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Genome Scan for Parent-of-Origin QTL Effects on Bovine Growth and Carcass Traits

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Genome scan for parent-of-origin QTL effects on bovine growth and carcass traits

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Parent-of-origin effects (POE) such as genomic imprinting influence growth and body composition in livestock, rodents, and humans. Here, we report the results of a genome scan to detect quantitative trait loci (QTL) with POE on growth and carcass traits in Angus × Brahman cattle crossbreds. We identified 24 POE–QTL on 15 *Bos taurus* autosomes (BTAs) of which six were significant at 5% genome-wide (GW) level and 18 at the 5% chromosome-wide (CW) significance level. Six QTL were paternally expressed while 15 were maternally expressed. Three QTL influencing post-weaning growth map to the proximal end of BTA2 (linkage region of 0–9 cM; genomic region of 5.0–10.8 Mb), for which only one imprinted ortholog is known so far in the human and mouse genomes, and therefore may potentially represent a novel imprinted region. The detected QTL individually explained 1.4 ∼ 5.1% of each trait's phenotypic variance. Comparative *in silico* analysis of bovine genomic locations show that 32 out of 1,442 known mammalian imprinted genes from human and mouse homologs map to the identified QTL regions. Although several of the 32 genes have been associated with quantitative traits in cattle, only two (*GNAS* and *PEG3*) have experimental proof of being imprinted in cattle. These results lend additional support to recent reports that POE on quantitative traits in mammals may be more common than previously thought, and strengthen the need to identify and experimentally validate cattle orthologs of imprinted genes so as to investigate their effects on quantitative traits.

Keywords: parent-of-origin, imprinting, QTL, growth traits, carcass traits, comparative genomics, beef cattle, BTA2

INTRODUCTION

Applications of marker-based technologies to genetic evaluation as well as to quantitative trait loci (QTL) mapping often assume Mendelian inheritance of equal expression of parental alleles in progeny (Andersson, 2001). On the other hand, genomic imprinting is the expression of only one of two copies of a gene in the progeny based on parent-of-origin of the alleles (Barlow, 1995). Several studies have reported parent-of-origin effects (POE) on quantitative traits in mammalian livestock: pigs (Vries et al., 1994; De Koning et al., 1999, 2000; Van Laere et al., 2003; Thomsen et al., 2004; Boysen et al., 2010), sheep (Cockett et al., 1996; Garfield et al., 2003; Vuocolo et al., 2007; Fleming-Waddell et al., 2009; Matika et al., 2010), and in cattle (Kuehn et al., 2007; Allan et al., 2009; Neugebauer et al., 2010; Pausch et al., 2011). In addition, reciprocal differences have been detected in *B. taurus* × *B. indicus* (BT × BI) calves for growth and carcass characteristics (Thallman et al., 1993; Rohrer et al., 1994; Amen et al., 2007a,b). Furthermore, since the calves used by Thallman et al. (1993), Rohrer et al. (1994), and Amen et al. (2007a,b) were gestated and raised by unrelated recipient cows which were randomly assigned to embryos

in a multiple ovulation and embryo transfer (MOET) program, the detected reciprocal effects are not due to the maternal effects of milk production, passive immunity or uterine environment (after day 7; Thallman et al., 1993; Rohrer et al., 1994) but appear to represent real genetic or epigenetic differences. The basis for this non-Mendelian effect on intrauterine growth remains unexplained, but increasing evidence strongly suggest that epigenetic inheritance involving imprinted genes is in play (Duselis et al., 2005; Jiang et al., 2007; Loschiavo et al., 2007; Cheverud et al., 2008; Hager et al., 2008; Wolf et al., 2008). Recently, a handful of known and putative imprinted genes have reportedly been associated with quantitative traits in beef cattle (Magee et al., 2010, 2011; Berkowicz et al., 2011; Chen et al., 2011; Sikora et al., 2011).

With the increasing role of epigenetic effects on complex traits of livestock, knowledge of the genomic regions harboring these loci will lead to the identification of the underlying causal genes. To date, only 14 of the roughly 142 genes previously known to be imprinted in mammals[1] have been experimentally shown to

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[1] www.geneimprint.com

be primarily imprinted in bovine embryos and fetuses (Dindot et al., 2004; Ruddock et al., 2004; Arnold et al., 2006; Zaitoun and Khatib, 2006; Kim et al., 2007; Tveden-Nyborg et al., 2008; Flisikowski et al., 2010). However, recent work in mouse has dramatically increased the number of mammalian imprinted genes to 1,300 (Gregg et al., 2010). Since only very few genome scans to identify POE has been published in cattle, in this paper we report the results of a genome scan to detect POE–QTL affecting seven growth and carcass traits in Angus × Brahman crossbred beef cattle.

MATERIALS AND METHODS

RESOURCE FAMILY STRUCTURE AND PHENOTYPES

Details about resource family structures and phenotypes of this study population have previously been described by Kim et al. (2003). The Angleton reference QTL population comprised 80 Brahman, Angus grandparents, and F_1 parents with 14 Angus and 15 Brahman reciprocal backcross, and three F_2 families. The average number of progeny per family was 19.1 ± 6.5, and steers and heifers ($n = 602$) were produced by MOET using randomly assigned multiparous Brahman × Hereford crossbred recipient dams. The progeny were raised under similar conditions from birth at the Texas A&M Agricultural Experiment Station in Angleton, TX, were weaned at approximately 7 months of age, backgrounded on pasture for an average of 215 days, and fed for approximately 170 days on a corn-based finishing diet. Cattle were then transported to the Rosenthal Meat Science and Technology Center in College Station, TX, USA where they were processed. Traits analyzed in this study were birth weight (BWT); weaning weight (WWT); yearling weight (YWT); slaughter weight (SWT); hot carcass weight (HCW), a measure of trimmed final carcass weight at approximately 20 months of age; adjusted subcutaneous fat thickness between the 12th and 13th ribs (ABF); and percentage of kidney, pelvic, and heart fat relative to carcass weight (KPH). The two carcass traits were evaluated according to United States Department of Agriculture specifications (USDA, 1989). Summary statistics for the traits in the population have previously been published (Kim et al., 2003).

GENETIC MAP CONSTRUCTION, INFORMATION CONTENT, AND SEGREGATION DISTORTION

A total of 357 genetic markers, mainly microsatellites, were scored for the construction of linkage maps, and the best orders and map distances between markers were determined using CRI-MAP, version 2.4 (Green et al., 1990) as previously described (Kim et al., 2003). The list of primers have been described and published in Kim et al. (2003). Four QTL genotype probabilities for an offspring, e.g., P(QQ), P(Qq), P(qQ), P(qq; Q allele is inherited from Angus and q from Brahman grand-parental breed, and the first letter indicates an allele inherited from the progeny's sire and the latter from its dam), were derived at a given chromosomal location by using the option of combined backcross and F_2 crosses in QTL Express software (Seaton et al., 2002). Information content (IC) based on these genotype probabilities was obtained (Knott et al., 1998) as:

$$IC = \sum_{i=1}^{N} \frac{(I_i - \bar{I})^2}{N}$$

where, for paternal expression IC, I_i is $[P(QQ) + P(Qq)] - [P(qQ) + P(qq)]$ for the ith individual, and I is the mean across all I_i values, and for maternal expression IC, I_i is $[P(QQ) + P(qQ)] - [P(Qq) + P(qq)]$. The more informative the marker region, the greater the value of IC which asymptotes at one.

The genotype probabilities can also be used to evaluate segregation distortion (SD) at a chromosomal location as:

$$SD = \sum_{i=1}^{N} I_i / N$$

for which an excess of one parentally inherited allele, e.g., $P(QQ + P(Qq)$, or $P(qQ) + P(qq)$ for paternally inherited alleles, causes SD value to deviate from zero toward 1 or -1. Deviation of the SD value from "0," i.e., under the null hypothesis condition of no SD can be tested by assuming a normal distribution under the Central Limit Theorem. It is then necessary to adjust the obtained comparison-wise P value for the test statistic to allow for multiple testing to a genome-wise significance level. As the average length of each chromosome was about 90 cM across the 29 autosomes, 45 cM was assumed to be the chromosome length unit for independence for each test, suggesting that 58 independent tests were performed across the whole genome. Consequently, the genome-wise P value was obtained by using the Bonferroni correction (Knott et al., 1998).

PARENT-OF-ORIGIN QTL ANALYSIS

Least squares interval mapping models were used for parent-of-origin QTL detection on the autosomal chromosomes. The base model was a Mendelian line-cross model (Mend), which assumes a one QTL and single-trait model with alternate QTL alleles fixed in each of the grand-parental breeds (Haley et al., 1994) is the MENDELIAN MODEL:

MENDELIAN MODEL: $Y = Xb + aP_a + dP_d + e$

where Y is a vector of phenotypes of F_2 or backcross individuals; X is a design matrix; b is a vector of fixed and covariate effects; a is the additive QTL effect, modeled as half of the difference between Angus and Brahman breed homozygotes; d is the dominance effect, modeled as the difference between the average of Angus and Brahman heterozygotes and the homozygote midpoint; P_a and P_d are vectors containing functions of genotype probabilities for each animal at the chromosomal position of the putative QTL conditional on flanking marker genotypes. The genotype probabilities were calculated differently according to the cross type of each animal. For example, the element of P_a was $P(Q^{mat}Q^{pat}) - P(q^{mat}q^{pat})$, $P(Q^{mat}Q^{pat})$, or $-P(q^{mat}q^{pat})$ for the F_2, Angus backcross and Brahman backcross types, respectively, and e is a vector of uncorrelated residuals with constant variance. The second model was the FULL IMPRINTING MODEL:

FULL IMPRINTING MODEL:

$$Y = Xb + a_{mat}P_{mat} + a_{pat}P_{pat} + dP_d + e$$

where Y, X, b, and e are as defined previously, and a_{pat}, a_{mat}, and d are the paternally inherited, maternally inherited, and dominance

QTL coefficients, respectively. Vector P_{pat} contains probabilities of inheriting an Angus allele, Q vs. Brahman allele, q from the sire, P_{mat} probabilities of inheriting an Angus allele, Q vs. Brahman allele, q from the dam, and P_d probabilities of being heterozygous. The parent-of-origin genotype probabilities were also derived differently according to the cross type of each animal. For example, elements of P_{pat} were $P(Q^{mat}Q^{pat}) + P(Q^{pat}q^{mat})$ and $P(Q^{mat}Q^{pat}) - P(q^{pat}Q^{mat})$ for type 1 (Angus $\times$ F$_1$) and type 2 (F$_1$ $\times$ Angus) Angus backcross progeny, respectively, and $-P(q^{mat}Q^{pat}) - P(q^{pat}q^{mat})$ and $P(Q^{mat}q^{pat}) - P(q^{mat}q^{pat})$ for type 1 (Brahman $\times$ F$_1$) and type 2 (F$_1$ $\times$ Brahman) Brahman backcross progeny, respectively, and $P(Q^{mat}Q^{pat}) + P(Q^{mat}q^{pat}) - P(q^{mat}Q^{pat}) - P(q^{mat}q^{pat})$ for F$_2$ individuals. The following define the paternal (Pat), maternal (Mat) expression models, and null model:

PATERNAL EXPRESSION MODEL: $Y = Xb + a_{pat}P_{pat} + e$,

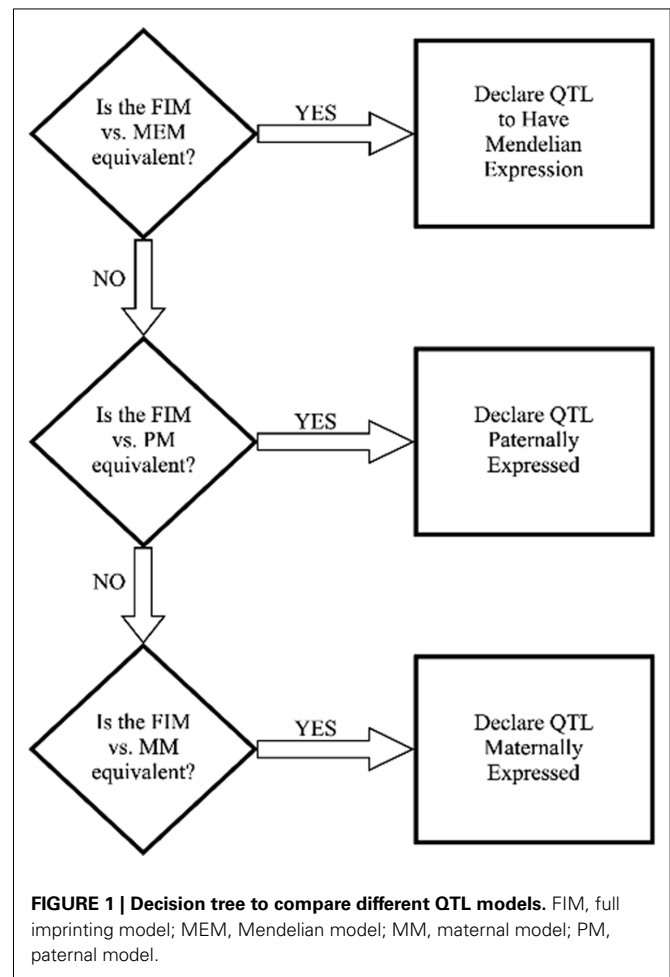MATERNAL EXPRESSION MODEL: $Y = Xb + a_{mat}P_{mat} + e$,

NULL MODEL: $Y = Xb + e$,

where all terms are as previously defined. All models were fitted at 1 cM increments along each of the chromosomes, similar to De Koning et al. (2000).

To define a QTL as being Mendelian, paternal, maternal, or partial expression QTL, the following decision tree (**Figure 1**), based on Kim et al. (2003), Thomsen et al. (2004), and McElroy et al. (2006), was used with some minor modifications for the specific tests:

If the MENDELIAN MODEL vs. the NULL MODEL was significant:

(1) The FULL IMPRINTING MODEL was tested against the MENDELIAN MODEL at the most likely QTL position detected in the full model around the region where the QTL was detected in the MENDELIAN MODEL. If this F-test was not significant, then the QTL was classified as Mend.
(2) If the FULL IMPRINTING MODEL vs. the MENDELIAN MODEL was significant, then the FULL IMPRINTING MODEL was tested against the PATERNAL and MATERNAL MODELS.
  (a) If the FULL IMPRINTING MODEL vs. the PATERNAL MODEL was not significant and the FULL IMPRINTING MODEL vs. the MATERNAL MODEL was significant at the most likely QTL position under the PATERNAL MODEL, then the QTL was classified as paternally expressed.
  (b) If the FULL IMPRINTING MODEL vs. the PATERNAL MODEL was significant and the FULL IMPRINTING MODEL vs. the MATERNAL MODEL was not significant at the most likely QTL position under the MATERNAL MODEL, then the QTL was classified as maternally expressed.
  (c) If the FULL IMPRINTING MODEL vs. the PATERNAL MODEL and the FULL IMPRINTING MODEL vs. the MATERNAL MODEL were both significant or both not significant, then the QTL was classified as partially expressed.

FIGURE 1 | Decision tree to compare different QTL models. FIM, full imprinting model; MEM, Mendelian model; MM, maternal model; PM, paternal model.

If the MENDELIAN MODEL vs. the NULL MODEL was not significant:

(1) The FULL IMPRINTING MODEL was tested against the NULL MODEL. If this test was significant, then the FULL IMPRINTING MODEL was tested against the MATERNAL MODEL and PATERNAL MODEL as described in step 2 above.
(2) If the FULL IMPRINTING MODEL vs. the NULL MODEL was not significant, then the PATERNAL MODEL and MATERNAL MODEL were tested against the NULL MODEL. If the PATERNAL MODEL vs. the NULL MODEL was significant, then the QTL was classified as paternally expressed. If the MATERNAL MODEL vs. the NULL MODEL was significant, then the QTL was classified as maternally expressed. It is unlikely that tests of both the PATERNAL and MATERNAL MODELS vs. the NULL MODEL will be significant if the test of the FULL IMPRINTING MODEL vs. the NULL MODEL is not significant.

A paternally (maternally) expressed QTL is one that shows a significant allelic effect when inherited from the sires (dams) of

progeny without showing a significant allelic effect when inherited from the dams (sires) of progeny. A partially expressed QTL shows unequal allelic effect in progeny, conditioned on the sex of the parent from which it was inherited. For all models, the estimated proportion of phenotypic variance explained by a detected QTL was calculated by comparing the reduction of the residual sums of squares with and without fitting the QTL in the model (Kim et al., 2003). For all models, fixed effects were included for year season of birth, gender, cross type (two double reciprocal backcrosses and F_2). Covariates were weaning age for WWT, yearling age for YWT, and days on feed and age at slaughter for postslaughter measures. For the QTL detected at the 5% GW level, 95% confidence intervals for the QTL location were obtained by using 10,000 bootstrap samples according to Visscher et al. (1996).

PERMUTATION TESTS

Significance thresholds to determine the presence of QTL, i.e., Full, Mend, Pat, or Mat model vs. Null model, were based on single-trait analysis under one QTL model. Permutation tests were performed with 10,000 replicates to empirically determine P values at the CW-significance level. Permutation of the phenotypes, fixed factors, and covariates to marker genotypes were restricted to within each of the five cross types. For a QTL detected at 5% CW-significance level, the P value for a GW significance level was then obtained using the Bonferroni correction:

$$P_{\text{genome - wise}} = 1 - (1 - P_{\text{chromosome - wise}})^{1/r}$$

where r is the proportion of total genome length attributed to the chromosome (De Koning et al., 2001). Significance thresholds to determine type of QTL, i.e., Full model vs. Mend, Pat or Mat model were determined at the 5% comparison-wise level. The overall significance level reached by a QTL was determined using the model that corresponded to the classification of the QTL, i.e., Mend, Full (partial), Pat, or Mat.

COMPARATIVE ANALYSIS OF GENOMIC REGIONS IN HUMAN AND MOUSE HOMOLOGS

A list of all known imprinted genes in the human and mouse genomes was compiled from the Catalog of parent-of-origin Effects Database[2], the MRC Mouse Imprinting Map Database[3] and from a structured query of publications in PubMed/MEDLINE to yield a total of 1,442 genes for analyses. These were cross-referenced with NCBI resources including OMIM, UniGene, and LocusLink. Bovine orthologs are either known or putative based on the most significant alignments produced by BLAST analyses against Bta genome sequence version 5.2. The positions of imprinted genes in the mapped QTL regions were inferred from the MARC linkage map (Ihara et al., 2004), and ILTX radiation hybrid (RH) map (Everts-van der Wind et al., 2005) because the microsatellite markers used in our study are found on these maps and can be localized in the bovine reference genome sequence. In addition, we cross-referenced the public database of the human

and mouse genomes for comparisons with cattle positions based on published comparative maps (Band et al., 2000; Everts-van der Wind et al., 2005). This was followed by presenting the genes to the gene ontology analysis database and we selected candidate genes by (1) its presence in matched syntenic regions between cattle vs. mouse and human genomes, (2) the most frequent gene ontology terms or by the terms that most closely related the gene to a quantitative trait of interest where available according to the methods described by Silva et al. (2007) slightly modified for our purposes. Briefly, we compiled a list of known and putative genes within 10 Mb of each mapped QTL region by using the NCBI Map Viewer of the bovine genome and compared them to the comprehensive list of all known and predicted imprinted genes in reported in mouse (Nikaido et al., 2003; Gregg et al., 2010). Some genes were selected to be associated with at least one growth-related phenotype, confirmed by citations on the NCBI PubMed browser[4], whereas others were included if they mapped to the closest genomic coordinates of the linkage and RH maps and the genome sequence of orthologous genes in cattle.

RESULTS

OVERALL QTL ANALYSES

The average marker POE IC derived from the simultaneous use of flanking markers was 83% (84%) under paternal (maternal) expression models and was higher than the 78% for the Mendelian model (Kim et al., 2003) in this same population. The chromosomal distribution of IC under POE and Mendelian models were generally consistent (results not shown). We also tested for SD at 1-cM intervals throughout the genome to ensure that there was no over-representation of Angus or Brahman alleles at any locus. We found only one position (7 cM on BTA2) at which there was evidence for an excess of Brahman alleles transmitted through F_1 sires (GW $P = 0.049$). Since no paternally expressed QTL were detected in this region (**Table 1**), we conclude that the SD may either be a chance event or may be due to a nearby locus that promotes meiotic drive of Brahman alleles to cause distortion of allelic segregation away from Mendelian expected ratios. The comparison-wise $-\log_{10}$ p-value corresponding to a 5% CW threshold in the gender-averaged QTL models was 2.24 ± 0.17 when averaged across models and traits. However, the $-\log_{10}$ p-values for the 5% CW thresholds were higher for the gender-specific QTL models (3.14 ± 1.15).

Twenty four POE–QTL were found on 15 autosomes with six QTL detected at the 5% GW-significance level and 18 at the 5% CW-significance level (**Table 1**). Six of the POE–QTL showed paternal expression. Three QTL were partially expressed and the remaining 15 QTL were maternally expressed. Five QTL had gender-specific effects for BWT on BTA3, 8, and 9, and for SWT and HCWT on BTA25. All of the detected QTL individually explained small portions of each trait's phenotypic variance ranging from 1.4% for the SWT QTL on BTA12 and YWT QTL on BTA2 to 5.1% for the BWT QTL on BTA9 (**Table 1**).

Table 1 | Most likely position, test statistic values and estimated effects of parent-of-origin QTL for growth and beef carcass traits that were detected with at least 5% chromosome-wise evidence for linkage.

Trait[a]	BTA	cM[b]	−logP[c]	P value[d]	QTL type[e]	Effect ± SE[f]	% σ_p^{2g}	Bracketing markers (cM)
BWT, kg	3	125	4.9	0.431	Mat-i	0.31 ± 0.46	3.8	BM2924 (113)–RM309 (128)
						2.06 ± 0.44		
	6	0	3.9	0.026	Pat	1.88 ± 0.49	2.5	ILSTS90 (0)–TEXAN24 (5)
	8	30	4.2	0.319	Partial-i	0.87 ± 0.53	4.9	BM3419 (21)–BM310 (31)–TGLA10 (33)
						0.80 ± 0.51		
						−1.64 ± 0.50		
						−0.15 ± 0.49		
						−0.10 ± 0.92		
						−3.05 ± 0.84		
	9	0	4.4	0.308	Partial-i	−0.13 ± 0.43	5.1	BMS2151 (0)–BM757 (1)–ETH225 (8)
						−1.11 ± 0.42		
						−0.93 ± 0.41		
						1.14 ± 0.41		
						0.20 ± 0.72		
						1.66 ± 0.69		
	18	91	2.9	0.271	Mat	−1.11 ± 0.34	1.8	EAC (82)–TGLA227 (92)
WWT, kg	2	2	2.3	0.602	Mat	4.67 ± 1.65	1.5	TGLA44 (0)–BM3627 (6)
	11	75	3.3	0.095	Mat	−8.50 ± 2.42	2.2	BM6445 (53)–BM746 (88)
YWT, kg	2	3	2.5	0.403	Mat	6.06 ± 2.03	1.6	BY42 (2)–BM3627 (6)
	5	64	2.3	0.629	Pat	−6.11 ± 2.19	1.4	CSSM22 (59)–IGF1 (62)–TEXAN15 (69)
SWT, kg	2	3	4.2	0.059	Mat	12.44 ± 3.11	3.1	BM81124 (1)–BY42 (2)–BM3627 (6)
	4	65	2.9	0.502	Mat	11.94 ± 3.71	2.0	BM1224 (54)–BM6458 (65)
	12	74	2.1	0.619	Pat	−9.57 ± 3.62	1.4	BM4028 (70)–EAB (73)–ILSTS33 (87)
	13	64	4.2	0.049	Mat	12.85 ± 3.18	3.1	TGLA381 (60)–RM327 (72)
	25	11	2.4	0.890	Mat-i	−14.34 ± 4.30	2.2	BMC4216 (0)–BM4005 (16)
						−6.83 ± 4.30		
HCW, kg	2	6	3.8	0.050	Mat	8.09 ± 2.12	2.8	BY42 (2)–BM3627 (6)–TGLA431 (9)
	4	65	2.9	0.341	Mat	8.12 ± 2.50	2.0	BM6458 (65)–TEXAN28 (78)
	5	71	2.9	0.427	Partial	−2.53 ± 2.32	3.0	TEXAN15 (69)–RM29 (71)–BM1819 (72)
						4.73 ± 2.32		
						9.81 ± 2.32		
	25	7	2.6	0.696	Mat-i	−10.62 ± 3.05	2.3	BMC4216 (0)–BM4005 (16)
						−4.98 ± 3.00		
ABF, mm	1	48	2.5	0.247	Mat	0.79 ± 0.27	1.7	BM4307 (37)–TGLA57 (49)
	3	62	2.2	0.489	Pat	0.90 ± 0.33	1.5	INRA3 (54)–HUJ246 (65)
	7	5	2.3	0.536	Pat	0.90 ± 0.32	1.5	BM7160 (0)–RM12 (10)
	20	56	2.7	0.369	Mat	0.82 ± 0.26	1.9	BM4107 (53)–BM5004 (73)
KPH, %	2	57	4.2	0.023	Pat	−0.14 ± 0.03	3.1	BM4440 (57)–NPY3R (58)–TEXAN8 (60)
	11	46	2.5	0.506	Mat	0.10 ± 0.04	1.7	TGLA327 (44)–CSSM16 (47)

[a]*BWT, birth weight; WWT, weaning weight; YWT, yearling weight; SWT, slaughter weight; HCWT, hot carcass weight; ABF, adjusted subcutaneous fat thickness between the 12th and 13th ribs; KPH, percentage of kidney, pelvic, and heart fat relative to carcass weight.*

[b]*Location at which the test statistic was maximized.*

[c]*Negative logarithm of the comparison-wise P-value of the test statistic against the null hypothesis of no QTL at the most likely position for the inferred QTL model.*

[d]*P-values are genome-wide levels of evidence for linkage.*

[e]*Detected QTL type: Pat, QTL with paternal expression; Mat, QTL with maternal expression; Partial, parent-of-origin QTL with expression of both parental alleles. For gender–QTL interaction analysis, -i indicates significance of the gender interaction term with the assumption of different effects for the two breed alleles.*

[f]*Estimates of paternal and maternal effects for Pat and Mat QTL, respectively, and of paternal, maternal, and dominance effects for partial QTL. For the gender-specific QTL, the estimates of the declared POE effect are in the order of male (regular font) and female (italic font) effects.*

[g]*Proportion of phenotypic variance due to the QTL, [100* (1−(residual SS under Ha/residual SS under Ho)*(df$_{Ho}$/df$_{Ha}$)], where df$_{Ho}$ and df$_{Ha}$ are degree of freedoms corresponding to the residuals under the Ho (no QTL) and Ha models, respectively.*

PARENT-OF-ORIGIN QTL ANALYSIS FOR GROWTH AND CARCASS TRAITS

Eighteen POE–QTL or 75% of the total QTL detected on 11 chromosomes influenced growth traits compared to six or 25% of POE–QTL which influenced carcass traits on six chromosomes (**Table 1**). Several maternally expressed QTL affecting postweaning growth traits were detected in the proximal region of BTA2: WWT, YWT, SWT, and HCWT (**Figure 2**). For all four QTL, the Angus allele conferred a weight advantage over the Brahman allele (**Table 1**). Two QTL affecting YWT and HCWT were detected at 64 and 71 cM on BTA5 with paternal and partial expression modes of inheritance, respectively. Significant interactions between progeny gender and POE–QTL were detected for BWT on BTA3, 8, and 9 (**Table 1**).

For the QTL on BTA3, the maternal expression was only significant in female progeny. For the partially expressed BWT QTL on BTA8, the maternally expressed and dominance effects were only significant in male and female progeny, respectively. For the partially expressed BWT QTL on BTA9, paternally expressed and dominance effects were only significant in female progeny, while the effects of maternal expression were similar between male and female progeny (**Table 1**). There were also significant interactions between progeny gender and maternally expressed QTL for SWT and HCWT on BTA25, for which the QTL effects were only significant in male progeny (**Table 1**). Since the proportions of phenotypic variance due to QTL were very small at only 1.4 ∼ 5%, and the linkage map was relatively sparse, the observed confidence intervals were relatively large (results not shown).

COMPARATIVE GENOMIC ANALYSIS OF IMPRINTED REGIONS

Table 2 summarizes our results of known bovine orthologs of genes imprinted in human and mouse that map to the bovine chromosomal regions detected as harboring imprinted QTL in

this study. This was defined as a region within 10 Mb of peak cM of estimated QTL position due to a relatively sparse linkage map and relatively large 95% confidence intervals. Our *in silico* comparative genomics analysis indicate that 32 out of 1,442 imprinted genes have been reported on the human and mouse homologs of bovine chromosomes 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, and 18, and none on BTA20 and 25. Of these, two genes (*GNAS* and *PEG3*) have experimental support for imprinting status in cattle, although the demonstrated parental allele for *GNAS* was consistent with maternally expressed QTL for SWT on BTA13 while the paternally expressed status of *ZIM2* and *PEG3* are opposite of the QTL found in this study for BWT on BTA18. Although the largest number of POE–QTL mapped to BTA2, we only found one gene (*IWS1* homolog) which recruits the HYPB/Setd2 histone methyltransferase to the RNA polymerase II elongation complex and is required for H3K36 trimethylation (H3K36me3), thereby affecting the histone modification state of active genes (Yoh et al., 2008) on the corresponding homologous human and mouse chromosomes. This may represent a novel region in the bovine genome that harbors imprinted genes affecting postnatal growth and development which are yet to be discovered in human and mouse.

DISCUSSION

PARENT-OF-ORIGIN QTL ANALYSIS AND EFFECTS

Of the 15 chromosomes identified in our study as harboring POE–QTL, 13 coincide with regions of imprinted gene locations or clusters in human and mouse species (**Table 2**) and BTA2 also point to a possible novel region in the bovine genome that require further exploration (**Table 1**). Recently, it has been shown that the common assumption of line-fixed QTL made in QTL analyses face several problems in this specific design and model assumption for detecting POE–QTL in out-crossing species like livestock (De Koning et al., 2002; Sandor and Georges, 2008). It appears that demonstrating genuine imprinting by comparing QTL allele substitution effect of a proven identity-by-descent (IBD) pair of alleles upon maternal vs. paternal transmission is difficult to achieve in livestock as it is very difficult to have a sufficiently large number of F_1 dams that have a genotype that is unambiguously IBD with that of one or more F_1 sires (Sandor and Georges, 2008). Several remedies prescribed by Sandor and Georges (2008) may not solve the inherent intractable problems of accurately estimating parental imprinting due to the unique scenarios presented by livestock breeds and breeding. Sandor and Georges (2008) argued that the ultimate proof to test parental imprinting hypothesis is the use of thousands or even millions of single nucleotide polymorphisms (SNPs) that will allow the recognition of haplotypes that are known with virtual certainty to be IBD even in the absence of pedigree data. However, our results would appear to suggest that our methodology was robust enough to identify regions with imprinted genes that may potentially underlie genuine imprinting effects in cattle.

Our study showed a putative cluster of growth-related POE–QTL on BTA2 influencing weights between weaning and slaughter. One of the reasons may be long term implementation of selection on growth in the US beef cattle during the last several decades (Koots et al., 1994a,b) causing dramatic changes of allele
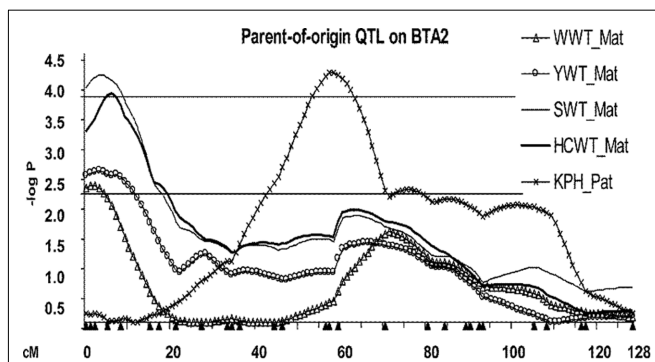

FIGURE 2 | Profile of POE–QTL on BTA2 for growth and carcass traits (WWT, weaning weight; YWT, yearling weight; SWT, slaughter weight; HCWT, hot carcass weight; KPH, percentage of kidney, pelvic, and heart fat relative to carcass weight). The negative of the logarithm (base 10) of the comparison-wise significance value is shown for the inferred QTL models against the chromosomal position. Upper and lower lines indicate the average –log$_{10}$ values of 2.24 and 3.85 across models, traits, and chromosomes for the detected QTL, representing 5% chromosome and 5% genome-wise significance thresholds, respectively. Filled triangles under the X-axis are marker positions. Mat, maternally expressed. Pat, paternally expressed.

Table 2 | Bovine orthologs of imprinted mammalian genes in human and mouse inside the regions harboring POE–QTL.

Chrm	Traits	Genomic region (Mb)	Linkage region (cM)[a]	Symbol	Description	Human location	Mouse location	Imprinting status	Type of expression	References
1	ABF, mm	37.8–52.0	35.2–46.2	RG9MTD1	RNA (guanine-9-) methyltransferase domain containing 1	3:101.3	16:56.0	IMPRINTED	P	Gregg et al. (2010)
1	ABF, mm	37.8–52.0	35.2–46.2	PCNP	PEST proteolytic signal containing nuclear protein	3:101.3	16:56.0	IMPRINTED	M	Gregg et al. (2010)
2	WWT, kg YWT, kg SWT, kg HCW, kg KPH, %	5.0–10.8	0–9.1	IWS1	IWS1 homolog (*S. cerevisiae*)	2:128.2	18:32.2	IMPRINTED	P	Gregg et al. (2010)
3	BWT, kg ABF, mm	47.3–57.1	62.4–67.9	CNN3	Calponin 3, acidic	1:95.4	3:121.1	IMPRINTED	M	Gregg et al. (2010)
3	BWT, kg ABF, mm	47.3–57.1	62.4–67.9	TMED5	Transmembrane emp24 protein transport domain containing 5	1:93.6	5:108.6	IMPRINTED	P	Gregg et al. (2010)
3	BWT, kg ABF, mm	119.1–127.9	117.8–125.2	NGEF	Neuronal guanine nucleotide exchange factor	2:233.7	1:89.4	IMPRINTED	M	Gregg et al. (2010)
3	BWT, kg ABF, mm	119.1–127.9	117.8–125.2	UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1	2:234.7	1:90.1	PREDICTED	n.d.	Brideau et al. (2010)
3	BWT, kg ABF, mm	119.1–127.9	117.8–125.2	COPS8	COP9 constitutive photomorphogenic homolog subunit 8 (Arabidopsis)	2:238.0	1:92.5	IMPRINTED	M	Gregg et al. (2010)
3	BWT, kg ABF, mm	119.1–127.9	117.8–125.2	RAMP1	Receptor (G protein-coupled) activity modifying protein 1	2:238.8	1:93.1	IMPRINTED	n.d.	Li et al. (2010)
3	BWT, kg ABF, mm	119.1–127.9	117.8–125.2	KIF1A	Kinesin family member 1A	2:241.7	1:94.9	IMPRINTED	M	Gregg et al. (2010), Li et al. (2010)
3	BWT, kg ABF, mm	119.1–127.9	117.8–125.2	MTERFD2	MTERF domain containing 2	2:242.0	1:95.2	IMPRINTED	M	Gregg et al. (2010)
3	BWT, kg ABF, mm	119.1–127.9	117.8–125.2	PASK	PAS domain containing serine/threonine kinase	2:242.0	1:95.2	IMPRINTED	n.d.	Li et al. (2010)
3	BWT, kg ABF, mm	119.1–127.9	117.8–125.2	STK25	Serine/threonine kinase 25 (STE20 homolog, yeast)	2:242.4	1:95.5	IMPRINTED	n.d.	Li et al. (2010)

(Continued)

Table 2 | Continued

Chrm	Traits	Genomic region (Mb)	Linkage region (cM)[a]	Symbol	Description	Human location	Mouse location	Imprinting status	Type of expression	References
3	BWT, kg ABF, mm	119.1–127.9	117.8–125.2	NEU4	Sialidase 4	2:242.8	1:95.9	PREDICTED	n.d.	Brideau et al. (2010)
3	BWT, kg ABF, mm	119.1–127.9	117.8–125.2	PLXNA1	Plexin A1	3:126.7	6:89.3	IMPRINTED	M	Gregg et al. (2010)
4	SWT, kg HCW, kg	70.4–81.8	63.9–72.0	HOXA10	Homeobox A10	7:27.2	6:52.2	PREDICTED	n.d.	Brideau et al. (2010)
4	SWT, kg HCW. Kg	70.4–81.8	63.9–72.0	MRPL32	Mitochondrial ribosomal protein L32	7:43.0	13:14.7	IMPRINTED	M	Gregg et al. (2010)
5	YWT, kg HCW. Kg	66.5–78.2	72.4–77.6	TDG	Thymine-DNA glycosylase	12:104.4	10:82.1	IMPRINTED	P	Gregg et al. (2010)
5	YWT, kg HCW, kg	66.5–78.2	72.4–77.6	TXNRD1	Thioredoxin reductase 1	12:104.6	10:82.3	IMPRINTED	P	Gregg et al. (2010)
5	YWT, kg HCW, kg	66.5–78.2	72.4–77.6	CKAP4	Cytoskeleton-associated protein 4	12:106.6	10:84.0	IMPRINTED	M	Gregg et al. (2010)
6	BWT, kg	5.5–19.4	6.8–15.7	SEC24D	SEC24 family, member D (*S. cerevisiae*)	4:119.6	3:123.0	IMPRINTED	P	Gregg et al. (2010)
7	ABF, mm	1.0–5.0	0–7.9	CRTC1	CREB regulated transcription coactivator 1	19:18.8	8:72.9	IMPRINTED	P	Gregg et al. (2010)
8	BWT, kg	16.3–27.2	19.1–30.7	SLC24A2	Solute carrier family 24 (sodium/potassium/calcium exchanger), member 2	9:19.5	4:86.6	IMPRINTED	P	Gregg et al. (2010)
9	BWT, kg	1.0–10.0	0–8.1	SMAP1	Small ArfGAP 1	6:71.4	1:23.9	IMPRINTED	M	Gregg et al. (2010)
11	WWT, kg KPH, %	74.1–86.8	72.4–84.5	HADHB	Mitochondrial trifunctional protein, beta subunit	2:26.5	5:30.5	IMPRINTED	P	Gregg et al. (2010)
12	SWT, kg	86.8–67.3	84.5–79.7	UBAC2	UBA domain containing 2	13:99.9	14:122.3	IMPRINTED	P	Gregg et al. (2010)
13	SWT, kg	46.6–58.4	49.9–58.9	ZMYND11	Zinc finger, MYND Domain containing 11	10:0.2	13:9.7	IMPRINTED	P	Gregg et al. (2010)
13	SWT, kg	46.6–58.4	49.9–58.9	RPS21	Ribosomal protein S21	20:61.0	2:180.0	IMPRINTED	M	Gregg et al. (2010)
13	**SWT, kg**	**46.6–58.4**	**49.9–58.9**	**GNAS**	**GNAS complex locus**	**20:57.4**	**2:174.1**	**IMPRINTED**	**M**	Ruddock et al. (2004), Sikora et al. (2011)
18	**BWT, kg**	**63.0–65.9**	**78.9–84.7**	**ZIM2**	**Zinc finger, imprinted 2**	**19:57.3**	**7:6.6**	**IMPRINTED**	**M**	Kim et al. (2004)
18	**BWT, kg**	**63.0–65.9**	**78.9–84.7**	**PEG3**	**Paternally expressed gene 3**	**19:57.3**	**7:6.7**	**IMPRINTED**	**P**	Flisikowski et al. (2010)
18	BWT, kg	63.0–65.9	78.9–84.7	APEG3	Antisense transcript gene of PEG3	19:57.3	7:6.7	IMPRINTED	P	Glasgow et al. (2005), Bischoff et al. (2009)

BWT, birth weight; WWT, weaning weight; YWT, yearling weight; SWT, slaughter weight; HCWT, hot carcass weight; ABF, adjusted subcutaneous fat thickness between the 12th and 13th ribs; KPH=percentage of kidney, pelvic, and heart fat relative to carcass weight. Gene names compiled from GenBank resources including OMIM, Unigene, LocusLink, curated imprinted genes from imprinted gene catalog (see text footnote 2) and mouse imprinting maps (see text footnote 3) and according to the HGNC. Bovine orthologs are according to B. taurus reference genome sequence version 5.2. Genes in bold have experimental proof of imprinting status in cattle. P, paternal expression, M, maternal expression, n.d., not determined.

[a]The distance in cM is according to the MARC linkage map (Ihara et al., 2004) between the markers used in our study.

frequencies for growth genes between breeds, which would enable detection of more growth QTL compared with QTL influencing composition in the breed-cross QTL models applied in this study. In addition, the identified imprinted regions may represent effects at the extreme ends of a spectrum of POE effects with potential allelic imbalance in gene expression, although more research is needed to ascertain the magnitude and direction of such effects.

Growth traits, notably BWT showed a large number of imprinted QTL, which is consistent with the known effects of genomic imprinting on growth, particularly embryonic and fetal growth (Cui et al., 2004; Constancia et al., 2005; Isles and Holland, 2005; Jiang et al., 2007; Charalambous et al., 2010). Carcass composition traits related to adiposity including ABF and KPH, had POE–QTL mapped to bovine chromosomes with relatively few known imprinted genes on their human and mouse homologs (**Table 2**). Obtaining significant results for body composition traits is consistent with imprinting effects on human adult obesity and body composition (Georges et al., 2003; Gorlova et al., 2003; Dong et al., 2005) and on adult obesity and body composition in mice (Casellas et al., 2009). It is now known that imprinting marks, such as DNA methylation and histone configurations, often persist into adulthood (Gorlova et al., 2003; Christensen et al., 2009; Trowbridge and Orkin, 2010; Woodfine et al., 2011; Wu et al., 2011), and that imprinting may play a physiological role in metabolism and body composition throughout life, thereby contributing both to normal variation and the architecture of complex traits rather than being restricted to prenatal and neonatal effects (Rance et al., 2005; Smith et al., 2006; Cheverud et al., 2008; Casellas et al., 2009; Hager et al., 2009; Garfield et al., 2011). Our current understanding of the function of imprinted genes is overwhelmingly biased toward growth and development (Constancia et al., 2005; Abu-Amero et al., 2006; Delaval et al., 2006; Fowden et al., 2006; Fradin et al., 2006; Smith et al., 2006, 2007; Wu et al., 2006; Jiang et al., 2007; Charalambous et al., 2010) and only recently have we begun to gain a better understanding in mice of the effects of genomic imprinting on physiological traits expressed long after embryogenesis and fetal development (Rance et al., 2005; Cheverud et al., 2008; Casellas et al., 2009; Hager et al., 2009; Garfield et al., 2011). The effects of imprinting on fetal and early postnatal development have been well characterized in mice (Cheverud et al., 2008; Garfield et al., 2011) but just beginning to get attention in other mammals. Wolf et al. (2008) recently reported that the effects of imprinted QTL in mice were mostly restricted to traits expressed after weaning, and they also show that the imprinting pattern of a locus can vary over ontogenetic time and, in contrast to current dogma, may often be stronger at later stages in life. This latter view is supported by recent analysis of *Grb10* gene in adult mouse where epigenetic effects began early (Charalambous et al., 2010) and persisted into late adulthood (Garfield et al., 2011).

POSITIONAL CANDIDATES IN IDENTIFIED POE–QTL REGIONS
Given the relatively large confidence intervals, it is possible that our 10 Mb intervals flanking the peak centimorgan may have underestimated the number of possible orthologs. But our analysis focused only on putative imprinted genes with experimental proof

in other species, making the size of the interval less critical in our selection of positional candidate genes. Altogether, 32 orthologous bovine genes were identified in the QTL regions homologous to human and mouse chromosomes from a pool of 1,442 known imprinted genes (**Table 2**). Although there is the possibility that one or more of these genes may be genuine positional candidates directly responsible for the imprinted QTL effects, another possibility is they are close to novel imprinted genes that are yet to be identified in human and mouse or may indicate underlying genes that are bovine-specific since imprinting status of genes are not necessarily conserved across mammalian species. The maternally expressed QTL location on BTA2 may be just one QTL manifesting at different time points on different stages of growth and development (Cheverud et al., 2008; Wolf et al., 2008; Brideau et al., 2010; Garfield et al., 2011). It is noteworthy that this region does not appear to possess a correspondingly large number of known imprinted orthologs in human and mouse (see text footnotes 1 and 2) although significant contribution of maternal effect QTL to early growth in mice appears consistent with our findings (Wolf et al., 2002; Casellas et al., 2009). Recent scans for GW imprinted QTL in mice mapped them to novel locations that have not previously been associated with imprinting effects nor previously known to harbor imprinted genes at all (Cheverud et al., 2008; Wolf et al., 2008). This is due to the fact that hitherto, most known imprinted genes were biased in location toward regions of the genome with chromosomal aberrations and biased to loci with large phenotypic effects. Therefore, only a few years after it was suggested that as many as 600 genes may be imprinted in mammals (Luedi et al., 2005), more recent research with next generation sequencing of mRNA libraries analyzed for parent-of-origin bias in expression overcame that previous bottleneck and suggest as many as 1,300 imprinted genes in mouse (Gregg et al., 2010).

Of the 32 genes mapped to the bovine QTL locations, only *PEG3* (Flisikowski et al., 2010) and *GNAS* (Khatib, 2004; Ruddock et al., 2004; Sikora et al., 2011) have experimental proof of being imprinted in cattle, while *ZIM2* found in the same domain as *PEG3* was biallelically expressed in testis (Kim et al., 2004). It is possible however, that the bovine *ZIM2* may be imprinted in other tissues of metabolic and developmental importance other than testis or even at other stages yet to be investigated. The paternally expressed *PEG3* gene (Flisikowski et al., 2010) on BTA18 lies within a QTL region identified in this study that is homologous to a well known imprinting domain. A novel mutation in this imprinting domain causing a 110-kb microdeletion results in the loss of paternal *MIMT1* expression leading to late term abortion and stillbirth in cattle (Flisikowski et al., 2010). Recently SNPs within this gene has been associated with traits related to calving, calf performance and gestation length suggesting that this domain on chromosome 18 plays a key role in regulating prenatal growth, development and fertility (Magee et al., 2010).

PARENT-OF-ORIGIN EFFECTS AND LONGITUDINAL GROWTH AND DEVELOPMENT
Phenotypic selection for growth in beef cattle has historically been very successful due to the ease of phenotype measurement and the moderate to high trait heritabilities (Koots et al., 1994a).

However, because of the moderate to high genetic correlations among growth traits at different ages (Koots et al., 1994b), selection to increase postnatal growth usually results in increased BWT and calving difficulty. This presents a special problem for understanding the genetic architecture of growth in mammalian livestock because even though phenotypic measurements represent a single point in time, phenotypes are highly correlated over an animal's life span from birth, through weaning to slaughter. From an epigenetic standpoint, imprinted genes underlying POE may change between birth and adulthood from mono-allelic to bi-allelic expression concomitant with aging (Bennett-Baker et al., 2003; Delaval et al., 2006; Fowden et al., 2006; Smith et al., 2006; Wolf et al., 2008), even switch which parental allele is expressed (Garfield et al., 2011), or the imprinting mechanism itself could exhibit polymorphism within a population (Xu et al., 1993). None of these possible mechanisms for the regulation of gene expression have been studied in cattle.

Bos belongs to the tribe Bovini and taurine and indicine cattle are considered subspecies within the *Bos* genus (Lenstra and Bradley, 1999). Crossbreeding between taurine and zebu-type cattle breeds is widely practiced to take advantage of combinations of dissimilar genotypes for traits in the crossbred progeny by exploiting heterosis. Speciation within the extant Bovini tribes began about one million years ago and is not yet complete since fertile offspring are produced by *B. taurus* × *B. indicus* crosses reflecting divergence time of only 100,000–200,000 years (Bradley et al., 1996). These may underlie significant reciprocal differences in pre- and post-weaning traits observed between *B. taurus* × *B. indicus* and *B. indicus* × *B. taurus* crosses. Reciprocal differences observed in interspecies hybrids of *Mus musculus* × *M. spretus* and *Peromyscus polionotus* × *P. maniculatus* (Vrana et al., 2000; Shi et al., 2005) which are somewhat analogous to *B. taurus* × *B. indicus* crosses result in altered embryonic and placental growth, which in *Mus musculus* × *M. spretus* has been attributed to loss of imprinting (LOI; Shi et al., 2004). This LOI suggests that an imbalance in the expression of imprinted genes could underlie the divergent growth phenotypes in reciprocal mammalian hybrids (Shi et al., 2004). This has led to the hypothesis that abnormal reprogramming after fertilization and during preimplantation development *in utero* may partly be responsible for hybrid dysgenesis, for which a strong epigenetic basis has been demonstrated (Wolf et al., 2002; Cui et al., 2004; Duselis et al., 2005; Wu et al., 2006). This may help to partly explain our results in which a preponderance of maternally expressed QTL were found to affect growth. For now, it is unclear whether these differences result from strain-specific genetic variation, sex-specific gene expression, tissue-specific gene expression, or combinations of these effects. The observation that the most severe overgrowth is accompanied by widespread relaxation of imprinting of mostly paternally expressed genes (Shi et al., 2004) will be interesting to test in *B. taurus* × *B. indicus* crosses. The on-going speciation among *Bos* may involve subtle effects of LOI that may be amenable to molecular analysis in *B. taurus* × *B. indicus* crosses across multiple generations to ascertain transgenerational effects of imprinted genes.

Our inability to confirm some previous QTL influencing growth in this population (Kim et al., 2003), under the current POE model may partly be due to (1) different methods of estimating QTL breed-of-origin; (2) exclusion of the fixed effect of families nested within cross and of the random effect for recipient dams that were fitted in the previous study (Kim et al., 2003) which may have changed significance thresholds for QTL detection. Some previous Mendelian QTL detected in this population were re-classified as POE–QTL in this study, for instance QTL for BWT on BTA3, and QTL for post-weaning growth on BTA2 with increased statistical evidence for linkage (**Table 1**; Kim et al., 2003). This appears to be largely consistent with the predictions of simulations reported by Cui (2007), Cui et al. (2007), and De Koning et al. (2002) that imprinted QTL that may otherwise remain undetected when analyzing the genome with Mendelian models may become significant when tested against a Mendelian QTL using the null hypothesis of an imprinted QTL such as the methods used in this study. The underlying challenge of segregating QTL in founder lines leading to spurious imprinted QTL detection, especially for designs with a small number of F1 sires appear to be extenuated by the large number of imprinted genes coincident with the identified bovine QTL regions with 32 imprinted orthologs found in homologs of human and mouse. It will be worthwhile in a follow up study to see if all 32 genes are also imprinted in cattle, determine if they underlie the identified POE–QTL and ascertain whether they exert any influence on these quantitative traits.

PHENOTYPIC VARIANCE AND PARENT-OF-ORIGIN QTL EFFECTS

Phenotypic variance explained by the detected POE–QTL in our study are consistent with an average of 1–4% reported in mice and may underscore the subtle effects of imprinting (Hager et al., 2009). Although these effects are individually small and not as common as additive genotypic effects, they are about as frequent as QTL with dominance effects in intercross populations (Cheverud et al., 2008), and our results appear to demonstrate that this may be typical for other similar populations. QTL found for HCWT at 71 cM on BTA5 and for BWT at BTA8 and BTA9 showed partial (unequal) expression of POE–QTL with the involvement of both parental alleles. Similar partial imprinting has been reported for imprinted QTL in mice where the difference between the two homozygotes is larger than the difference between the two heterozygotes (Wolf et al., 2008). This observation may reflect subtle differences resulting from complex molecular events underlying complex traits (Allis et al., 2007), because even in the simple case of monoallelic expression, patterns of effects on higher-order phenotypes, such as body weight and obesity, may not correspond to mRNA levels in a simple linear fashion (Cheverud et al., 2008). In addition, imprinted QTL effects may reflect strict mono-allelic expression during one stage of development/life and Mendelian expression at another stage (Bennett-Baker et al., 2003; Wolf et al., 2008) or as recently shown in mouse, a later stage switch of which parental allele becomes transcriptionally active (Garfield et al., 2011).

CONCLUSION

In conclusion, our results further demonstrate that non-Mendelian growth and carcass QTL subject to POE are not rare phenomena in livestock species and indicate the need to perform POE analyses to better understand the genetic architecture of complex traits. POE remain a complex and intriguing phenomenon to

study in mammalian livestock and more methodological work is required to characterize how imprinted genes interact with the growth trajectory over an animal's lifespan. The current paucity of known imprinted genes in the bovine genome strengthens the need to identify imprinted genes in cattle. This will enable and improve our ability to evaluate them as candidate genes underlying POE–QTL, for possible use in breeding programs under specific selection regimes such as in crossbreeding systems with specialized sire and dam lines (Vries et al., 1994; Neugebauer et al., 2010).

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