QTL (Casas et al., 2003) is near the single SNP associated with PWG on BTA 10, and the YW-associated SNP on BTA 23 is in the same region as BWT and WG QTL (Kneeland et al., 2004). No cattle growth or carcass QTL are near the growth-associated SNP between 80 and 100 Mbp on BTA 7. This region, however, corresponds to segments of mouse chromosome 13 and rat chromosome 2 covered by QTL for mouse tail length and BW at 10 wk (Cheverud et al., 2001) and a QTL for rat BW at 5 to 6 mo (Ueno et al., 2004).

Some apparently significant maternal estimates obtained with predicted dam genotypes may be meaningful. Eight of the 9 SNP with $P_b < 0.05$ for association with WG coincide with milk yield and composition QTL, including percent protein on BTA 4 (Mosig et al., 2001), milk and fat yield on BTA 5 (Bennewitz et al., 2003) and BTA 6 (Harder et al., 2006), fat yield on BTA 17 (Harder et al., 2006), percent protein and milk yield on BTA 20 and BTA 23 (Plante et al., 2001; Viitala et al., 2003; Ashwell et al., 2004), and percent protein on BTA 28 (Ashwell et al., 2001). Literature QTL support is lacking for the SNP associated with maternal WG effect on BTA 19, which is centromeric to fat content and yield QTL (Bennewitz et al., 2003).

SNP Affecting Multiple Traits

Three of the traits examined measure growth in distinct stages: conception to birth (BWT), birth to weaning (WG), and weaning to yearling (PWG). The 2 other traits are cumulative measures of growth through weaning and yearling ages, where WW is the sum of BWT and WG, and YW the sum of BWT, WG, and PWG. Estimated SNP effects reflect the part-whole relationship between the component and cumulative traits. For direct and maternal effects, correlations between sums of component trait effects and cumulative trait effect estimates are high ($r > 0.98$), and regressions of the summed effects on cumulative effects are near unity ($b = 1.00 \pm 0.02$).

Strong positive correlations between estimated effects among SNP meeting significance criteria for pairs of individual traits (Table 4) suggest limited opportunity for using the same SNP to simultaneously select for increased growth in one phase accompanied by decreased growth in another phase. Evaluation of relative indices indicates SNP that may differentially affect birth weight and postnatal growth. Among the 45 SNP associated with calf genotype, according to stringent $P_b < 0.05$, with at least one of the indexes, only 8 were estimated to have opposite effects on BWT and one or both gain measurements. The remaining 37 SNP met $P_b < 0.05$ for association with BWT, with estimated effects on BWT and BW gains in the same direction, but the BWT effects were large relative to BW gain.

Several more SNP appear to be associated with relative differences between birth weight and postnatal growth using criteria relaxed to FDR <0.1. Among the 252 SNP meeting FDR <0.1 for direct association with WmB, 2% are associated with both component traits at FDR <0.1, whereas 54% are associated with one component at FDR <0.1 but FDR >0.5 for the other component suggests independence from the other component. Of the 244 SNP meeting FDR <0.1 for PWmB, 23% are associated with both BWT and PWG, and 38% are associated with one but independent of the other. Of the 32 SNP associated with YmB, 19% meet FDR <0.1 for BWT and one or both postnatal traits, and 13% appear to be associated with BWT but lack association with either postnatal trait.

Application

Most of the SNP with highly significant associations between genotype and growth phenotypes in this study coincide with described previously QTL for growth or correlated traits. Estimated effects suggest selection using these significant SNP may lead to similar changes in BW at different stages. The SNP could be used in selection to increase market weight and revenue from calf sales, although undesirable increases in birth weight and calving difficulty may occur. Similarly, attempts to reduce calving difficulty by using these SNP to reduce

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birth weight may also reduce sale weight and income. Genotypes for these SNP having similar effect on all phases of growth may still be useful in breeding decisions. Where intermediate optima for BW traits exist, schemes that maintain intermediate allele frequencies across all loci or balance positive changes at some loci with negative changes at other loci affecting growth are envisioned. Selection for specialized high-growth terminal and low- to moderate-growth maternal lines might also be assisted by genotypes for these SNP having substantial effects on birth and postnatal weights.

In addition to the SNP with effects large enough to be detectable under stringent multiple-testing criteria are thousands of SNP located throughout the genome that may be associated with small but real effects, which are indistinguishable from spurious associations meeting nominal significance criteria without additional information. Individually, the small to moderate real effects may not be meaningful, but collectively they may conform to a polygenic model and account for substantial variation in a genomic selection context (Meuwissen et al., 2001; Goddard and Hayes, 2009). The aggregate of these SNP, particularly the ones apparently associated with pre- or postnatal growth, but independent of the other component, may be useful in selection to increase postnatal growth relative to BWT.

Further investigation, including validation of these findings in other cattle and environments, is needed to develop DNA-based selection strategies to address the antagonism between birth weight and postnatal growth. Extending birth-postnatal weight to a more general multiple-trait selection problem, the ultimate solution to SNP-assisted selection for economically important traits may lie in a multiple-trait approach to genomic selection that incorporates economic values to predict aggregate merit of individual SNP.

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