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A large-sample QTL study in mice: III. Reproduction

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Abstract

Using lines of mice having undergone long-term selection for high and low growth, a large-sample ($n \approx 1000$ F_2) experiment was conducted to gain further understanding of the genetic architecture of complex polygenic traits. Composite interval mapping on data from 10-week-old F_2 females ($n = 439$) detected 15 quantitative trait loci (QTLs) on 5 chromosomes that influence reproduction traits characterized at day 16 of gestation. These QTL are broadly categorized into two groups: those where effects on the number of live fetuses (LF) were accompanied by parallel effects on the number of dead fetuses (DF), and those free of such undesirable effects. QTL for ovulation rate (OR) did not overlap with QTL for litter size, potentially indicating the importance of uterine capacity. Large dominance effects were identified for most QTL detected, and overdominance was also present. The QTL of largest effects were detected in regions of Chromosome 2, where large QTL effects for growth and fatness have also been found and where corroborating evidence from other studies exists. Considerable overlap between locations of QTL for reproductive traits and for growth traits corresponds well with the positive correlations usually observed among these sets of phenotypes. Some support for the relevance of QTL × genetic background interactions in reproduction was detected. Traits with low heritability demand considerably larger sample sizes to achieve effective power of QTL detection. This is unfortunate as traits with low heritability are among those that could most benefit from QTL-complemented breeding and selection strategies in food animal production.

Reproductive efficiency is a major component of food production systems, and its improvement leads to economic benefits of large impact (e.g., Lush 1945; Bonsma 1965; Lasater 1972; Neumann and Lusby 1986; Beef Improvement Federation 1990). Unfortunately, reproductive phenotypes normally have low heritabilities and are difficult to improve genetically. Identification of individual genetic effects in the form of quantitative trait locus (QTL) detection would be relevant to eventual development of DNA-assisted genetic improvement paradigms. QTL studies targeting female reproductive traits have, however, been scarce (e.g., Rothschild et al. 1996; Kirkpatrick et al. 1998; Rohrer et al. 1999; Spearow et al. 1999) relative to those for traits such as growth and body composition. This is partly due to the intrinsic difficulties in measuring female reproduction, requiring production of one additional generation. In addition, the relatively low heritabilities of female reproductive characters also pose challenges for QTL analyses in terms of reduced power of detection.

Mice provide a powerful experimental model that facilitates enhanced genetic dissection of complex traits, often, as is the case for female reproductive traits, with potentially important biomedical implications for related traits in humans (Frankel 1995; Avner 1998; Moore and Nagle 2000; Lee 2002). In the context of a large experiment to evaluate the genetic architecture of complex traits using lines selected long-term for high and low growth (Rocha et al. 2004a,b), we now report QTL results obtained for

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correlated female reproductive traits such as litter size and its component traits ovulation rate and embryonic survival.

Materials and methods

Relevant information pertaining to the parental high-growth (M16i) and low-body-weight (L6) selection lines, development of the F_2 intercross population and marker genotyping have been presented in a companion paper (Rocha et al. 2004a). Only methods relevant to the specific female reproduction phenotypes evaluated and their statistical data analysis are described here.

Phenotypes. Ten-week-old F_2 females, of a cross between the high-growth M16i line and the low-body-weight L6 line, were exposed to unrelated F_1 males (B6C3F1/J) until a copulatory plug was detected. Pregnant females (n = 439) were subsequently euthanized at day 16 of gestation to obtain counts of the number of *corpora lutea* (OR) and numbers of live (LF) and dead (DF) fetuses. Three estimates of embryonic survival rates were subsequently computed: preimplantation survival {PRES = [(LF+DF)/OR]*100}, post-implantation survival {POSTS = [LF/(LF+DF)]*100}, and total survival (TOTS = [LF/OR]*100). In a preliminary study to evaluate correlated responses to selection for growth on reproductive phenotypes, least-squares means for the M16i and L6 selection lines (n = 10 females per line) were, respectively, 14.4 vs. 6.8 for OR, 11.5 vs. 6.2 for LF, and 79.5% vs. 90.6% for TOTS.

Marker linkage map. Recombination frequencies and genetic distances of the marker linkage map constructed with data only from the pregnant females used in this study exhibited small fluctuations relative to the marker map constructed for the full population (Rocha et al. 2004a). However, the overall agreement between the two correlated maps was reasonable and the female-specific map (not shown) was used for all QTL analyses for reproductive traits.

Data analyses. Descriptive statistics for the six reproductive traits measured in this study are presented in Table 1. Pairwise phenotypic correlations are shown in Table 2. Appropriate statistical models were identified for each trait by fitting generalized liner models (PROC GLM; SAS Institute Inc. 1985) including fixed effects of replicate/parity, full-sib family/litter, and respective interactions, if significant.

Table 1. Descriptive statistics for reproductive traits in this study[a]

Traits[b]	μ	σ	*Range*
OR	12.3	2.1	7–21
LF	9.2	2.8	1–17
DF	1.2	1.5	0–11
PRES (%)	84.5	17.2	11.1–100
POSTS (%)	88.4	14.3	21.4–100
TOTS (%)	74.8	20.0	11.1–100

[a]All traits measured at day 16 of gestation in 439 F_2 females exposed to mating at 10 weeks of age.
[b]OR, LF, DF, PRES, POSTS, and TOTS are ovulation rate (number of *corpora lutea*), Number of live fetuses, number of dead fetuses, preimplantation embryo survival {[(LF + DF)/OR]*10}, postimplantation fetal survival {[(LF/(LF + DF)]*100}, and total embryo and fetal survival [(LF/OR)*100].

With the exception of LF, all reproductive traits required data transformations to stabilize and normalize their variances, although the subsequent implementation of a permutation approach for QTL significance threshold determinations (Churchill and Doerge 1994) somewhat minimized the relevance of the need for these transformations. A logarithmic transformation was adopted for OR, a square-root transformation for DF, while a weighted arc sine transformation (Freeman and Tukey 1950) was utilized for embryo survival traits. With the exception of that for DF, all transformations were fairly successful. The necessity for these transformations and the relative inadequacy of that for DF reflect the fact that all these traits conform to binomial or ordinal distributions. However, studies addressing this issue (Hackett and Weller 1995; Visscher et al. 1996; Rebai 1997; Rao and Li 2000; Kadarmideen and Dekkers 2001) agree that more sophisticated statistical approaches to these types of traits, like threshold and logistic models, offer only minor advantages relative to linear models based on normal distributions like those adopted in this study.

For QTL analyses, besides unadjusted-trait models, three sets of covariate adjustments were implemented: (1) 6-week body weight, (2) OR, and (3) both 6-week body weight and OR. These statistical adjustments respectively represent attempts to identify QTLs possibly impacting reproductive traits through pathways other than those contributing to overall growth and body size, and QTLs involved in specific mechanisms of uterine capacity (Christenson et al. 1987). For composite interval mapping (CIM; Zeng 1993, 1994; Basten et al. 2001), a 0.01 threshold was adopted in the forward–backward stepwise regression procedure utilized to select background factors.

Table 2. Phenotypic correlations (top row) and QTL congruencies[a] (bottom row) among the reproduction and growth traits

Traits[b]	*OR*	*LF*	*DF*	*PRES*	*POSTS*	*TOTS*	*WT6*	*WT10*
OR	1.0	0.48	0.06[ns]	−0.13	0.08[ns]	−0.06[ns]	0.42	0.38
		0.0	0.0	0.0	NE	0.0	0.11	0.11
LF	—	1.0	−0.41	0.63	0.56	0.83	0.33	0.28
			0.33	0.75	NE	0.40	0.11	0.11
DF	—	—	1.0	0.10	−0.94	−0.50	0.03[ns]	0.07[ns]
				0.25	NE	0.25	0.06	0.06
PRES	—	—	—	1.0	0.03[ns]	0.80	0.11	0.08[ns]
					NE	0.60	0.17	0.17
POSTS	—	—	—	—	1.0	0.61	0.04[ns]	−0.01[ns]
						NE	NE	NE
TOTS	—	—	—	—	—	1.0	0.11	0.05[ns]
							0.24	0.22
WT6	—	—	—	—	—	—	1.0	0.69
								0.67
WT10	—	—	—	—	—	—	—	1.0

[a]QTLs common to both traits (overlapping confidence intervals) as a proportion of the total number of QTLs detected for the two traits. Comparisons between correlations and congruencies should be made using absolute values.
[b]OR, LF, DF, PRES, POSTS, TOTS, WT6, and WT10 are ovulation rate (number of *corpora lutea*), number of live fetuses, number of dead fetuses, preimplantation embryo survival {[(LF + DF)/OR]*100}, postimplantation fetal survival {[(LF/(LF + DF)]*100}, total embryo and fetal survival [(LF/OR)*100], body weight (females only) at 6 weeks, and body weight (females only) at 10 weeks. Correlations were significant ($p < 0.05$) unless otherwise noted (ns). No QTLs were detected for POSTS so congruencies were not estimated (NE).

An initial set of 100 permutations (Churchill and Doerge 1994) for each trait revealed considerable trait differences with respect to estimated genomewide significance thresholds. Hence, these reproductive traits were divided into four sets for this particular purpose. One thousand permutations were separately conducted for DF, PRES, and POSTS (including the respective covariate adjustments), yielding 0.05 genomewide significance threshold logarithm of odds (LOD) scores of 4.1, 4.3, and 4.4, respectively. The remaining characters (OR, LF, TOTS) were treated as a composite trait for which a joint total of 1000 permutations were also conducted, resulting in a permutation-derived 0.05 genomewide significance threshold LOD score of 3.3 that was adopted for all of these three traits. These significance thresholds do not reflect adjustments that account for the fact that multiple traits were analyzed, but these are usually never adopted in exploratory QTL studies of this type due to the consequences that would then result for the statistical power of the experiments.

Results

Although F_2 females were mated at 10 weeks of age, correlations obtained between the reproductive traits measured in this study and 6-week weight (WT6) were slightly higher than those for 10-week weight (Table 2). Thus, WT6 was used to adjust reproductive traits in some of the exploratory QTL models that were evaluated. Relationships between the reproductive traits and WT6 fit the expected linear trend with a positive regression coefficient (e.g., Kirkpatrick et al. 1998), with heavier females displaying better reproductive performance. Only the relationship between OR and WT6 displayed a curvilinear nature, but even this was only a slight departure from the linear trend. The relationships between the embryo survival traits and OR also fit a linear trend, with a negative regression coefficient as expected.

QTL analyses. Consideration of the covariate adjustments for WT6 and OR in the context of the models fitted for some of the traits yielded QTL results that were in general very similar to those obtained from models without such adjustments. Therefore, only QTL results from unadjusted models are presented here. These results are detailed in Tables 3, 4, and 5. The QTL congruencies among these reproductive traits and among these and selected growth traits presented in Table 2.

A total of 15 QTLs were detected on 5 chromosomes and attributed locus symbols following the Mouse Genome Database (MGD; www.informatics.jax.org/) guidelines: 3 QTLs were detected for OR and for LF, 1 QTL was detected for DF, 4 QTLs were detected for PRES and for TOTS, and no QTLs were detected for POSTS. With a single exception (QTL for TOTS on MMU1), *M16i* alleles had additive effects that increased numerical values of the reproductive traits studied (Table 3). This was also true for the QTL detected for DF, for which the *M16i*-inherited allele increased the number of dead fetuses.

Table 3. QTLs detected and respective statistics by chromosome

MMU	*Symbol*[a]	*Flanking markers*[b]	*Position*[c] *(cM)*	a[d]	d[e]	*%V*[f]	*LOD*	*Other studies*[g]
1	*Estq4*	*180–72*	41.0 29.8–49.5	−0.07	−3.8	4.2	3.5	R
2	*Lfq2*	*6–133*	38.4 37.1–40.9	0.57	0.27	13.2	7.7	K, S
2	*Dfq1*	*6–133*	41.6 32.2–49.2	0.12	11.5	51.5	4.4	K, S, R
2	*Espq1*	*6–133*	44.1 36.6–49.8	0.86	0.51	43.2	6.7	K, S, R
2	*Estq1*	*6–133*	50.1 44.4–62.7	0.07	−15.2	39.2	6.4	R
2	*Espq2*	*133–224*	66.8 53.4–74.0	0.18	−1.8	6.3	6.0	R
2	*Lfq1*	*133–224*	70.2 56.5–77.2	0.29	−0.99	8.4	8.2	R
2	*Estq2*	*133–224*	70.2 62.7–78.9	0.23	−1.3	6.7	6.4	R
2	*Espq4*	*224–22*	77.3 74.0–83.0	0.29	−0.57	5.9	5.3	R
8	*Orq3*	*4–31*	24.9 14.0–33.0	0.25	0.09	3.4	3.4	R
8	*Orq1*	*31–121*	46.3 33.0–55.5	0.33	−0.02	6.7	3.5	R
10	*Espq3*	*65–35*	48.9 28.5–55.9	0.28	1.0	11.0	5.5	C, R
10	*Lfq3*	*65–35*	50.2 26.5–58.5	0.23	1.1	8.0	3.7	C, R
10	*Estq3*	*65–35*	52.7 32.5–58.5	0.29	1.2	11.2	4.8	C, R
11	*Orq2*	*2–4*	16.1 ?–37.0	0.21	0.67	3.9	3.5	R

[a]*Orq, Lfq, Dfq, Espq,* and *Estq* are symbols attributed to QTLs detected for OR, LF, DF, PRES, and TOTS, respectively, representing the traits: ovulation rate (number of *corpora lutea*), number of live fetuses, number of dead fetuses, preimplantation embryo survival {[(LF + DF)/OR]*100}, and total embryo and fetal survival [(LF/OR)*100]. Numeric indices of QTLs reflect a descending rank of their maximum LOD scores within trait.
[b]MIT markers (e.g., within MMU1, 180 represents *D1Mit180*).
[c]Approximate positions (Mouse Genome Database) of maximum likelihood peaks (top) and respective one LOD confidence intervals (bottom). A ''?'' indicates that a confidence interval extends to the beginning or end of a chromosome.
[d]Additive effect (Falconer and Mackay 1996) in phenotypic SD units (transformed scale). Negative values indicate increasing effect of the *L6* allele.
[e]Degree of relative dominance: 0 indicates additivity, 1 indicates full dominance of the *M16i* allele, and −1 indicates full dominance of the *L6* allele. Values outside of this range indicate overdominance.
[f]Percentage of phenotypic variance accounted for by QTL.
[g]Studies detecting QTLs for similar traits in the same genomic region, listed in order of location on each chromosome (from proximal to distal). C, Collins et al. (1993); K, Kirkpatrick et al. (1998); and S, Spearow et al. (1999). QTL for growth traits detected in the same genomic region in this study (Rocha et al. 2004a) are also referenced here (R).

Large dominance effects were evident for most QTL, and evidence for significant overdominance effects was also present (Tables 3 and 4). Reproductive traits, primarily of low heritability, and important components of overall fitness exhibit appreciable heterosis, which, under classical and prevailing quantitative genetics theory, implies relevance of dominant gene action in their genetic architecture (Falconer and Mackay 1996; Merila and Sheldon 1999). These concepts are validated by the average, maximum, and minimum values reported for the degrees of relative dominance of the QTL effects detected for the different reproductive traits (Table 4). The strong overdominance effect of the QTL for DF (*Dfq1*) explains the large apparent discrepancy between the percentage of variation accounted for by the QTL and the percentage of the F_2 range that is accounted for by its additive effects ($2a$; Table 5).

Similar to results for growth and body composition (Rocha et al. 2004a,b), genomic regions of Chromosome 2 exhibited particularly strong and potentially biologically relevant effects on reproductive phenotypes (Table 3). Chromosomal likelihood plots for MMU2 are presented in Figure 1. Highly significant evidence of transmission ratio distortion was observed along this chromosome (Table 6), possibly reflecting QTL effects detected for

Table 4. Summary of estimates of QTL effects and gene action across reproduction traits

Trait[a]	*No. QTL*[b]	*No. Chr*[b]	*Avg. a*[c]	*Max. a*	*Min. a*	*Avg. d*[d]	*Max.*[d]	*Min. d*
OR	3	2	0.26	0.33	0.21	0.25	0.67	−0.02
LF	3	2	0.36	0.57	0.23	0.13	1.1	−0.99
DF	1	1	0.12	—	—	11.5	—	—
PRES	4	2	0.40	0.86	0.18	−0.22	1.0	−1.8
POSTS	0	0	—	—	—	—	—	—
TOTS	4	3	0.17	0.29	−0.07	−2.9	1.2	−15.2

[a]OR, LF, DF, PRES, POSTS, and TOTS are ovulation rate (number of *corpora lutea*), number of live fetuses, number of dead fetuses, preimplantation embryo survival {[(LF + DF)/OR]*100}, postimplantation fetal survival {[LF/(LF + DF)]*100}, and total embryo and fetal survival [(LF/OR)*100].
[b]Number of QTLs and number of chromosomes in which QTLs were detected for the trait.
[c]Average of absolute values of additive effects (Falconer and Mackay 1996) in phenotypic SD units (transformed scale).
[d]Average of degree of directional dominance (not average of absolute values of *d*).

embryonic survival in this region. The transmission ratio distortion is represented by a considerable excess of *M16i* allele homozygotes, in agreement with QTL results showing that *M16i* alleles increase embryo and fetal survival. Interestingly, Siracusa et al. (1989, 1991) and Montagutelli et al. (1996) have

Table 5. Summary of magnitudes of QTL effects across reproduction traits

Trait[a]	*Avg. %Var*[b]	*Max. %Var*	*Min. %Var*	*Total %Var*[c]	*Avg. CI*[d]
OR	4.7	6.7	3.4	9.9 (10.1)	20.8 (22.5–19.0)
LF	9.9	13.2	8.0	32.0 (37.8)	18.8 (32.0–3.8)
DF	51.5	—	—	51.5 (5.2)	17.0 —
PRES	16.6	43.2	5.9	51.6 (79.0)	17.6 (27.4–9.0)
POSTS	—	—	—	— —	— —
TOTS	15.3	39.2	4.2	40.7 (33.6)	20.1 (26.0–16.2)

[a]OR, LF, DF, PRES, POSTS, and TOTS are ovulation rate (number of *corpora lutea*) number of live fetuses, number of dead fetuses, preimplantation embryo survival {[(LF + DF)/OR]*100}, postimplantation fetal survival {[LF/(LF + DF)]*100}, and total embryo and fetal survival [(LF/OR)*100].
[b]%Var refers to percentage of phenotypic variance accounted for by QTLs detected for the trait.
[c]Total percentage of phenotypic variance accounted for by all QTLs detected for the trait. In parenthesis is the percentage of the F_2 range accounted for when additive effects (2*a*) of all QTLs detected for the trait are summed (transformed scale).
[d]Average length (range) of the one LOD confidence intervals (CIs) defined for the trait QTLs (situations where one of the CI boundaries could not be defined are excluded from this average). In parenthesis are the corresponding maximum and minimum lengths of such CIs.

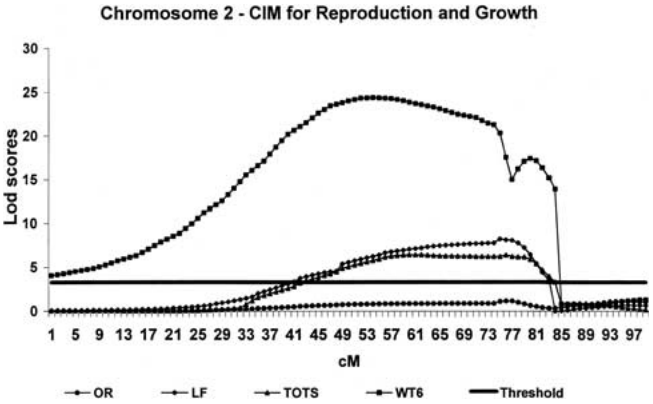

Fig. 1. Likelihood plots for Chromosome 2 from application of composite interval mapping for OR, LF, TOTS, and WT6.

also reported deviations from Mendelian inheritance for this central region of MMU2.

An interaction involving the QTL for PRES on MMU10 (*Espq3*; Table 3) and the effect of family/litter was significant ($p = 0.017$), suggesting the presence of QTL× environment effects, or alternatively, QTL× genetic background effects on reproduction. A possible representation of this interaction is graphically provided in Figure 2, where families/litters exhibiting the same mode of gene action for this QTL were clustered, their QTL genotypic values averaged, and represented together.

Discussion

The search for QTLs influencing female reproductive characteristics was part of a large experiment to understand the genetic architecture of many complex traits. For the growth traits in this study (Rocha et al. 2004a), a total of 89 QTL were detected for 9 characteristics. In contrast, only 15 QTLs were de-

Table 6. Evidence for transmission ratio distortion on Chromosome 2

Marker	*Location*[a]	*M16i/M16i*[b]	*M16i/L6*[b]	*L6/L6*[b]	*Chi-square*
		251[c]	501[c]	251[c]	
D2Mit6	12.5	262	525	216	6.4*
D2Mit133	77.8	324	541	138	75.2***
D2Mit224	83.2	326	537	140	74.0***
D2Mit22	97.6	293	539	171	35.3***
D2Mit49	107.1	267	528	208	9.7**
D2Mit148	126.2	255	504	244	0.3

[a]Based on linkage map (cM) calculated from this population.
[b]*M16i/M16i*, number of F2 mice homozygous for *M16i* allele; *M16i/L6*, number of F2 mice heterozygous for *M16i* and *L6* alleles; *L6/L6*, number of F2 mice homozygous for *L6* allele.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[c]Values based on Mendelian (1:2:1) expectations.

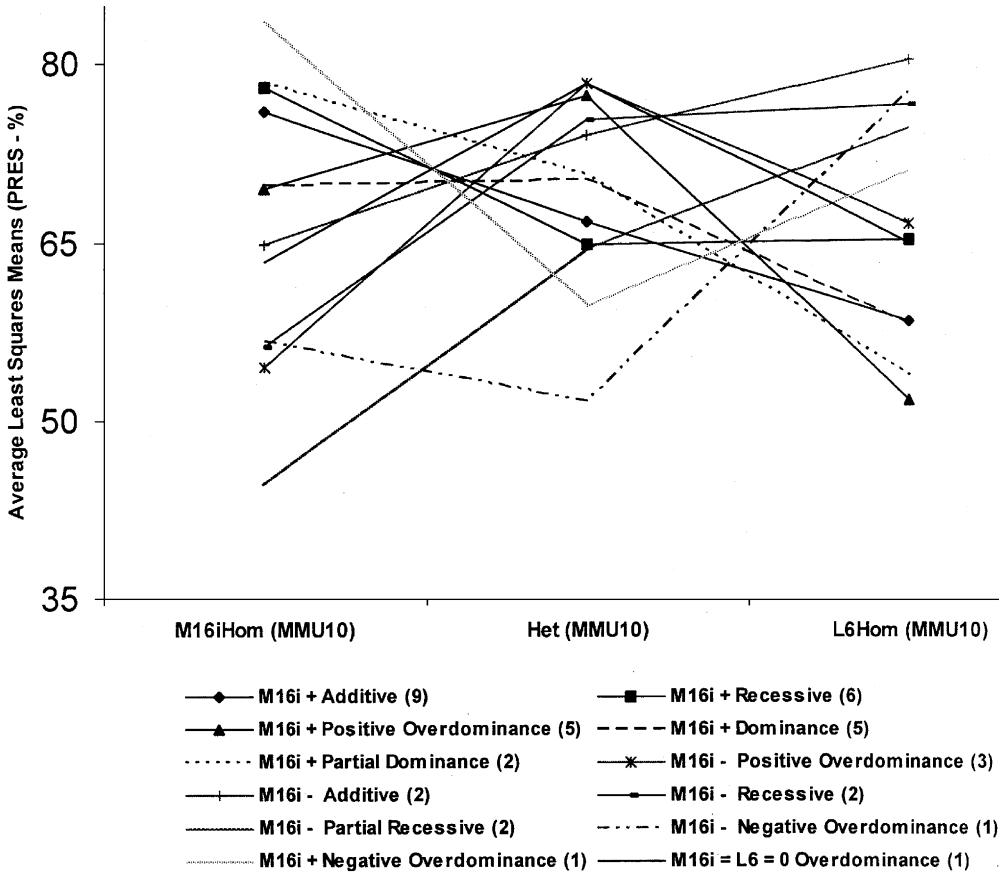

Fig. 2. Graphical representation of the interaction detected between the QTL for PRES on MMU10 (*Espq3*) and the effect of F_2 family/litter, as evaluated from the linked-marker effect for *D10Mit65*. Families/litters exhibiting the same mode of gene action for this QTL are clustered, their QTL genotypic values averaged, and represented together. The symbols + and – indicate, respectively, an increasing or decreasing additive effect of the *M16i* allele on the phenotypic measurements for PRES. Numbers of families/litters for each cluster are in parentheses.

tected for the six reproduction traits. Part of this difference is due to sample size since more than twice as many records were available for growth-related phenotypes that were measured in both sexes. However, the lower heritability of reproduction is likely to be another important component of this difference, indicating that considerably larger sample sizes will be necessary if the same effective power is to be accomplished in QTL detection studies that target traits with low heritability. This is a challenging aspect of QTL analysis, since low-heritability traits would be among those that could most benefit from QTL-complemented breeding and selection strategies in livestock production systems. Other studies have produced similar results with respect to the scarcity of QTLs detected for reproductive traits (e.g., Kirkpatrick et al. 1998; Spearow et al. 1999), but it is possible that, with proportionally larger sample sizes, numbers and distributions of QTL effects for reproduction would approach those found for growth traits (Rocha et al. 2004a).

Instances of linked QTLs in MMU2 and MMU8 (Table 3) may represent artifacts of composite interval mapping, requiring the implementation of multiple-QTL models (Kao et al. 1999) to adequately resolve whether one or more QTLs are present. These issues will also be the subject of future experimental studies, including fine-mapping. Minimum values for additive and variance effects of the QTLs detected for reproductive traits are considerably larger than those corresponding minima reported for growth QTLs (Rocha et al. 2004a) in this study. This may reflect the characteristic potential for upward bias that has been attributed to QTL studies of less-than-ideal sample sizes (Beavis 1998; Melchinger et al. 1998; Utz et al. 2000).

Large dominance effects were evident for most reproductive QTLs detected, matching theoretical expectations for these traits, which usually exhibit considerable heterosis (Falconer and Mackay 1996). Some large overdominance effects were also observed, corroborating the relevance of this mode of

gene action for traits related to overall fitness, as has also been noted by Kirkpatrick et al. (1998) and Brunsch et al. (1999). Also matching expectations were the variance components results, with litter (family of dam) effects being considerably less important as sources of variation for these reproductive traits than they were for early growth traits (data not shown; Rocha et al. 2004a).

Interestingly, there was no congruency between QTLs detected for OR and those detected for the other reproductive traits, despite the significant phenotypic correlations present especially between ovulation rate and numbers of live fetuses. Although we have not estimated the genetic correlations between traits, this result may indicate that QTL detected for litter size and for embryonic survival reflect components of uterine capacity (Christenson et al. 1987). Detected QTLs for live fetuses (as a proxy for litter size) were either associated with QTLs for dead fetuses (e.g., MMU2 QTL for *Lfq2*) or appeared in the absence of such an association (e.g., MMU2 and MMU10 QTLs for *Lfq1* and *Lfq3*). However, no QTLs were found for postimplantation embryo survival. A QTL study that specifically targeted components of uterine capacity in mice was that of Moce et al. (2004), but no overlap between QTL detected in their study and the present study was identified.

Almost all genomic regions where QTLs were identified for reproductive traits also harbored QTLs for growth traits (Rocha et al. 2004a), agreeing well with the positive correlations usually observed between these two sets of traits (Collins et al. 1993; Kirkpatrick et al. 1998). Previous studies have found that a region of MMU2 plays the most significant role in the selection response for growth and body composition of the M16 line (Pomp et al. 1994; Drudik et al. 1995). Thus, it is not surprising that QTLs in this region also exert the greatest influence on reproductive phenotypes in the context of this M16i × L6 cross. Reproduction QTLs on MMU2 are similar in location and large magnitude to those found for growth and body composition traits (Rocha et al. 2004a,b), re-emphasizing the remarkable influence of this genomic region on the control of economically and biomedically relevant complex traits (Lembertas et al. 1997; Pomp 1997; Mehrabian et al. 1998). The most proximal of these QTLs (*Lfq2* and *Espq1*) are specifically corroborated by findings from other reproductive QTL studies (Kirkpatrick et al. 1998; Spearow et al. 1999), which identified QTLs for litter size and hormone-induced ovulation rate, respectively.

Alternative interpretations of the transmission ratio distortion, such as potential maintenance of parental line heterozygosity in this genomic region, are possible. However, Siracusa et al. (1989, 1991) and Montagutelli et al. (1996) have also identified somewhat similar situations of deviations from Mendelian inheritance associated with this same region of MMU2, in the context of mouse interspecific crosses. A more thorough investigation of these common and intriguing findings in different mouse crosses is warranted. Future QTL analyses should also make an effort to model and account for this transmission ratio distortion effect to prevent biases that may derive from it, even if such biases are expected to be of relatively minor significance and to have little impact on the overall validity of reported QTL.

The interaction detected with the effect of family/litter for one of the QTLs in MMU10 (Fig. 2) suggests the possible relevance of epistatic (or, alternatively, QTL × maternal environment) effects for these reproductive traits, perhaps underlying their low heritabilities, and illustrating how expectations of additivity can sometimes be unwarranted with respect to the interpretation and utilization of QTL data and results (Rocha et al. 1995). Moce et al. (2004) also report QTLs with large dominance effects affecting components of litter size on Chromosomes 1 and 10, but their estimated map locations are either considerably more proximal (MMU1) or more distal (MMU10) than those for QTLs detected in this study. Spearow et al. (1999) report yet another reproductive QTL on Chromosome 10, but the map location reported is considerably more proximal than that for the QTL detected on MMU10 in this study. A marginally significant QTL for litter size reported by Collins et al. (1993) on MMU10, however, falls in the same genomic location as that harboring the *Lfq3* QTL detected in this study.

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