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Evaluation of Reciprocal Cross Design on Detection and Characterization of Non-Mendelian QTL in F_2 Outbred Populations: I. Parent-of-origin Effect

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ABSTRACT : A simulation study was conducted to evaluate the effect of reciprocal cross on the detection and characterization of parent-of-origin (POE) QTL in F_2 QTL populations. Data were simulated under two different mating designs. In the one-way cross design, six F_0 grand sires of one breed and 30 F_0 grand dams of another breed generated 10 F_1 offspring per dam. Sixteen F_1 sires and 64 F_1 dams were randomly chosen to produce a total of 640 F_2 offspring. In the reciprocal design, three F_0 grand sires of A breed and 15 F_0 grand dams of B breed were mated to generate 10 F_1 offspring per dam. Eight F_1 sires and 32 F_1 dams were randomly chosen to produce 10 F_2 offspring per F_1 dam, totaling 320 F_2 offspring. Another mating set comprised three F_0 grand sires of B breed and 15 F_0 grand dams of A breed to produce the same number of F_1 and F_2 offspring. A chromosome of 100 cM was simulated with large, medium or small QTL with fixed or different allele frequencies in parental breeds. A series of tests between Mendelian and POE models were applied to characterize QTL as Mendelian, paternal, maternal or partial expression QTL. The overall detection powers were similar between the two mating designs. However, the proportions of paternally expressed QTL that were declared as paternal QTL type were greater in the reciprocal cross design than in the one-way cross, and *vice versa* for Mendelian QTL. When QTL alleles were segregating in parental breeds, a significant proportion of Mendelian QTL were spuriously declared POE QTL, suggesting that care must be taken to characterize imprinting QTL in a QTL mapping population with a small number of F_1 parents. (**Key Words :** Quantitative Trait Loci, Swine, Detection Power, Imprinting, Simulation)

INTRODUCTION

Genetic improvement schemes and quantitative trait loci (QTL) mapping experiments in livestock usually assume Mendelian inheritance, in which parents contribute equally to progeny. Genomic imprinting, a non-Mendelian effect where only one of the two parental copies of a gene is expressed, has been an interesting research area in mammalian genetics due to its unique expression and inheritance mechanisms, and its important role in growth, development, and behavior (Tycko and Morison, 2002; Wilkens and Haig, 2003). One typical imprinted gene, insulin-like growth factor 2 (IGF2), influences body composition in swine (Jeon et al., 1999; Nezer et al., 1999), and a causative SNP in the IGF2 gene was identified (Nezer et al., 2003; van Laere et al., 2003). Genomic regions with imprinting or parent-of-origin (POE) effects can be detected using QTL interval mapping in F_2 crosses between lines or breeds that segregate for marker alleles because of the ability to follow parental origin. Development and application of statistical methods to detect chromosomal regions or QTL with imprinting effects in a breed-cross design were implemented for F_2 crosses of swine breeds (de Koning et al., 2000; Thomsen et al., 2004; Kim et al., 2005a), and there have been several reports suggesting that non-Mendelian or POE effects on quantitative traits in swine exist (de Koning et al., 2001; Kim et al., 2007).

Most F_2 mating designs in pig QTL populations are based on one-way cross, *i.e.*, all grandsires are from one breed and all grand-dams from anther breed (Kim et al., 2005c; Shulin et al., 2005; Choi et al., 2006). The one-way mating design can generate progeny with phenotypic differences due to breed-specific maternal environmental effects, mitochondrial inheritance, genomic imprinting, or sex chromosome-linked effects (Thallman et al., 1992). Recently, reciprocal cross designs have been used for QTL detection in swine, in which individuals of two breeds were used as both grand-sires and grand-dams (Rohrer et al., 2006). However, characterization of imprinting QTL due to the reciprocal cross is unknown in F_2 outbred populations.

The purpose of this study was to evaluate the effect of

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reciprocal mating designs on detection and characterization of POE QTL using a series of Mendelian and non-Mendelian QTL mapping models.

MATERIALS AND METHODS

QTL analysis models

Least squares interval mapping models that are based on a breed-cross F_2 design were used for Mendelian and POE QTL detection (Haley et al., 1994; de Koning et al., 2000). The models assume that alternate breed alleles are fixed in grand-parental breeds, and the Mendelian (Mend) model is:

$$\text{Mend model: } Y = Xb + aP_a + dP_d + e$$

where Y is a vector of phenotypes of F_2 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 two breed homozygotes; d is dominance effect, modeled as the difference between the average of two breed heterozygotes and the homozygote midpoint; P_a and P_d are vectors containing functions for genotype probabilities for each animal at the chromosomal position of the putative QTL conditional on flanking marker genotypes. The second model was the full (partial) expression model (Full):

$$\text{Full model: } Y = Xb + a_{pat}P_{pat} + a_{mat}P_{mat} + dP_d + e$$

where Y, X, b, and e are as previously defined 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 one breed allele, Q, vs. the other breed allele, q, from its sire, P_{mat} probabilities of inheriting one breed allele, Q vs. the other breed allele, q from its dam, and P_d probabilities of being heterozygous.

The next models are the paternal (Pat) and maternal (Mat) expression models, and the null model:

$$\text{paternal expression model: } Y = Xb + a_{pat}P_{pat} + e$$

$$\text{maternal expression model: } Y = Xb + a_{mat}P_{mat} + e$$

$$\text{null model: } Y = Xb + e$$

where all terms are as previously defined. All models were tested at each 1 cM position along the chromosomes.

To define a QTL as a Mendelian, paternal, maternal, or partial expression QTL, the following decision tree, based on trees already described as used previously (Thomsen et al., 2004; Kim et al., 2005a; McElroy et al., 2006), was used with some minor modifications for the specific tests:

If the Mend model vs. the null model was significant:

The Full model was tested against the Mend model at the most likely position under the full model around the region where QTL was detected in the Mend model. If this *F*-test was not significant, then the QTL was classified as a Mend QTL.

If the Full model vs. the Mend model was significant, then the Full model was tested against the Pat and Mat models.

If the Full model vs. the Pat model was not significant and the Full model vs. the Mat model was significant at the most likely position under the Pat model, then the QTL was classified as a paternally expressed QTL.

If the Full model vs. the Pat model was significant and the Full model vs. the Mat model was not significant at the most likely position under the Mat model, then the QTL was classified as a maternally expressed QTL.

If the Full model vs. the Pat model and the Full model vs. the Mat model were both significant or both not significant, then the QTL was classified as a partially expressed QTL.

If the Mend model *vs.* the null model was not significant:

The Full model was tested against the null model. If this test was significant, then the Full model was tested against the Mat model and Pat model as described above.

If the Full model vs. the null model was not significant, then the Pat model and Mat model was tested against the null model. If the Pat model vs. the null model was significant, then the QTL was classified as a paternally expressed QTL. If the Mat model vs. the null model was significant, then the QTL was classified as a maternally expressed QTL.

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 is one that shows an allelic effect when inherited from the sires and dams of progeny, but the effect is different depending on the sex of the parents from which it was inherited.

For QTL detection, i.e., Full, Mend, Pat, or Mat model vs. null model, empirically derived 5% chromosome-wise significance thresholds were used for each model. Lack-of-fit tests, *i.e.*, Full model vs. Mend, Pat or Mat model, were performed at a 5% comparison-wise level using standard *F* statistic thresholds.

Simulation

To compare the power and ability to distinguish alternative Mendelian or POE QTL types, F_2 populations were simulated based on two designs: one-way cross and reciprocal cross. The one-way cross design comprised six F_0 grandsires of one breed and 30 F_0 grand-dams of another

Table 1. Expected QTL effects and proportion of F_2 phenotypic variances due to the QTL used to simulate large, medium, and small QTL with Mendelian and parent-of-origin inheritance patterns in an F_2 breed cross

QTL inheritance mode	Genetic variance	QTL allele frequency[a]	QTL effect[b]			% of F_2 variance explained[c]		
			Large	Medium	Small	Large	Medium	Small
Additive (a)	$0.5a^2$	1.0/0.0	0.800	0.500	0.320	32.0	12.5	5.1
		0.8/0.2	0.480	0.300	0.192	11.5	4.5	1.8
Complete dominance	$0.5a^2+0.25d^2$	1.0/0.0	0.654	0.408	0.261	32.0	12.5	5.1
($a = d$)		0.8/0.2	0.392/0.235	0.245/0.147	0.157/0.094	9.1	3.5	1.5
Paternal or	a^2	1.0/0.0	0.566	0.354	0.226	32.0	12.5	5.1
maternal expression		0.8/0.2	0.340	0.212	0.136	11.5	4.5	1.8

[a] Upper and lower values for each QTL inheritance mode are expectation under the condition that alternate QTL alleles are fixed (1.0/0.0) or differently distributed (0.8/0.2) within parental breeds, respectively.

[b] Different QTL effects under varying genetic models were set such that large, medium and small QTL explained 32%, 12.5% and 5.1% of the phenotypic variance, respectively. Error variances were set equal to 0.680, 0.875 and 0.949 for the large, medium and small QTL, respectively, such that overall phenotypic variances were 1, when alternate breed alleles are fixed in parental breeds. When the allele frequencies differ, expected values of additive and dominant effects are $\Delta f \times a$ and $\Delta f^2 \times d$ (de Koning et al., 2002), where Δf is allele frequency difference (FD) in grand-parental breeds, *e.g.,* for large complete dominant QTL with FD (0.8/0.2), Δf = 0.8-0.2 = 0.6, and $\Delta f \times a$ = 0.6×0.654 = 0.392, and $\Delta f^2 \times d = 0.6^2 \times 0.654$ = 0.235.

[c] Expected values of proportion of phenotypic variance due to QTL are obtained using the formulae of genetic variance by functions of QTL effects for the given QTL inheritance modes.

breed, to generate 10 F_1 offspring per dam. Sixteen F_1 sires and 64 F_1 dams were randomly chosen to produce a total of 640 progeny. In the reciprocal cross design, three F_0 grand sires of breed A were mated to 15 F_0 grand-dams of breed B to generate 10 F_1 offspring per dam. Eight F_1 sires and 32 F_1 dams were randomly chosen to produce 10 F_2 offspring per dam, for a total of 320 F_2 offspring. Also, using three F_0 grand sires of breed B and 15 F_0 grand-dams of breed A, the same number of F_1s were generated and chosen to produce a total of 320 F_2 offspring.

A chromosome of 100 cM was simulated with 11 markers at 10 cM intervals. Markers were simulated with four alleles with frequencies of 0.5, 0.3, 0.1, 0.1 in one breed and 0.1, 0.1, 0.3, 0.5 in the other breed. This simulation was based on the marker information content in an experimental QTL population using F_0s of Korean Native Pig and Yorkshire (data not shown). A series of biallelic additive, dominant, paternally, and maternally expressed QTL were simulated at position 75 cM on the chromosome with large, medium and small effects, which explain 32%, 12.5% and 5.1% of phenotypic variances, respectively. Table 1 explains the expected QTL effects and genetic variances for various levels of QTL size and alternate allele frequencies. The QTL genotypes for the F_0 parents were drawn from two alternative sets of frequencies of the favorable QTL allele in the two parental breeds: 1.0:0.0 and 0.8:0.2. Three-hundred replicate data sets were simulated for each set. Thresholds at the 5% chromosome-wise level for QTL detection for the three models were derived from three-thousand replicates with QTL effects set to zero.

RESULTS

Power to detect QTL and their characterization

Table 2 presents the power to detect Mendelian and POE QTL and proportions of declared QTL types in one-way and reciprocal mating designs. Nearly all QTL were detected when alternate QTL alleles were fixed in parental breeds across all QTL types, sizes and mating designs. However, the power to detect QTL decreased when alternate alleles were not fixed in parental breeds; this was more pronounced for small QTL. Additive QTL had a greater detection power than dominance QTL, *e.g.,* 10% difference for small QTL with segregating alleles in parental breeds in the one-way cross design (Table 2). Also, the proportions of detected QTL were greater for maternally expressed QTL compared to paternally expressed QTL, *e.g.,* 97% vs. 94% for medium QTL with segregating alleles in grand parental breeds in the reciprocal design. This result was consistent with the simulation results of de Koning et al. (2002), in which maternally expressed QTL had a greater power to detect QTL than paternally expressed QTL when a small number of F_1 sires were used. Generally, the overall detection powers were similar in the two mating designs across all QTL types, sizes, and allele frequency difference (FD) (Table 2).

Detected QTL were well defined as their corresponding QTL types under alternate allele fixation in parental breeds, *e.g.,* more than 90% of Mendelian, paternally, and maternally expressed QTL were classified as Mend, Pat and Mat QTL, respectively, for a given QTL size and mating design. However, when QTL alleles were segregating in parental breeds, the proportion of QTL that were declared as their respective QTL types decreased. Also, a significant proportion of Mendelian QTL were spuriously declared as POE QTL, and vice versa, *e.g.,* for the dominance QTL in the one-way cross design, only 52.3% of the small QTL were classified as Mend QTL and 16% of the QTL as paternal, maternal or partially expressed QTL (Table 2).

The proportion of additive or dominant QTL that were declared as Mend QTL was marginally greater in the one-

Table 2. Power to detect QTL under different genetic models and proportion of detected QTL declared as Mendelian, paternally, maternally, or partially expressed QTL in different inheritance modes, sizes, and mating designs

QTL size (allele frequency)[b]	One-way cross[a]					Reciprocal cross[a]				
	Detection power (%)[c]	Paternal QTL[d]	Maternal QTL[d]	Mend QTL[d]	Partial QTL[d]	Detection power(%)[c]	Paternal QTL[d]	Maternal QTL[d]	Mend QTL[d]	Partial QTL[d]
Additive										
Large (1.0/0.0)	100	0.0	0.0	95.0	5.0	100	0.0	0.0	93.7	6.3
Large (0.8/0.2)	100	1.0	2.7	83.3	13.0	100	1.7	2.3	81.3	14.7
Medium (1.0/0.0)	100	0.0	0.0	96.0	4.0	100	0.0	0.0	93.7	6.3
Medium (0.8/0.2)	95.3	4.0	6.0	81.7	3.7	96.7	5.3	4.7	82.3	4.3
Small (1.0/0.0)	100	1.3	2.3	94.0	2.3	99.7	1.7	2.7	93.0	2.3
Small (0.8/0.2)	78.7	9.7	6.3	61.3	1.3	75.7	10.7	7.0	57.3	0.7
Dominance										
Large (1.0/0.0)	100	0.0	0.0	94.7	5.3	100	0.0	0.0	95.0	5.0
Large (0.8/0.2)	99.3	1.0	1.3	84.3	12.7	99.0	1.3	3.7	80.0	14.0
Medium (1.0/0.0)	100	0.0	0.0	97.3	2.7	100	0.0	0.0	94.0	6.0
Medium (0.8/0.2)	92.7	4.3	5.0	80.7	2.7	91.3	5.0	5.3	76.0	5.0
Small (1.0/0.0)	99.7	0.7	0.7	94.3	4.0	99.3	0.7	0.3	93.7	4.7
Small (0.8/0.2)	68.3	8.3	6.0	52.3	1.7	65.7	6.7	4.7	52.7	1.7
Paternal										
Large (1.0/0.0)	100	93.7	0.0	0.0	6.3	100	97.0	0.0	0.0	3.0
Large (0.8/0.2)	98.3	90.7	0.0	1.3	6.3	98.7	92.3	0.0	1.7	4.7
Medium (1.0/0.0)	100	94.0	0.0	0.0	6.0	100	95.7	0.0	0.0	4.3
Medium (0.8/0.2)	94.3	83.7	0.0	7.0	3.7	94.0	86.3	0.3	4.0	3.3
Small (1.0/0.0)	99.7	91.3	0.0	3.7	4.7	99.7	92.0	0.0	2.3	5.3
Small (0.8/0.2)	76.3	62.0	0.0	10.7	3.7	76.0	59.7	1.7	10.7	4.0
Maternal										
Large (1.0/0.0)	100	0.0	94.0	0.0	6.0	100	0.0	95.7	0.0	4.3
Large (0.8/0.2)	99.7	0.0	94.3	0.3	5.0	99.7	0.0	96.0	0.7	3.0
Medium (1.0/0.0)	100	0.0	95.3	0.0	4.7	100	0.0	93.7	0.0	6.3
Medium (0.8/0.2)	96.0	0.3	86.7	4.7	4.3	97.0	0.7	84.0	8.0	4.3
Small (1.0/0.0)	99.7	0.0	90.3	3.3	6.0	99.7	0.0	92.7	4.3	2.7
Small (0.8/0.2)	76.7	1.3	58.0	13.7	3.7	75.0	1.3	58.7	12.0	3.0

[a] In the one-way cross design, six F_0 grand sires of one breed and 30 F_0 grand dams of another breed generate 10 F_1 offspring per dam. Sixteen F_1 sires and 64 F_1 dams are randomly chosen to produce 10 F_2 offspring per F_1 dam, for a total of 640 F_2 offspring. In the reciprocal design, one mating set comprised three F_0 grand sires of A breed and 15 F_0 grand dams of B breed to generate 10 F_1 offspring per dam. Eight F_1 sires and 32 F_1 dams are randomly chosen to produce 10 F_2 offspring per F_1 dam, for a total of 320 F_2 offspring. Another mating set used three F_0 grand sires of B breed and 15 F_0 grand dams of A breed to produce the same number of F_1 and F_2 offspring as the previous mating set.

[b] Large, medium and small indicate QTL effects, such that QTL effects explain 32%, 12.5% and 5.1% of phenotypic variance, respectively, under the condition that alternate alleles are fixed within F_0 grandparents from the two breeds.

[c] Proportion of replicates in which QTL were detected at 5% chromosome-wise level in at least one of the paternal, maternal, Mendelian, or partial expression models.

[d] Relative proportion of declared QTL type for the detected QTL. Paternal (maternal) QTL: 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. Mend QTL: shows additive and/or dominant effects. Partial QTL: shows an allelic effect when inherited from the sires and dams of progeny, but the effect is different depending on the sex of the parents from which it was inherited.

way cross compared to the reciprocal cross design for all QTL sizes and FD, *e.g.,* 84.3% vs. 80% for large dominant QTL when alternate alleles segregated in parental breeds. However, for paternally expressed QTL, the proportion of QTL declared as Pat QTL was consistently greater in the reciprocal cross design, *e.g.,* 97% vs. 93.7% for large QTL under alternate allele fixation in parental breeds in the reciprocal and the one-way cross, respectively. There was no consistent difference between the two mating designs in the proportion of maternal expression QTL that were classified as Mat QTL for a given QTL size and FD (Table 2).

Estimates of QTL effects

Table 3 lists the means of estimates of QTL effects by QTL that were declared Pat, Mat or Mend QTL. Mean estimates of effects of the QTL declared as their corresponding QTL types were generally similar to their expectation under alternate allele fixation in parental breeds, but estimates were biased upward when alternate alleles segregated, which was more pronounced for small QTL.

Estimates for detected QTL that were not classified as their corresponding QTL types were significantly downward biased, *e.g.,* for the large additive QTL with FD

Table 3. Mean and standard deviation (in parentheses) of estimates of QTL effects for paternally, maternally or Mendelian expressed QTL, depending on the difference in QTL modes, sizes, and mating designs for an F_2 breed cross under two alternate mating designs

QTL size	One-way cross[a]				Reciprocal cross[a]			
(allele frequency)[b]	Paternal[c]	Maternal[c]	Additive[d]	Dominant[d]	Paternal[c]	Maternal[c]	Additive[d]	Dominant[d]
Additive								
Large (1.0/0.0)	-	-	0.80 (0.05)	0.01 (0.08)	-	-	0.79 (0.05)	0.00 (0.07)
Large (0.8/0.2)	0.20 (0.01)	0.20 (0.04)	0.51 (0.01)	0.01 (0.09)	0.26 (0.06)	0.20 (.06)	0.49 (0.12)	0.00 (0.08)
Medium (1.0/0.0)	-	-	0.51 (0.06)	0.00 (0.09)	-	-	0.51 (0.06)	-0.01 (0.08)
Medium (0.8/0.2)	0.19 (0.05)	0.18 (0.04)	0.33 (0.08)	0.00 (0.10)	0.22 (0.04)	0.18 (.04)	0.32 (0.08)	-0.01 (0.09)
Small (1.0/0.0)	0.23 (0.04)	0.20 (0.04)	0.32 (0.06)	0.01 (0.01)	0.22 (0.05)	0.20 (.02)	0.32 (0.06)	0.00 (0.09)
Small (0.8/0.2)	0.15 (0.03)	0.14 (0.02)	0.24 (0.05)	0.01 (0.12)	0.14 (0.03)	0.14 (.02)	0.25 (0.05)	0.00 (0.11)
Dominance								
Large (1.0/0.0)	-	-	0.66 (0.05)	0.66 (0.08)	-	-	0.65 (0.05)	0.65 (0.07)
Large (0.8/0.2)	0.23 (0.04)	0.19 (0.05)	0.40 (0.10)	0.29 (0.14)	0.19 (0.05)	0.20 (.05)	0.40 (0.12)	0.27 (0.13)
Medium (1.0/0.0)	-	-	0.41 (0.06)	0.41 (0.08)	-	-	0.41 (0.06)	0.40 (0.08)
Medium (0.8/0.2)	0.17 (0.05)	0.16 (0.03)	0.27 (0.07)	0.19 (0.12)	0.19 (0.05)	0.15 (.04)	0.28 (0.08)	0.17 (0.11)
Small (1.0/0.0)	0.14 (0.01)	0.17 (0.04)	0.26 (0.06)	0.27 (0.10)	0.17 (0.01)	0.16 (.00)	0.26 (0.06)	0.27 (0.09)
Small (0.8/0.2)	0.14 (0.02)	0.13 (0.02)	0.20 (0.06)	0.15 (0.13)	0.14 (0.03)	0.15 (.02)	0.21 (0.07)	0.14 (0.11)
Paternal								
Large (1.0/0.0)	0.57 (0.04)	-	-	-	0.56 (0.03)	-	-	-
Large (0.8/0.2)	0.36 (0.09)	-	0.17 (0.03)	0.17 (0.02)	0.35 (0.10)	-	0.19 (0.01)	0.01 (0.10)
Medium (1.0/0.0)	0.36 (0.04)	-	-	-	0.36 (0.04)	-	-	-
Medium (0.8/0.2)	0.24 (0.06)	-	0.20 (0.05)	0.01 (0.14)	0.24 (0.06)	-0.11 (0.00)	0.18 (0.11)	-0.10 (0.18)
Small (1.0/0.0)	0.23 (0.04)	-	0.21 (0.06)	0.06 (0.15)	0.23 (0.04)	-	0.25 (0.06)	0.05 (0.12)
Small (0.8/0.2)	0.17 (0.04)	-	0.20 (0.03)	0.03 (0.13)	0.17 (0.04)	-0.02 (0.12)	0.20 (0.07)	0.00 (0.14)
Maternal								
Large (1.0/0.0)	-	0.57 (0.03)	-	-	-	0.56 (0.03)	-	-
Large (0.8/0.2)	-	0.36 (0.09)	0.20 (0.00)	-0.08 (0.00)	-	0.35 (0.09)	0.29 (0.05)	-0.06 (0.11)
Medium (1.0/0.0)	-	0.36 (0.04)	-	-	-	0.35 (0.04)	-	-
Medium (0.8/0.2)	0.12 (0.00)	0.23 (0.05)	0.16 (0.11)	-0.02 (0.17)	0.14 (0.03)	0.23 (0.06)	0.24 (0.05)	-0.03 (0.09)
Small (1.0/0.0)	-	0.23 (0.04)	0.25 (0.02)	0.03 (0.08)	-	0.23 (0.04)	0.23 (0.05)	0.03 (0.12)
Small (0.8/0.2)	0.06 (0.10)	0.17 (0.03)	0.19 (0.05)	-0.01 (0.16)	-0.01 (0.13)	0.17 (0.04)	0.21 (0.03)	0.03 (0.12)

[a, b] Described in Table 2.

[c] For paternally or maternally expressed QTL, expected QTL effects (a) are 0.566, 0.354, and 0.226 with allele frequency (1.0/0.0), and 0.34, 0.21, and 0.14 with allele frequency (0.8/0.2), for large, medium and small QTL, respectively.

[d] For additive QTL ($d = 0$), expected additive (dominant) QTL effects are 0.8 (0.0), 0.5 (0.0), and 0.32 (0.0) with allele frequency (1.0/0.0), and 0.48 (0.0), 0.30 (0.0), and 0.19 (0.0) with allele frequency (0.8/0.2), respectively. For dominance QTL ($a = d$), expected additive (dominant) QTL effects are 0.65 (0.65), 0.41 (0.41) and 0.26 (0.26) with allele frequency (1.0/0.0), and 0.39 (0.24), 0.25 (0.15) and 0.16 (0.09) with allele frequency (0.8/0.2), respectively.

= 0.6 that were declared Pat QTL in the one-way cross, the estimate of paternal expression effect was 0.20 (expectation was 0.34). The exceptions to this were the paternally (maternally) expressed QTL that were falsely declared partially expressed, for which the estimates of paternal (maternal) QTL effects in the Full model were similar to those of the respective effects of Pat (Mat) type QTL (results not shown).

For Mendelian QTL that were declared Mend QTL, the estimates of QTL effects were more biased and slightly greater in the one-way cross than in the reciprocal cross when alternate alleles were not fixed in the parental breeds, e.g., 0.51 vs. 0.49 and 0.29 vs. 0.27 for additive and dominant effects of large additive and dominance QTL, respectively (Table 3). However, there were no significant differences between the two mating designs in estimates of QTL effect for paternally or maternally expressed QTL that were declared as their corresponding types.

Estimates of QTL position

Position estimates of the detected QTL that were declared as their corresponding types were close to unbiased (75 cM) and had high precision (low standard deviation) when alternate alleles were fixed in parental breeds across all QTL types, sizes, and mating designs. However, position estimates tended to be biased and less precise when alternate allele frequencies differed or detected QTL were not classified as their corresponding QTL types, which was more pronounced when QTL effects were small (results not shown). There were no significant differences between the two mating designs in position estimates of the detected QTL that were declared as their corresponding QTL types across all QTL types and sizes (results not shown).

DISCUSSION

The results of our simulation confirmed previous reports (Alfonso and Haley, 1998; de Koning et al., 2002), in which the power to detect Mendelian or POE QTL decreased in the breed-cross QTL model when alternate breed-specific QTL alleles were not fixed in grand-parental breeds, because QTL effects that were based on the differences between breed-origin alleles were diluted when some of the breed-specific alleles were not inherited to F_2s from their corresponding F_0 grand-parental breeds. The decreased proportion of QTL detection differed depending on QTL mode, *i.e.,* dominance QTL had smaller power to detect QTL compared to additive, paternally or maternally expressed QTL (Table 2). However, these results were not surprising, because the decreasing magnitudes of QTL effect are much greater for dominant QTL. That is, expected values of additive and dominance effects are $\Delta f \times a$ and $\Delta f^2 \times d$, respectively (de Koning et al., 2002), where Δf is allele frequency difference (FD) in grand-parental breeds, such that for the large complete dominant QTL with FD (0.8/0.2), $\Delta f = 0.8\text{-}0.2 = 0.6$, $\Delta f \times a = 0.6 \times 0.654 = 0.392$, and $\Delta f^2 \times d = 0.6^2 \times 0.654 = 0.235$, which explains the smaller proportion of F_2 phenotype variance compared to the large additive or POE QTL (Table 1).

Generally, overall detection powers were similar between the two mating designs for a given QTL type, size, and FD. However, the proportions of detected QTL that were declared as their corresponding QTL differed between the two crosses. For example, paternally expressed QTL had a greater proportion of detected QTL that were classified as Pat QTL in the reciprocal cross design compared to the one-way cross, while there were no consistent differences between the two mating designs in the proportion of maternally expressed QTL that were declared as Mat QTL (Table 2). As described in our previous simulation study about combined line-cross and half-sib analysis (Lee et al., 2007), the use of a small number of F_1 sires, which is a common practice in most porcine QTL mapping populations, may cause biased selection of F_1 sires, *i.e.,* genetic materials of parental breeds are not randomly transmitted to F_2 progeny due to sampling effects of F_1 sires. This would cause QTL alternate alleles to be distributed in unexpected patterns (*e.g.,* homozygous F_1 sires for the QTL), causing a smaller proportion of paternally expressed QTL to be classified as Pat QTL when QTL alleles segregate within parental breeds. However, the reciprocal cross, in which F_1 sires are sired or dammed by both breeds, can offset non-random transmissions of alternate alleles to F_1 sires, resulting in a greater proportion of paternally expressed QTL to be declared Pat QTL under the different allele frequencies in the parental breeds. However, for maternally expressed QTL, a much larger number (64) of F_1 dams were used (compared to 16 F_1 sires in each cross design), such that the chance of selecting large proportions of homozygous F_1 dams would not occur non-randomly.

Dominance QTL had a marginally greater proportion of QTL with Mend QTL type in the one-way cross than in the reciprocal cross, especially when QTL effects were large or medium with segregating alternate alleles within parental breeds (Table 2). However, the method of classifying Mend QTL in this study is not the best strategy when QTL have Mendelian inheritance with segregating alternate alleles in the parental breeds. In this case, we proposed an alternate strategy to better characterize Mendelian QTL type in terms of allele frequency in parental breeds (Kim et al., 2005b; Lee et al., 2007).

When QTL alleles were segregating in parental breeds, a significant proportion of Mendelian QTL were spuriously declared Pat, Mat, or partially expressed QTL across all QTL sizes, and this spurious QTL declaration rate did not diminish even when both breeds were used as grand-sires or grand-dams in the reciprocal cross design (Table 2). This result was consistent with the previous report by de Koning et al. (2002), in which more than 10% of large or medium Mendelian QTL were spuriously detected as imprinting QTL when few F_1 sires were used to detect QTL with segregating alleles within parental breeds. As de Koning et al. (2002) indicated, use of a few F_1 parents is not a good option for the generation of F_2 breed-cross populations to detect imprinting QTL. Also, a significant proportion of POE QTL were spuriously declared Mendelian QTL in both mating designs when the QTL were small and the alternate alleles were not fixed in parental breeds (Table 2). These simulation results suggest that great care must be taken to characterize QTL inheritance mode, i.e., POE *vs.* Mendelian expression, especially when QTL magnitude is small in a QTL mapping population with a small number of F_1 parents.

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REFERENCES

Alfonso, L. and C. S. Haley. 1998. Power of different F_2 schemes for QTL detection in livestock. Anim. Sci. 66:1-8.

Choi, B. H., J. S. Lee, G. W. Jang, H. Y. Lee, J. W. Lee, K. T. Lee, H. Y. Chung, H. S. Park, S. J. Oh, S. S. Sun, K. H. Myung, I. C. Cheong and T. H. Kim. 2006. Mapping of the porcine Calpastatin gene and association study of its variance with economic traits in pigs. Asian-Aust. J. Anim. Sci. 19:1085-1089.

De Koning, D. J., A. P. Rattink, B. Harlizius, J. A. M. van Arendonk, E. W. Brascamp and M. A. M. Groenen. 2000. Genome-wide scan for body composition in pigs revealed important role of imprinting. PNAS. 97:7947-7950.

De Koning, D. J., A. P. Rattink, B. Harlizius, J. A. M. van Arendonk, E. W. Brascamp and M. A. M. Groenen. 2001. Detection and characterization of quantitative trait loci for meat quality traits in pigs. J. Anim. Sci. 79:2812-2819.

De Koning, D. J., H. Bovenhuis and J. A. M. van Arendonk. 2002. On the detection of imprinted quantitative trait loci in experimental crosses of outbred species. Genetics 161:931-938.

Haley, C. S., S. A. Knott and J.-M. Elsen. 1994. Mapping quantitative trait loci in crosses between outbred lines using least squares. Genetics 136:1195-1207.

Jeon, J. T., O. Carlborg, A. Tornsten, E. Giuffra, V. Amarger, P. Chardon, L. Anderson-Elklund, K. Andersson, I. Hansson, K. Lundstroem and L. Andersson. 1999. A paternally expressed QTL affecting skeletal and cardiac muscle mass in pigs maps to the IGF2 locus. Nature Genetics 21:157-158.

Kim, J.-J., M. F. Rothschild, J. Beever, S. Rodriguez-Zas and J. C. M. Dekkers. 2005a. Joint analysis of two breed cross populations in pigs to improve detection and characterization of quantitative trait loci. J. Anim. Sci. 83:1229-1240.

Kim, J.-J., H. Zhao, H. Thomsen, M. F. Rothschild and J. C. M. Dekkers. 2005b. Combined line-cross and half-sib QTL analysis of crosses between outbred lines. Genet. Res. 85:235-248.

Kim, T. H., B. H. Choi, H. K. Lee, H. S. Park, H. Y. Lee, D. H. Yoon, J. W. Lee, G. J. Jeon, I. C. Cheong, S. J. Oh and J. Y. Han. 2005c. Identification of quantitative traits loci (QTL) affecting growth traits in pigs. Asian-Aust. J. Anim. Sci. 18: 1524-1528.

Kim, E. H., B. H. Choi, K. S. Kim, C. K. Lee, B. W. Cho, T.-H. Kim and J.-J. Kim. 2007. Detection of Mendelian and parent-of-origin quantitative trait loci in a cross between Korean Native Pig and Landrace I. growth and body composition traits. Asian-Aust. J. Anim. Sci. 20:669-676.

Lee, Y.-M., E.-H. Kim and J.-J. Kim. 2007. Evaluation of reciprocal cross design on detection and characterization of Mendelian QTL in F2 outbred populations. Asian-Aust. J. Anim. Sci. 20:1625-1630.

McElroy, J., J.-J. Kim, D. Harry, S. Brown, J. C. M. Dekkers and S. Lamont. 2006. Trait loci affecting white meat percent and other growth and carcass traits in commercial broiler chickens. Poult. Sci. 85:593-605.

Nezer, C., L. Moreau, B. Brouwers, W. Coppieters, J. Detileux, R. Hanset, L. Karim, A. Kvasz, P. LeRoy and M. Georges. 1999. An imprinted QTL with major effect on muscle mass and fat deposition maps to the IGF2 locus in pigs. Nature Genetics 21:155-156.

Nezer, C., C. Collette, L. Moreau, B. Brouwers, J.-J. Kim, E. Giuffra, N. Buys, L. Andersson and M. Georges. 2003. Haplotype sharing refines the locataion of an imprinted quantitative trait loci with major effect on muscle mass to a 250-kb chromosome segment containing the porcine IGF2 gene. Genetics 165:277-285.

Rohrer, G. A., R. M. Thallman, S. Shackelford, T. Wheeler and M. Koohmaraie. 2006. A genome scan for loci affecting pork quality in a Duroc-Landrace F2 population. Anim. Genet. 37:17-27.

Shulin, Y., Z. Zhu and K. Li. 2005. Potential of the quantitative trait loci mapping using crossbred population. Asian-Aust. J. Anim. Sci. 18:1675-1683.

Thallman, R. M., J. O. Sanders and J. F. Taylor. 1992. Non-Mendelian genetic effects in reciprocal cross Brahman× Simmental F_1 calves produced by embryo transfer. Beef Cattle Research in Texas, PR-5053:8-14. Tex. Agri. Exp. Sta., College Station.

Thomsen, H., H. K. Lee, M. F. Rothschild, M. Malek and J. C. M. Dekkers. 2004. Characterization of quantitative trait loci for growth and meat quality in a cross between commercial breeds of swine. J. Anim. Sci. 82:2213-2228.

Tycko, B. and I. M. Morison. 2002. Physiological functions of imprinted genes. J. Cellular Physiol. 192:245-258.

Van Laere, A. S., M. Nguyen, M. Braunschweig, C. Nezer, C. Collette, L. Moreau, A. L. Archibald, C. S. Haley, N. Buys, M. Tally, G. Andersson, M. Georges and L. Andersson. 2003. A regulatory mutation in IGF2 causes a major QTL effects on muscle growth in the pig. Nature 425:832-836.

Wilkins, J. F. and D. Haig. 2003. What good is genomic imprinting: the function of parent-specific gene expression. Nature Review Genetics 4:1-10.