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Quantitative Trait Loci for Murine Growth

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ABSTRACT

Body size is an archetypal quantitative trait with variation due to the segregation of many gene loci, each of relatively minor effect, and the environment. We examine the effects of quantitative trait loci (QTLs) on age-specific body weights and growth in the F_2 intercross of the LG/J and SM/J strains of inbred mice. Weekly weights (1–10 wk) and 75 microsatellite genotypes were obtained for 535 mice. Interval mapping was used to locate and measure the genotypic effects of QTLs on body weight and growth. QTL effects were detected on 16 of the 19 autosomes with several chromosomes carrying more than one QTL. The number of QTLs for age-specific weights varied from seven at 1 week to 17 at 10 wk. The QTLs were each of relatively minor, subequal effect. QTLs affecting early and late growth were generally distinct, mapping to different chromosomal locations indicating separate genetic and physiological systems for early and later murine growth.

UNTIL recently studies of the inheritance of complex characters, such as body size and morphology, have been restricted to purely quantitative analyses of the portions of population variability due to inherited genetic *vs.* other factors (FALCONER 1989). Our understanding of the genetic basis for quantitative characters has been hampered by the large number and small effect of the individual genes involved in their inheritance, the so-called polygenes or quantitative trait loci (QTLs). The underlying genetic basis of complex characters, or their genetic architecture, has been assumed to be based on the joint action of many genes, each of relatively small effect. Because of their relatively small effects, the biological and physiological properties of QTLs are poorly understood. However, recent developments in molecular and statistical genetics (LANDER and BOTSTEIN 1989; DIETRICH *et al.* 1992, 1994) have allowed the measurement of individual gene effects on complex morphological characters to proceed. In this paper, we consider the effects of QTLs on murine growth.

Body weight or size in general has long been considered as a paradigm for quantitative inheritance. The original work on quantitative inheritance by GALTON (1889) included studies of stature in humans. Likewise, body weight has been the object of genetic experiments on mice and other animals (GOODALE 1938, 1941; MACARTHUR 1944). This is due to size's biological role regulating a host of allometric (size-related) morphological and physiological characters (HUXLEY 1932; PETERS 1983; SCHMIDT-NIELSEN 1984), its relative ease of measurement, and its genetic characteristics. Body weight variation in mice is normally distributed and seems to be controlled by many genes, each with relatively small additive effects on the phenotype (FALCONER 1953; CHAI 1956b). Thus, it fits the quantitative genetic model for continuous variation quite well (FALCONER 1989). The ubiquitous importance of body size scaling in physiological and morphological features indicates that QTLs for body size will also have pleiotropic effects on many other biologically important characters.

Body size growth in mice follows a sigmoidal curve with increases in growth rate to ~3 wk followed by a slow decrease in growth rate to ~60 or 70 days. The form of the growth curve and general dynamics of growth in mice is typical for eutherian mammals (TANNER 1963; RUTLEDGE *et al.* 1972; RISKA *et al.* 1984). Body size in mice continues to increase after 70 days, but this growth is at a very slow rate and does not significantly involve osteological characters.

In rodents, body size growth occurs through different physiological mechanisms at different life history stages. After ~2–3 wk of age, growth is controlled through the action of the growth hormone axis (GREENSPAN and BAXTER 1994; PARKS *et al.* 1995), much of the effect of growth hormone being mediated by insulin-like growth factor I (IGF-1) (VAN DEN BRANDE 1993; LEROITH *et al.* 1995). Normal variation in this late postnatal growth period is likely to be produced by genes downstream from these physiological regulators. In contrast, pre- and neonatal growth seem more closely related to insulin-like growth factor-II (IGF-2) (D'ERCOLE and UN-

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DERWOOD 1986; SIZONENKO and AUBERT 1986; DECHIARA *et al.* 1990) and local growth factors (RAPPAPORT 1993).

Quantitative genetic studies indicate that individual genes may have opposite pleiotropic effects on early and late growth. For example, genes causing relatively fast early growth may also cause slower than average later growth (CHEVERUD *et al.* 1983; RISKA *et al.* 1984; LEAMY and CHEVERUD 1984). This suggestion is based on the negative genetic correlation observed between early and late growth rates in randombred mice (RISKA *et al.* 1984). Negative genetic correlations indicate the negative pleiotropic effect of single genes on early and late growth or linkage disequilibrium between separate genes affecting early and late growth. As further evidence for antagonistic pleiotropy for early and late growth, the second principal component for age-specific weights is typically a contrast between early and late weights, describing variation in which a smaller than average mouse at a young age is larger than average at a later age, and vice versa (CHEVERUD *et al.* 1983; RISKA *et al.* 1984; LEAMY and CHEVERUD 1984).

These quantitative genetic results imply a genetic regulation of somatic growth such that animals displaying fast early growth are genetically down-regulated at later ages while animals experiencing slow early growth display compensatory late growth rate increases. This results in a targeting of growth to a more restricted range than implied by variation in either early or late growth rates or targeted growth (TANNER 1963).

Thus, we hypothesize that two sets of QTLs will be discovered, one with effects on early growth and a second set with effects on later growth. It is possible that these two sets will overlap, in part, including genes with opposite effects on early and late growth. Genes that result in fast early growth may also result in slower late growth.

MATERIALS AND METHODS

Mouse strains: Large (LG/J) and Small (SM/J) inbred mouse strains were chosen for this analysis. These strains are particularly useful for detecting body size growth QTLs due to their histories and the extensive genetic work previously performed on the strains by C. K. CHAI (1956a,b, 1957, 1961, 1968). The LG/J strain originated from GOODALE's (1938, 1941) selection experiment for large size at 60 days. After the strain was accessioned by the Jackson Laboratories, it was systematically inbred and maintained by sib-mating (CHAI 1956a). The SM/J strain was derived from a population that had been selected for 26 generations for small size at 60 days by MACARTHUR (1944). After accession by Jackson Laboratories, the strain was inbred using sib-mating. CHAI's (1956a,b) studies showed that the LG/J and SM/J strains differ by ~8 SD in body size (~24 g difference at 60 days of age; 13.6 g for the SM strain and 37.4 g for the LG strain) and that the difference was due to a large number of genes. He estimated that the minimum number of effective genes responsible for the strain differences in 60 day weight was 11.

CHAI's (1956b, 1957) breeding experiments with these strains also indicated that body size differences between the strains are largely additive genetic in nature, with perhaps some contribution from the effects of dominance. He found that the mean of the F_1 hybrids was nearly exactly midway between the parental strain's means (midparental strain values, male = 27.92 g, female = 23.00 g; observed F_1 means, male = 27.94 g, female = 23.68 g). Also, backcross means for the F_1 backcrossed to each parental strain fell at the midpoint of the crossed strains. Thus, the difference between these strains display the general quantitative genetic properties characteristic of body size variation in natural populations. Age-specific weights for parental strain mice are not available in this experiment because limited strain availability required all animals acquired to be used in the intercross rather than being bred within strain.

Breeding and husbandry: Ten SM/J males were mated with 10 LG/J females producing 41 F_1 hybrid animals. The reciprocal cross was not performed due to the limited availability of SM/J females. The F_1 hybrids were randomly mated starting at 10 wk of age producing 535 F_2 animals. F_1 parents produced multiple litters of varying size over a 3-month period. Males were removed from the breeding cage when their mate was gravid. Offspring were weaned at 21 days and then randomly housed in single sex cages of five animals each. The animals were fed *ad libitum* with Purina PicoLab Rodent Chow 20 (5353) (St. Louis, MO), an irradiated diet with 20% protein and 4.5% fat.

Growth measurements: The F_2 hybrids were weighed at 10 weekly intervals starting at 7 days of age. Weights were recorded to 0.1 g with a digital balance directly linked to a computer. The 10 weekly weights for F_2 hybrids were tested for a series of covarying environmental factors, including dam, litter size at birth, experimental block (F_2 hybrids were born in five distinct periods), parity, and sex. Since all F_1 dams are genetically identical, removing the dam effect controls for environmental maternal effects. Litter sizes were not standardized at birth to maximize the number of F_2 animals raised. Individual dams reached breeding age at various times over a 3-month period and were bred repeatedly after successfully weaning each litter. Therefore at any given period of time, dams of varying parity were producing litters. Each covariate had a significant effect on weight at several ages, although the effect of parity disappeared after controlling for experimental block. Inspection of weights plotted against litter size and subsequent statistical analyses indicated that there was no effect of litter size on weight for litters of <10 animals but that animals born into larger litters had a reduced weight.

The raw weights were corrected for the effects of each covariate in sequence by adding the difference in means between each class and a standard class to the individual data values. The sequence of covariate correction was dam, litter size (litter size ≤ 10 *vs.* litter size > 10), experimental block, and sex. Dam and experimental block were treated as random effects. The results must be considered as pooled across classes for these variables.

In addition to being corrected for these general covariates, body weights were also corrected for the effects of loci on chromosomes other than the one being analyzed (ZENG 1994). For this purpose only, missing marker genotypes were replaced by predicted values based on the presence of other linked markers. Removal of unlinked genetic effects was accomplished by obtaining the residuals of the regression of age-specific body weight on marker genotypes from all other chromosomes and submitting these residuals to chromosome-specific analysis. Age-specific weights were added back into the residual values.

Various age-specific growth rates were obtained from the corrected weekly body weights for analysis of murine growth. Early growth (E) is defined as growth from 1 to 3 wk. A middle

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TABLE 1

Microsatellite loci scored in the F_2 hybrids of SM/J and LG/J

Locus	Interval length	*N*	Locus	Interval length	*N*	Locus	Interval length	*N*
C1	16.5		*C7*	1.0		*C14*	2.5	
D1Mit3	6.3	521	*D7Mit21*	51.9	513	*D14Nds1*	42.0	512
D1Mit20	35.3	497	*D7Nds1*	12.5	519	*D14Mit5*	19.2	500
D1Mit7	10.9	530	*D7Mit17*	12.8	508	*D14Mit7*	25.0	505
D1Mit11	25.1	485	*D7Mit9*	35.7	500			
D1Mit14	41.6	522	*D7Nds4*	9.7	523	*C15*	4.6	
D1Mit17	9.4	515				*D15Mit13*	23.9	525
			C8	31.0		*D15Mit5*	28.0	520
C2	2.4		*D8Mit8*	83.9	520	*D15Mit2*	27.2	489
D2Mit1	NA	520	*D8Mit56*	12.0	508	*D15Mit42*	9.4	515
D2Mit17	5.2	510						
D2Mit28	12.7	483	*C9*	17.0		*C16*	14.0	
D2Mit22	30.0	115	*D9Mit2*	12.5	513	*D16Mit2*	30.0	488
			D9Mit4	13.7	529	*D16Mit5*	33.6	518
C3	4.6		*D9Mit8*	44.8	507			
D3Mit54	20.0	502	*D9Mit19*	3.0	511	*C17*	11.2	
D3Mit3	14.4	298				*D17Mit46*	9.9	475
D3Mit22	20.2	470	*C10*	9.0		*D17Mit16*	37.2	143
D3Mit12	70.7	513	*D10Mit2*	43.7	505	*D17Mit39*	14.7	529
D3Mit32	14.8	505	*D10Mit20*	19.7	492			
			D10Mit10	19.4	496	*C18*	17.0	
C4	8.1		*D10Mit14*	16.5	473	*D18Mit12*	2.5	516
D4Mit2	29.5	496				*D18Mit17*	44.9	514
D4Mit17	11.2	496	*C11*	1.0		*D18Mit8*	26.0	508
D4Mit45	19.0	484	*D11Mit62*	44.3	492			
D4Mit16	22.1	466	*D11Mit64*	9.1	512	*C19*	15.0	
D4Mit13	32.4	493	*D11Mit15*	21.1	487	*D19Mit16*	4.6	440
			D11Mit14	31.4	478	*D19Mit14*	50.1	452
C5	1.0		*D11Mit48*	3.0	462	*D19Mit2*	17.5	467
D5Mit47	24.6	222						
D5Mit61	64.5	49	*C12*	1.0				
D5Mit6	8.1	505	*D12Mit37*	18.0	516			
D5Mit26	30.2	240	*D12Mit2*	19.9	500			
D5Mit32	10.5	511	*D12Mit5*	8.9	490			
D5Mit43	7.0	140	*D12Mit6*	21.9	527			
			D12Nds2	26.0	470			
C6	4.0							
D6Mit1	51.9	499	*C13*	7.0				
D6Mit9	15.1	496	*D13Mit1*	55.3	519			
D6Nds5	28.0	484	*D13Mit9*	34.8	514			
D6Mit15	7.0	508	*D13Mit35*	6.0	515			

Interval length following the locus and sample size (*N*) are given. The interval length for C*x* indicates the distance from the most centromeric mapped locus in the MOUSE GENOME DATABASE (1995) and the first scored marker. The interval length following the last scored marker is between it and the most telomeric mapped locus in the MOUSE GENOME DATABASE (1995). NA, recombination between loci approached 50%.

growth period (M) was defined as growth from 3 to 6 wk while a late growth period (L) was defined as growth from 6 to 10 wk. Six-week weight gain (SW) was defined as growth from 1 to 6 wk and is essentially the combination of early and middle growth. Additionally, data were analyzed for each age-specific weight.

DNA scoring: Total cellular DNA was extracted from spleens according to the protocol in ROUTMAN and CHEVERUD (1994b, 1995). PCR amplification of microsatellite loci was performed according to the protocol described by DIETRICH *et al.* (1992) and modified by ROUTMAN and CHEVERUD (1994b, 1995). These modifications involved changes in the annealing temperature and polymerase concentrations suggested by DIETRICH *et al.* (1992) and the addition of loading dye to the reaction before PCR. The PCR product was visualized using 5–6% agarose gels and ethidium bromide. We estimate that these procedures allowed detection of ~90% of the polymorphic loci among SM/J × LG/J hybrids (ROUTMAN and CHEVERUD 1995).

Seventy-five microsatellite loci were scored on 535 F_2 hybrid mice. The loci scored are listed in Table 1 and displayed as a genetic map in Figure 1. Each autosome is represented in the sample. Insufficient variability was present on the *X* chromosome to allow its inclusion in this study. A total of 55 intervals covering ~1500 cM were defined by the genotypes. The average interval length was 27.5 cM with a range of 2.5–

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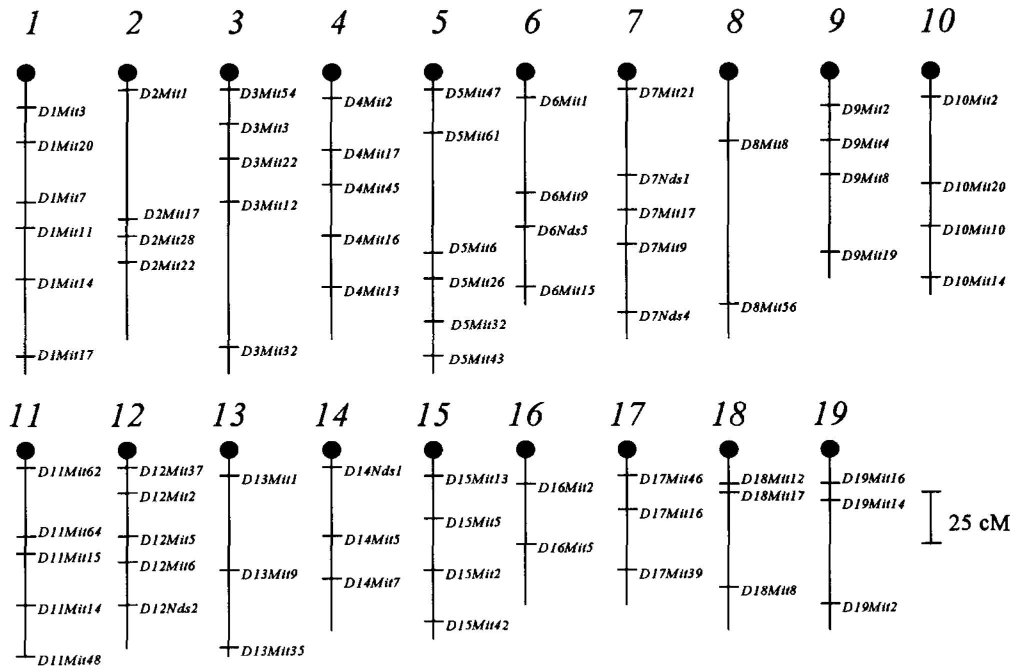

FIGURE 1.—Relative positions of microsatellite markers scored in the cross of LG/J with SM/J.

84 cM. Primer pairs were obtained from Research Genetics (Huntsville, AL). Loci varied in the amount of missing data, altogether ~36,000 genotypes, or 90% of the total, were successfully scored (see Table 1). At most loci, ~7% of the gel lanes could not be scored with confidence. At other loci, such as *D2Mit22* and *D5Mit43,* scoring was successful at much lower rates, whole 96-well plates not consistently providing reliable results. The reliable data obtained for these loci was included in the analysis when the locus filled a relatively large interval. Also, one locus, *D10Mit20,* could only be scored as a dominant marker since the SM/J homozygote and heterozygote were not reliably distinguishable.

The relative positions of these markers are given by DIETRICH and co-workers (1992, 1994), however, map distances are known to vary between crosses. Therefore, ROUTMAN and CHEVERUD (unpublished data) mapped the microsatellite markers in this experiment using the MAPMAKER 3.0b program (LANDER *et al.* 1987; LINCOLN *et al.* 1992a). The relative positions of the markers as estimated from this cross are presented in Table 1. Details of the mapping protocol followed are given by ROUTMAN and CHEVERUD (unpublished data). We attempted to obtain markers as near the centromere and telomere as possible to cover complete chromosomes. Distances from the most centromeric and telomeric locus included in the MOUSE GENOME DATABASE (1995) are also provided in Table 1.

Statistical procedures: The presence and relative positions of potential QTLs was determined using the interval mapping methods described by LANDER and BOTSTEIN (1989) as realized in the MAPMAKER/QTL 1.1b computer program (PATERSON *et al.* 1988; LINCOLN *et al.* 1992b). First, a single QTL model, including both additive and dominance genotypic effects, was fitted to the data. If a statistically significant result was obtained, the chromosomal pattern of LOD scores and genetic effects was inspected to discern whether a second QTL may also be present on the chromosome. Indications of potential second QTLs include a secondary peak LOD score, an exceptionally wide LOD score peak, or abrupt changes in the sign of the estimated additive or dominance effects. If a second QTL was suspected, a series of two-QTL per chromosome models were tested. A two-QTL model was accepted if the likelihood ratio test indicated a statistically significant improvement in fit at the 5% level relative to the best-fit one-QTL model.

Statistical significance of the one-QTL models was evaluated using LOD scores. Because of multiple comparisons problems (LANDER and BOTSTEIN 1989; LANDER and SCHORK 1994), the level of statistical significance for a given LOD score was determined by simulation. Five hundred simulated populations were produced by randomly generating 535 body weights from a normal distribution with a mean of zero and a variance of one. This random body weight data was combined with the observed genotypic data and each chromosome analyzed by interval mapping to obtain a distribution of LOD scores under the null hypothesis of no QTL effect. The 90th, 95th and 99th percentile of the LOD score distributions estimate the 10, 5 and 1% critical values for LOD scores. A sample of 500 simulated experiments is adequate to provide accurate estimates of the 90th (top 50 LOD scores) and 95th (top 25 LOD scores) percentiles and a general estimate of the 99th percentile (top 5 LOD scores) of the null distribution. Results significant at the 10% level are presented because they often correspond to locations with strongly significant results for adjacent age-specific weights or growth and these instances should be noted as potential type I errors.

RESULTS

Variation in age-specific weights and growth: The means and phenotypic standard deviations for age-specific weights and growth rates after correction for covariates are presented in Table 2. The coefficients of variation (mean/SD) for age-specific weights do not increase with age but remain relatively stable at ~12%. Correlations between the age-specific weights decline as the time between weights increases (see Table 2). Correlation of early and later weights is ~0.30, indicating that they share only 10% of their variance in com-

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TABLE 2

Means ± standard deviations after correction for covariates and correlations for age-specific weights and growth periods

Age		Age (in weeks)												
		1	2	3	4	5	6	7	8	9	10	E	M	SW
1	4.83 ± 0.60													
2	8.26 ± 0.99	0.79												
3	12.56 ± 1.40	0.73	0.81											
4	19.21 ± 1.98	0.67	0.71	0.81										
5	24.80 ± 2.31	0.52	0.61	0.70	0.87									
6	27.37 ± 2.57	0.45	0.53	0.62	0.78	0.91								
7	29.72 ± 3.01	0.40	0.48	0.55	0.71	0.85	0.93							
8	31.44 ± 3.50	0.33	0.43	0.49	0.64	0.78	0.88	0.94						
9	33.71 ± 3.82	0.29	0.38	0.46	0.59	0.75	0.84	0.92	0.94					
10	35.51 ± 4.20	0.28	0.37	0.44	0.56	0.71	0.81	0.88	0.91	0.94				
E	7.73 ± 1.04	0.41	0.64	0.92	0.70	0.64	0.57	0.51	0.47	0.44	0.42			
M	14.80 ± 2.02	0.06	0.11	0.09	0.43	0.66	0.83	0.80	0.77	0.75	0.72	0.08		
SW	22.54 ± 2.35	0.24	0.38	0.48	0.68	0.85	0.97	0.92	0.87	0.84	0.81	0.51	0.89	
L	8.14 ± 2.60	0.01	0.07	0.09	0.13	0.25	0.32	0.49	0.60	0.69	0.81	0.12	0.33	0.34

Growth periods are designated as early (E), middle (M), six week (SW), and late (L). Correlations >0.08 are significant at the 5% level.

mon. All correlations among age-specific weights are significant at the 5% level. The first two principal components of the age-specific weight correlation matrix are given in Table 3. The first component, accounting for 71% of the total variation, describes an overall measure of size in which animals with extreme scores are either larger or smaller than average at all ages. The second principal component, accounting for 17% of the total variation, contrasts early with later weights, so that animals with extreme scores are larger than average at a young age but smaller than average at a later age, and vice versa.

Correlations among growth rates were quite low, although still statistically significant at the 5% level. Early and late growth share only ~1% of their variance in common while middle growth rate shares ~10% of its variance each with early and late growth. These results indicate the relative independence of early and late growth in the F_2 population. The first two principal components of the growth rate correlation matrix (Table 3) indicate a first factor affecting all growth rates in a common fashion accounting for 46% of the variance and a second component that contrasts early with later growth, accounting for 31% of the total variation.

TABLE 3

Principal component loadings for age-specific weights and growth rates

Age	PC1	PC2
1	0.622	0.654
2	0.703	0.594
3	0.770	0.514
4	0.871	0.298
5	0.928	0.017
6	0.940	−0.168
7	0.933	−0.289
8	0.897	−0.375
9	0.871	−0.426
10	0.843	−0.428
E	0.421	−0.905
M	0.770	0.304
L	0.792	0.184

Abbreviations as in Table 2.

Quantitative trait loci: Quantitative trait loci affecting age-specific weights and growth were detected on 16 of the 19 autosomes, only chromosomes *5, 17,* and *18* failing to reach significance at the 5% level as determined by the randomization procedure (see Table 4). A potential QTL on chromosome *18* is significant at the 10% level. Each chromosome can be considered independently because the phenotypes were corrected for the effects of markers on other chromosomes before analysis. Given independence, we expect only one false significant result by chance for each trait.

Analyses of multiple-locus models indicate that several chromosomes, including chromosomes *1–4, 6, 7, 11,* and *12,* carry two or more quantitative trait loci affecting growth and age-specific weights (Table 4). In each of these instances, multiple-QTL models fit significantly better at the 5% level than a single-QTL model for the chromosome (chromosomes *1, 3, 4, 6, 7,* and *11*) or the loci mapped to grossly different locations with nonoverlapping age distributions (chromosomes *2* and *12*). Statistical significance of multiple-QTL models was obtained by comparing the LOD score for the multiple-QTL model with the score obtained with one fewer QTL using the likelihood ratio test to obtain a chi-square value with 2 degrees of freedom. Chromosome *13* may also carry

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TABLE 4

Quantitative trait loci for age-specific weights and growth periods

Locus	Age	dist (cM)	a	d	$2a/s_P$	d/s_P	QTL No.	Percent VAR	LOD score
				Chromosome *1* (1.659, 2.152, 2.958)					
D1Mit3	2	0	0.13	−0.02	0.27	−0.02	2	4.5	3.59
	3	0	0.16	0.03	0.22	0.02	2	6.5	4.11
	4	0	0.31	0.07	0.31	0.04	1	1.9	2.20
	5	0	0.37	0.03	0.32	0.01	1	2.0	2.39
	6	0	0.37	−0.11	0.29	−0.04	1	2.7	3.18
D1Mit20	6	22	0.21	0.76	0.16	0.30	2	6.3	4.58
	7	20	0.59	0.69	0.39	0.23	1	5.2	3.37
	8	21	0.64	0.99	0.37	0.28	1	5.1	3.32
	9	20	0.81	0.98	0.43	0.26	1	6.3	4.26
	10	20	0.80	1.10	0.38	0.26	1	5.3	3.89
	M	26	0.50	0.46	0.50	0.23	1	4.8	3.84
	SW	20	0.49	0.56	0.41	0.24	1	4.1	2.67
	L	35	0.31	0.38	0.24	0.15	1	1.9	2.25
D1Mit11	1	16	0.00	0.24	−0.01	0.40	1	5.4	3.53
	2	14	−0.06	0.28	−0.11	0.28	1	3.2	2.09
D1Mit14	3	14	−0.13	0.50	−0.19	0.36	1	5.8	2.97
	4	16	−0.31	0.39	−0.31	0.20	2	5.3	4.34
	5	25	−0.28	0.31	−0.24	0.13	2	4.0	3.73
	6	26	−0.34	0.24	−0.27	0.09	3	8.2	5.99
	8	40	−0.38	0.24	−0.22	0.07	2	6.7	4.64
	10	40	−0.45	0.37	−0.21	0.09	2	7.2	5.33
	E	20	−0.10	0.28	−0.19	0.27	1	5.3	2.55
	M	22	−0.30	−0.23	−0.30	−0.12	2	7.7	5.37
	SW	22	−0.36	0.03	−0.31	0.01	2	6.8	4.14
				Chromosome *2* (1.321, 1.590, 2.368)					
D2Mit17	2	0	−0.10	0.22	−0.21	0.22	1	2.5	2.86
	3	0	−0.14	0.31	−0.20	0.22	1	2.7	3.05
	E	0	−0.10	0.24	−0.20	0.23	1	2.8	3.17
D2Mit22	7	2	0.48	−0.01	0.32	0.00	1	2.3	2.65
	8	2	0.65	0.03	0.37	0.01	1	3.0	3.38
	9	2	0.70	−0.11	0.37	−0.03	1	3.0	3.50
	10	2	0.76	−0.05	0.36	−0.01	1	3.1	3.60
	M	2	0.40	−0.15	0.40	−0.07	1	3.4	3.92
	SW	2	0.34	−0.01	0.29	0.00	1	1.8	2.03
	L	2	0.45	−0.08	0.35	−0.03	1	2.6	2.91
				Chromosome *3* (1.780, 2.024, 2.915)					
D3Mit22	1	10	0.14	0.11	0.46	0.18	1	2.3	1.83
	2	8	0.17	0.16	0.35	0.16	1	2.1	1.71
	3	20	0.32	−0.01	0.45	−0.01	1	2.2	1.81
	4	12	0.41	0.26	0.42	0.13	1	2.3	1.99
	5	4	0.37	0.30	0.32	0.13	1	2.4	2.18
	6	4	0.34	0.35	0.26	0.14	1	2.5	2.25
	10	10	0.41	0.91	0.19	0.22	1	2.6	2.13
D3Mit12	1	45	−0.18	0.13	−0.61	0.21	2	9.6	3.87
	2	52	−0.21	0.31	−0.42	0.32	2	8.6	3.85
	3	41	−0.48	0.33	−0.68	0.23	2	10.2	2.75
	4	49	−0.46	0.39	−0.47	0.20	2	7.8	3.85
	5	55	−0.26	0.56	−0.22	0.24	2	5.9	3.53
	10	28	−0.22	−1.99	−0.10	−0.47	2	12.4	3.55
	L	44	−0.05	−1.15	−0.04	−0.44	1	8.4	2.26

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TABLE 4

Continued

Locus	Age	dist (cM)	a	d	$2a/s_P$	d/s_P	QTL No.	Percent VAR	LOD score
				Chromosome *4* (1.638, 2.052, 2.535)					
D4Mit2	5	18	0.42	0.20	0.36	0.09	1	3.1	2.58
	6	24	0.58	0.11	0.45	0.04	1	4.7	4.47
	7	24	0.59	0.25	0.39	0.08	1	5.1	4.85
	8	22	0.95	0.17	0.54	0.05	1	6.4	5.60
	9	22	0.99	0.22	0.52	0.06	1	6.2	5.29
	10	20	1.04	0.45	0.50	0.11	1	6.3	5.13
	M	22	0.41	−0.06	0.41	−0.03	1	3.6	3.13
	SW	15	0.46	0.15	0.39	0.07	1	5.4	4.91
	L	22	0.39	0.27	0.30	0.10	1	2.4	1.89
D4Mit45	3	6	0.16	0.29	0.23	0.21	1	2.9	2.63
	E	12	0.14	0.23	0.27	0.22	1	3.5	3.17
	SW	19	0.27	0.04	0.23	0.02	2	6.0	5.73
				Chromosome *5* (1.843, 2.337, 2.983)					
				No QTLs					
				Chromosome *6* (1.658, 1.904, 2.388)					
D6Mit1	4	0	0.25	0.09	0.25	0.05	2	8.0	7.77
	5	0	0.26	−0.10	0.22	−0.04	2	9.1	8.45
D6Mit9	2	8	0.16	0.01	0.32	0.01	1	1.9	1.88
	3	8	0.33	0.03	0.55	−0.01	1	4.4	4.21
	E	8	0.25	−0.01	0.48	−0.01	1	4.5	4.31
D6Nds5	4	8	0.53	0.13	0.54	0.07	1	6.6	6.83
	5	14	0.71	0.06	0.62	0.03	1	8.2	7.13
	6	16	0.90	0.27	0.70	0.11	1	11.5	10.10
	7	16	1.12	0.06	0.74	0.02	1	12.4	10.94
	8	18	1.18	0.14	0.67	0.04	1	10.1	9.13
	9	20	1.19	−0.05	0.62	−0.01	1	9.0	8.19
	10	18	1.39	0.09	0.66	0.02	1	10.4	9.24
	M	26	0.60	0.17	0.60	0.09	1	8.5	8.51
	SW	18	0.82	0.22	0.70	0.09	1	11.1	10.02
	L	16	0.49	−0.24	0.38	−0.09	1	3.4	2.81
				Chromosome *7* (1.669, 2.130, 2.807)					
D7Mit21	1	27	0.18	0.13	0.60	0.22	1	7.6	3.75
	2	33	0.32	0.23	0.64	0.23	1	8.8	6.22
	3	34	0.54	0.24	0.77	0.17	1	12.7	8.52
	4	29	0.78	0.50	0.79	0.25	1	13.7	7.76
	5	29	0.53	0.66	0.46	0.29	1	12.3	9.01
	6	26	0.47	0.77	0.37	0.30	1	12.6	8.80
	7	26	0.50	0.82	0.34	0.27	1	12.0	8.63
	8	25	0.40	0.84	0.23	0.24	1	8.7	6.86
	9	27	0.82	1.36	0.43	0.36	1	16.2	8.51
	10	36	0.64	1.00	0.31	0.24	1	11.7	7.37
	E	36	0.38	0.19	0.72	0.18	1	11.3	7.91
D7Nds1	5	12	0.49	0.08	0.43	0.04	3	18.0	12.73
	6	10	0.47	−0.09	0.37	−0.04	3	18.0	12.65
	7	10	0.59	−0.08	0.39	−0.03	3	16.3	12.00
	8	6	0.69	−0.21	0.39	−0.06	3	12.7	9.79
	9	0	0.65	−0.07	0.34	−0.02	3	18.4	11.25
	10	8	0.75	−0.40	0.36	−0.10	3	15.2	10.44
	M	10	0.41	0.20	0.40	0.10	1	3.9	4.09
	SW	6	0.65	0.23	0.55	0.10	1	8.2	8.48
	L	4	0.38	−0.12	0.30	−0.04	1	2.0	2.03

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TABLE 4

Continued

Locus	Age	dist (cM)	a	d	$2a/s_P$	d/s_P	QTL No.	Percent VAR	LOD score
				Chromosome *7* (1.669, 2.130, 2.807)					
D7Mit9	1	4	0.02	0.13	0.07	0.22	2	9.2	5.20
	3	18	0.00	0.40	0.00	0.29	2	15.6	10.17
	4	16	0.05	0.64	0.05	0.32	2	18.3	9.84
	5	16	−0.20	0.82	−0.17	0.36	2	17.7	11.37
	6	17	0.04	0.92	0.03	0.36	2	17.8	11.73
	7	17	0.07	0.90	0.05	0.30	2	16.3	10.98
	8	18	0.15	0.97	0.08	0.28	2	10.2	8.90
	9	16	0.10	1.12	0.05	0.29	2	13.6	9.95
	10	20	0.09	1.45	0.05	0.35	2	15.0	9.53
	SW	20	0.06	0.60	0.05	0.26	2	10.6	9.81
				Chromosome *8* (1.490, 1.835, 2.602)					
D8Mit8	3	0	0.19	0.06	0.27	0.04	1	1.4	1.62
	4	2	0.27	0.16	0.27	0.08	1	1.6	1.72
	5	0	0.32	0.18	0.28	0.08	1	1.9	2.14
	6	0	0.47	0.06	0.37	0.02	1	3.0	3.46
	7	18	0.57	−0.14	0.38	−0.05	1	3.5	2.02
	8	18	0.61	−0.34	0.35	−0.10	1	3.3	1.75
	9	0	0.49	−0.02	0.25	−0.01	1	1.5	1.69
	10	0	0.57	−0.03	0.27	−0.01	1	1.8	2.05
	E	0	0.18	0.05	0.35	0.05	1	2.4	2.70
	M	28	0.45	−0.22	0.45	−0.11	1	4.9	2.07
	SW	0	0.46	0.06	0.39	0.02	1	3.4	3.91
				Chromosome *9* (1.666, 1.923, 2.935)					
D9Mit4	6	8	0.34	−0.32	0.27	−0.13	1	2.4	2.27
	7	10	0.52	−0.36	0.35	−0.12	1	3.4	3.55
	8	8	0.68	−0.16	0.39	−0.05	1	3.4	3.48
	9	10	0.75	−0.40	0.39	−0.11	1	4.0	4.18
	10	6	0.77	−0.34	0.37	−0.08	1	3.6	3.68
	M	10	0.29	−0.24	0.29	−0.12	1	2.3	2.33
	SW	6	0.35	−0.26	0.30	−0.11	1	2.6	2.50
	L	6	0.44	−0.06	0.34	−0.02	1	2.4	2.48
				Chromosome *10* (1.685, 2.047, 2.808)					
D10Mit10	3	14	0.18	−0.21	0.26	−0.15	1	2.2	1.96
	4	14	0.33	−0.16	0.34	−0.08	1	2.3	2.12
	5	12	0.56	−0.04	0.48	−0.02	1	4.4	3.98
	6	8	0.55	−0.10	0.42	−0.04	1	3.7	3.26
	7	2	0.64	−0.05	0.42	−0.02	1	3.6	3.72
	8	2	0.64	−0.05	0.37	−0.01	1	2.7	2.76
	9	0	0.74	−0.20	0.39	−0.05	1	3.2	3.59
	10	0	0.76	−0.18	0.36	−0.04	1	2.9	3.25
	E	14	0.14	−0.12	0.27	−0.12	1	2.0	1.89
	M	4	0.36	0.13	0.35	0.06	1	2.4	2.24
	SW	6	0.50	−0.02	0.43	−0.01	1	3.5	3.19
				Chromosome *11* (1.758, 2.100, 2.835)					
D11Mit62	1	12	0.13	0.10	0.42	0.16	1	3.8	2.85
	2	38	0.03	0.27	0.07	0.27	1	2.8	1.96
	3	40	0.11	0.38	0.15	0.27	1	3.4	2.86
	4	23	0.16	0.53	0.16	0.27	1	4.4	2.40
	E	44	0.03	0.22	0.07	0.21	1	1.8	2.07
	L	0	−0.40	−0.23	−0.31	−0.09	1	2.4	2.60

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TABLE 4

Continued

Locus	Age	dist (cM)	*a*	*d*	$2a/s_P$	d/s_P	QTL No.	Percent VAR	LOD score
				Chromosome *11* (1.758, 2.100, 2.835)					
D11Mit14	4	14	0.25	0.34	0.25	0.17	2	6.4	3.91
	5	20	0.32	0.58	0.27	0.25	1	4.4	2.98
	6	30	0.30	0.55	0.24	0.21	1	3.4	3.33
	7	30	0.26	0.52	0.17	0.17	1	2.1	2.04
	8	30	0.20	0.62	0.12	0.18	1	1.8	1.64
	9	30	0.19	0.76	0.10	0.20	1	2.1	1.99
	M	30	0.18	0.37	0.18	0.18	1	2.1	1.95
	SW	30	0.26	0.51	0.22	0.22	1	3.3	3.14
				Chromosome *12* (1.709, 2.032, 2.796)					
D12Mit5	3	2	0.23	−0.12	0.32	−0.09	1	2.3	2.40
	E	4	0.19	−0.09	0.37	−0.09	1	2.9	2.78
D12Mit37	M	12	0.06	−0.42	0.06	−0.21	1	1.9	1.57
	SW	14	0.08	−0.42	0.07	−0.18	1	1.5	1.34
	L	10	−0.45	−0.07	−0.35	−0.03	1	2.4	2.30
				Chromosome *13* (1.550, 1.846, 2.589)					
D13Mit1	3	0	0.13	0.19	0.19	0.13	1	1.5	1.79
	4	0	0.33	0.16	0.33	0.08	1	2.6	2.98
	5	0	0.33	0.19	0.29	0.08	1	2.1	2.48
	6	0	0.31	0.20	0.24	0.08	1	1.7	1.94
	7	0	0.44	0.12	0.29	0.04	1	2.1	2.37
	8	0	0.54	0.11	0.31	0.03	1	2.2	2.52
	9	0	0.56	0.07	0.29	0.02	1	2.0	2.32
	10	0	0.69	0.03	0.33	0.01	1	2.6	2.97
	E	0	0.07	0.15	0.14	0.15	1	1.3	1.53
	L	20	0.51	−0.48	0.39	−0.18	1	4.4	2.36
				Chromosome *14* (1.503, 1.866, 2.490)					
D14Mit5	1	18	0.08	0.05	0.25	0.08	1	1.3	1.45
	2	18	0.13	0.06	0.26	0.07	1	1.5	1.62
	3	18	0.12	0.19	0.17	0.13	1	1.3	1.43
	5	18	0.37	0.12	0.32	0.05	1	2.5	2.69
	6	18	0.48	0.07	0.37	0.03	1	3.4	3.79
	7	18	0.61	0.25	0.40	0.08	1	4.3	4.72
	8	16	0.71	0.19	0.41	0.05	1	4.0	4.19
	9	18	0.79	0.16	0.41	0.04	1	4.3	4.69
	10	18	0.92	0.32	0.44	0.08	1	5.1	5.64
	E	0	0.00	0.21	0.01	0.20	1	1.6	1.78
	M	8	0.42	−0.22	0.41	−0.11	1	4.3	4.00
	SW	12	0.45	0.04	0.38	0.02	1	3.4	3.26
	L	18	0.44	0.24	0.34	0.09	1	2.9	3.14
				Chromosome *15* (1.569, 1.792, 2.351)					
D15Mit2	3	4	0.21	0.11	0.30	0.08	1	1.9	1.76
	5	8	0.37	0.13	0.32	0.06	1	2.2	1.85
	7	12	0.46	0.36	0.31	0.12	1	2.8	2.04
	9	0	0.52	0.26	0.27	0.07	1	1.8	1.74

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TABLE 4

Continued

Locus	Age	dist (cM)	a	d	$2a/s_P$	d/s_P	QTL No.	Percent VAR	LOD score
			Chromosome *16* (1.298, 1.568, 2.284)						
			No QTLs						
			Chromosome *17* (1.401, 1.705, 2.311)						
D17Mit46	2	2	0.00	0.24	0.01	0.24	1	2.1	1.92
			Chromosome *18* (1.491, 1.843, 2.403)						
D18Mit17	9	18	0.40	0.81	0.21	0.21	1	3.2	1.50
	10	28	0.41	0.94	0.19	0.23	1	3.4	1.58
	L	26	0.34	0.49	0.26	0.19	1	3.0	1.55
			Chromosome *19* (1.451, 1.729, 2.419)						
D19Mit14	9	50	0.53	−0.16	0.28	−0.04	1	1.9	2.01
	10	50	0.52	−0.02	0.25	−0.01	1	2.1	1.65

For each significant QTL effect on age-specific weights (in weeks) and growth periods [early (E), middle (M), six week (SW), and late (L)], the map distance (dist) between the nearest proximal marker locus and the QTL is indicated. Also included are the raw and standardized additive (a, $2a/s_P$) and dominance (d, d/s_P) genotypic values for each phenotype at each QTL. The genotypic values and map positions presented are those estimated from the most complete QTL model (single or multiple QTLs) accepted as significant. Any single chromosome may carry 1, 2, or 3 QTLs for a given phenotype. QTL No. designates whether the QTL indicated was the first, second, or third included in the full model. The percent of F_2 corrected phenotypic variance accounted for and the LOD score associated with the corresponding single or multiple QTL model is indicated by percent VAR and LOD score, respectively. Significance testing was performed on each chromosome separately using the 10, 5 and 1% critical LOD score values listed after each chromosome name. These should be compared with the LOD scores for single QTL models for each character (QTL No. = 1). Significance tests for multiple QTL models are performed using the maximum likelihood ratio test comparing LOD scores for multiple QTL models with those for the model with one fewer QTL.

two distinct QTLs based on age distribution and map location of genotypic effects.

The percent effect of each chromosome on age-specific weight and growth is given in Table 4. Statistically significant chromosomal effects range from 2 to 18% of the phenotypic variance in the F_2 generation after correction for covariates. Most of the high percentage effects are associated with chromosomes containing multiple QTLs. When these effects are apportioned equally to each QTL, the maximum percent effect for any single locus is ~10–12% [effects of the QTL 18 cM distal to marker *D6Nds5* (*D6Nds5* + 18 cM) on late age-specific weights].

Adding the contributions from each chromosome, the percentage of variance after correction for covariates explained by QTLs rises from 30% at 1 week to 75% at 10 wk (Table 5). The increased percent variance accounted for by QTLs in older animals is largely due to changes in the number of QTLs detected at each age, increasing from seven at 1 week to 17 at 10 wk. Approximately 40% of the variance in early, middle, and late growth periods is accounted for by the QTLs.

Raw and standardized additive (a; a/σ_P) and dominance (d; d/σ_P) genotypic values for each QTL are presented in Table 4. Both raw and standardized additive genotypic values at most QTLs increase with age as these loci affect growth. The largest raw additive genotypic effect is 1.4 g, or a nearly 3 g difference (0.66 standard deviations) between homozygotes, at *D6Nds5* + 18 cM for 10-week weight. The QTL at *D7Mit21* + 29 for 4-week weight had the most extreme standardized genotypic value at 0.79 SD units (1.56 g difference). Most significant differences between homozygotes for adult weight are on the order of 1 g and 0.33 standard deviations. As expected given the origins of the strains, the LG/J allele resulted in larger size and faster growth at nearly all QTLs. Exceptions include the QTL affecting early growth and weight from 3 to 10 wk at *D1Mit14* + 20 cM, the QTL affecting early growth and weight at *D2Mit17,* and the QTL affecting early weights at *D3Mit12* + 45 cM. For these QTLs, the SM/J allele leads to larger size. Two QTLs, at *D11Mit62* and at *D12Mit37* + 10 cM, show faster growth for the SM/J allele during the late growth phase, perhaps indicating delayed growth due to the SM/J allele.

The most extreme dominance genotypic value is nearly −2 g (−0.47 standard deviations) at *D3Mit12* + 36 cM for 10-week weight. Also at 10 wk, the heterozygote was 1.5 g larger than the midpoint of the homozygotes at *D7Mit9* + 18 cM. The LG/J allele is dominant to the SM/J allele seven times with the reverse holding true five times. However, in three of the instances in

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TABLE 5

Total genotypic effects on growth and age-specific weights

Age	No. of QTL	Percent VAR	Percent V/QTL	a	a_s	a/QTL	d	d_s	d/QTL
1	7	29.3	4.2	0.35	1.18	0.05	0.88	1.47	0.13
2	10	30.4	3.0	0.58	1.18	0.06	1.76	1.77	0.18
3	16	56.3	3.5	1.98	2.82	0.12	2.65	1.89	0.17
4	13	52.3	4.0	2.90	2.93	0.22	3.51	1.77	0.27
5	15	58.6	3.9	4.92	4.04	0.33	3.53	1.77	0.24
6	15	62.5	4.2	5.50	4.28	0.37	3.67	1.42	0.24
7	14	64.3	4.6	7.42	4.93	0.53	3.32	1.10	0.27
8	14	56.3	4.0	7.65	4.37	0.55	3.55	1.01	0.25
9	16	66.9	4.2	10.22	5.35	0.64	4.73	1.24	0.30
10	17	76.1	4.5	9.87	4.70	0.58	3.65	0.87	0.21
E	11	39.4	3.6	1.19	2.28	0.11	1.33	1.28	0.12
M	12	40.9	3.4	3.78	3.75	0.32	−0.22	−0.11	−0.02
SW	14	54.0	3.9	4.82	4.10	0.34	1.73	0.73	0.12
L	12	38.3	3.2	2.86	2.20	0.24	−1.05	−0.40	−0.09

Number of QTLs, summed percent phenotypic variance explained by QTLs after covariate correction (percent VAR), summed additive genotypic value (a), summed standardized additive genotypic value (a_s), additive genotypic value per QTL (a/QTL), summed dominance genotypic values (d), summed standardized dominance genotypic values (d_s), and dominance deviation per QTL (d/QTL).

which SM/J is dominant to LG/J, the SM/J allele also has a positive additive genotypic effect. Therefore higher weight is dominant to lower weight at most loci showing clear dominance.

A wide range of genetic architectures are displayed, from additivity, for example at *D1Mit3* + 0 cM, *D2Mit22* + 2 cM, and *D6Nds5* + 18 cM, to LG/J dominant to SM/J, at *D1Mit20* + 20 cM and *D7Mit21* + 28 cM, SM/J dominant to LG/J, at *D1Mit14* + 22 cM and *D9Mit4* + 8 cM, overdominance, at *D1Mit11* + 14 cM and *D7Mit9* + 18 cM, and underdominance, at *D3Mit12* + 36 cM for late growth and 10-week weight.

The sums of the additive and dominance genotypic values for growth rates and age-specific weights are given in Table 5. The sum of the additive genotypic values increases with age, from a 0.7-g multiple homozygote difference at 1 week to a 20-g multiple homozygote difference at 10 wk. Sums of standardized additive genotypic values also increase over this age range from ~1.2 SD in the first few weeks to 5.0 SD in the last few weeks. Some of this increase in homozygote difference is accounted for by the increase in the number of loci affecting weight (from 7 to 17 loci) but average additive genetic values also increase with age from ~0.05 g (0.17 standard deviations) in the first few weeks to 0.60 g (0.30 standard deviations) in the last few weeks. This indicates that individual loci have larger effects at later ages due to the accumulation of effects.

Dominance genotypic value increases over the first 3 wk before leveling out at ~3.5 g from week 4 on. When considered in terms of standard deviation units, dominance increases over the first 3 wk to 1.9 SD and then declines to ~1 SD at later ages. This indicates that the multiple heterozygote is born larger than either multiple homozygote and grows at the same or slightly faster rate than the LG/J homozygote and much faster than the SM/J homozygote during the early growth period. However, heterozygote growth then slows relative to the multiple homozygotes during the middle and late growth periods resulting in a relative diminution of dominance genotypic values with age. This is reflected in large dominance ratios ($\Sigma d/\Sigma a$ = 2.5 and 3.0) at 1 and 2 wk contrasted with a much reduced ratio ($\Sigma d/\Sigma a$ = 0.37) by 10 wk.

QTLs affecting early and late growth typically map to distinct chromosomal locations (see Figure 2). Genotypic effects on the middle growth period map either with early or late growth QTLs. If the 20 intervals affecting early growth and/or early age-specific weights are cross-tabulated against the 14 intervals affecting late

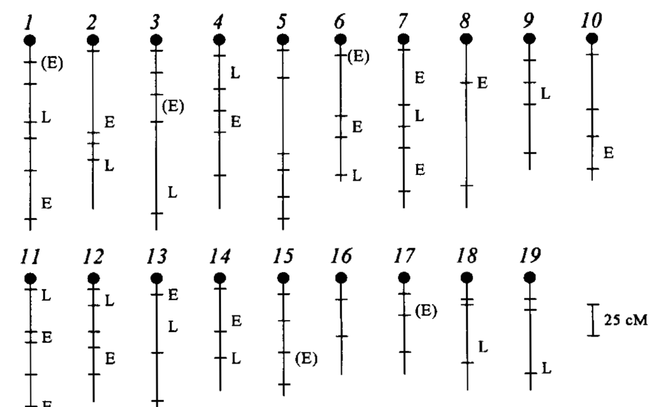

FIGURE 2.—Relative positions of QTLs affecting early (E) and late (L) growth. Parenthetical entries represent locations with exclusive effects on early or late weights but not on growth itself.

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growth and/or exclusively late age-specific weights, only four intervals hold potential sites of common QTLs for early and late growth, downstream from *D3Mit22, D3Mit12, D13Mit1,* and *D14Mit5*. If the distribution of effects on early and late growth are unrelated, five co-occurrences in 55 intervals would be expected by chance. Thus the co-occurrences noted may be due to chance alone.

DISCUSSION

Interval mapping located many genes with relatively small effects on age-specific body weights and growth. The maximum effect for a single QTL was ~10% with an average effect per QTL of ~4% of the phenotypic variance after correction for covariates. Therefore, in this cross, body weight behaves as an archetypal quantitative trait with genetic variation due to many loci, each of relatively small effect. The results obtained here are consistent with the results of CHAI (1956a,b, 1957) almost 40 years ago. Using biometric analysis, he estimated that there were a minimum of 11 effective genes responsible for weight differences at 60 days. We found 16 QTLs for 63-day weight (9 wk). That the observed number of loci is slightly larger than the minimum biometric estimate is to be expected because there are slight variations in the magnitude of genetic effects, several loci show over- or underdominance and thus do not contribute to strain differences, and there may be some false positive results. The overall difference between multiple homozygotes at 63 days is 20.44 g in our experiment. This difference estimates the expected difference between the parental strains, LG/J and SM/J. CHAI (1956a,b, 1957) found a 24-g difference at 60 days. These two lines of evidence suggest that most, if not all, of the genetic effects on later body weights are accounted for by the QTL mapped here.

A few SM/J alleles were discovered that resulted in higher weight or faster growth than their companion LG/J-derived alleles. All of these "contra" effects are for early body weights and growth except for the QTL at *D11Mit62* + 0 cM and *D12Mit37* + 10 cM, which show positive effects on late growth for the SM/J alleles. The concentration of "contra" alleles at early ages is expected from the history of the strains. LG/J and SM/J were selected for large and small body size, respectively, at 60 days (GOODALE 1938, 1941; MACARTHUR 1944). Early growth and body weight is only weakly correlated with the selection criterion so alleles affecting early growth and weight would be randomly fixed by drift, rather than selection preferentially fixing positive alleles in the LG/J strain and negative alleles in the SM/J strain as expected in adults. The two contra genes for late growth may represent situations in which the SM/J allele leads to a slower growth rate but extends the period of growth.

The genetic architecture of loci affecting body weight and growth in this cross changes with age. Early body weights and growth show a high "*d*/*a*" ratio, indicating strong dominance and overdominance for alleles resulting in large body size. However, at later ages, additive genotypic values increase while dominance values remain stable (thereby decreasing relative to the phenotypic variance). This indicates that multiple heterozygotes grow relatively fast early but then slow to a lower rate relative to the homozygotes at later ages, as indicated by the negative sums for dominance values for middle and late growth.

Strong positive dominance and overdominance for early growth and weight may result from strong selection for early growth rate. The importance of strong early growth for survival in natural populations cannot be overestimated. In many mammalian populations, there is a high death rate among newborns presenting a major opportunity for selection during this age period. While much of the variation in neonatal size and growth in mice is due to the dam, ≥30% of the variation is due to the direct effects of genes carried by the neonates themselves (RUTLEDGE *et al.* 1972; ATCHLEY and RUTLEDGE 1980; CHEVERUD *et al.* 1983; RISKA *et al.* 1984; LEAMY and CHEVERUD 1984). High growth rates are likely to be strongly selected for in weanlings. In this context, it is interesting to note that the allele leading to larger size was typically dominant to the alternate allele regardless of whether the allele for higher vigor originated in the SM/J or LG/J parental strain. It was also with early growth and weight that overdominance was most prevalent.

We found that there are two distinct sets of genes affecting growth, genes affecting early growth and genes affecting later growth. The early growth effects tend to taper off by ~6 wk of age while the effects of later growth genes first appear in the 3–6-week interval. This results in many of the QTL having significant effects for the early and middle growth periods or the middle and late growth periods but not for postnatal growth as a whole. Intervals between marker loci affecting both early and late growth occur at the level expected by chance.

The four specific co-occurrences of early and late growth found here may be spurious. The two chromosome *3* QTLs have an odd age distribution of effects, with a gap in significant results between 5 or 6 wk and 10 wk. The genetic architecture of late growth and 10-week weight at these two loci contrasts with the architecture displayed at earlier times, with strong overdominance arising at the *D3Mit22* locus and strong underdominance at the *D3Mit12* locus. The opposite additive genotypic effects at early ages and contrasting dominance at later ages for these linked QTL made interval mapping difficult. It is possible that the later effects represent different loci from the early effects although further work is needed to evaluate this possibility. The other two loci with common early and late growth ef-

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fects, distal to *D13Mit1* and *D14Mit5*, have a 20-cM distance between the most likely locations for early and late growth. Finer mapping of these regions is required to determine whether these effects map to different locations.

Early and late growth in rodents have a different cellular basis and are regulated, in part, by different physiological systems (CHEEK 1975; FALCONER *et al.* 1978; ATCHLEY *et al.* 1984; RISKA *et al.* 1984). IGF-2 is found in high concentrations prenatally and until ~3 wk of age in rodents (SARA *et al.* 1981; SARA and HALL 1990). During this period, growth in most tissues is due to increases in cell number. By 4 wk, IGF-2 concentrations have declined to fairly low levels. Growth hormone and IGF-1, while present in the circulation early in life, do not have major general growth-promoting effects, as they do during later growth periods (RAPPAPORT 1993). At about the same time that IGF-2 concentrations decline, growth-hormone-dependent growth and associated increases in IGF-1 begins in rodents (HALL *et al.* 1981; SARA *et al.* 1981; PALMITER *et al.* 1983; SARA and HALL 1990). During this later growth period, growth occurs primarily by increase in cell size, especially in neural, muscular, and adipose tissues.

Our results indicate that distinct genetic systems are responsible for early and later growth in the mouse. These genetic systems relate to the distinct physiological systems for early and late growth discussed above. The late growth QTLs are likely to be genes operating in the growth hormone axis (GREENSPAN and BAXTER 1994; PARKS *et al.* 1995), either responsible for regulating growth hormone levels at later ages, for mediating the growth hormone—IGF-1 relationship, or in the reception and processing of IGF-1 signals at the cellular or nuclear level in the target tissues. These QTLs provide a fruitful pool of genes mediating the effects of the growth hormone axis on somatic growth.

The physiology of prenatal and neonatal growth is less well known than for later growth, although a major role for IGF-2 has been postulated (SARA *et al.* 1981; DECHIARA *et al.* 1990; SARA and HALL 1990; RAPPAPORT 1993). The early growth genes identified in the LG/J by SM/J cross are likely candidates for genes playing an important role in the early growth process. Future identification of these loci will aid our understanding of early growth processes.

Based on extrapolations from map positions of markers and growth-related loci given in the MOUSE GENOME DATABASE (1995), it is possible to identify potential candidate genes for some of the QTLs identified here. The early-growth QTL at *D7Mit9* + 16 cM maps to within ~2 cM of the insulin-like growth factor II locus (*Igf2*). Several genes affecting cell proliferation map near early-growth QTLs, including growth-arrest-specific 2 and 10 (*Gas2, Gas10*) near *D7Mit21* + 30 cM and *D1Mit3* + 0 cM, respectively, platelet-derived growth factor (*Pdgfec*) near *D15Mit2* + 8 cM, and proliferin (*Plf*) near *D13Mit1* + 0 cM. The early-growth QTL at *D10Mit10* + 14 cM maps quite close to the pygmy (*pg*) locus. The early growth failure pygmy mutant, which was originally used to define this locus, arose in MACARTHUR's (1944) small selection line, which was inbred to produce the SM/J mice studied here. The locus at *D11Mit62* + 0 cM for 10 week weight maps quite close to the Ames dwarf locus (*df*). This mutant produces its effect postnatally due to a lack of growth-hormone producing cells in the pituitary. The *df* mutant arose in the GOODALE (1938, 1941) large mice, which gave rise to the LG/J strain used here. At 10 wk of age, the LG/J derived allele results in a significant reduction in body weight in the F_2 animals derived from the LG/J by SM/J cross. Several QTL map near loci related to hormonal factors affecting growth, including the QTL at *D2Mit22* + 2 cM, which maps quite close to the growth hormone releasing hormone (*Ghrh*) and agouti (*a*) loci, the QTL at *D3Mit22* + 10 cM, which maps near the thyroid-stimulating hormone β locus (*Tshb*), the QTL at *D6Mit9* + 8, which maps near the thyrotropin-releasing hormone locus (*Trh*), and the QTL at *D14Mit5* + 18 cM, which maps near the gonadotropin-releasing hormone locus (*Gnrh*). Whether any of these candidate genes are actually responsible for the QTL effects measured here will require further research.

We found that phenotypic variance for age-specific weights increased with age in the F_2 population. However, coefficients of variation, which control for the effects of increased size with age, remain stable after 2 wk. This contrasts with RISKA *et al.*'s results (1984), in which coefficients of variation at later ages are lower than for earlier ages. Therefore, our F_2 population does not display targeted growth.

We found relatively low phenotypic correlations between early and later weights and growth in this F_2 population. Low phenotypic, genetic, and nonmaternal environmental correlations between early and late weights has been a common finding in studies of rodent growth (RUTLEDGE *et al.* 1972; CHEVERUD *et al.* 1983; ATCHLEY *et al.* 1984; LEAMY and CHEVERUD 1984; RISKA *et al.* 1984). A lack of correlation between characters can have two genetic sources. Correlation will be low when the loci do not display pleiotropic effects, each locus affecting only one trait, and/or when loci displaying positive pleiotropy are balanced by loci displaying negative pleiotropy. The overall genetic correlation between traits is a weighted average of positive pleiotropy, independence, and negative pleiotropy at individual loci (CHEVERUD 1984). In this F_2 population, low correlations between early and later weight are due to a lack of pleiotropy rather than a balance between positive and negative pleiotropy.

This result is contrary to expectations based on earlier biometric studies (CHEVERUD *et al.* 1983; LEAMY and CHEVERUD 1984; RISKA *et al.* 1984). Significant negative correlations for early and later growth have been re-

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ported in a randombred mouse strain (RISKA *et al.* 1984), and principal components analyses of age-specific weights often describe a major component contrasting early with later weight (CHEVERUD *et al.* 1983; LEAMY and CHEVERUD 1984). Our result indicates that these statistical reifications of gene effects may not be due to the physiology of gene action but rather to the structure of the statistical procedures used. For example, the principal components analysis of phenotypic correlations among age-specific weights in our F_2 population has a second principal component that contrasts early and later growth (Table 3) even though few, if any, loci have negative pleiotropic effects for these traits. The principal components result is not based on the physiology of individual gene action but on the mathematical modeling of collective gene effects. One must be careful to avoid reifying the statistical effects of genes.

Differences between results for our population and randombred strains may be more complex. The negative genetic correlation between early and later growth rates observed by RISKA *et al.* (1984) may be due to alleles with pleiotropic effects segregating at either the same or different loci in the randombred population compared to our F_2 population. The overall effect of these pleiotropic alleles on adult body size may have been minor compared with alleles with only early or late effects. Having a relatively small effect on the selection criterion, pleiotropic alleles may have been eliminated from the parental strains. Alternatively, the negative biometric correlation in the randombred strain may be due to linkage disequilibrium between loci affecting early and later growth. Certainly many of the QTL discovered here are linked and could persist in linkage disequilibrium under colony conditions.

We have found a large number of individual genes, each with relatively small effects on murine growth and body weight. The discovery of these genes provides candidates for further study of the genetic regulation of growth and for the evolution of quantitative characters in natural populations (CHEVERUD and ROUTMAN 1993; ROUTMAN and CHEVERUD 1994a).

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