

1 **Fine-mapping of muscle weight QTL in LG/J and SM/J intercrosses**  
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17 **Running title:** Muscle weight in LG/J and SM/J strains  
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## 29 **Abstract**

30 **Introduction.** Muscle functional capacity is an important determinant of health and fitness. Genetic  
31 variation plays a substantial role in variation in strength, but the underlying genetic mechanisms remain  
32 poorly understood.

33 **Aim.** The objective of the present study was to examine the mechanisms underlying variation in muscle  
34 mass, a predictor of strength, between LG/J and SM/J strains, which are the inbred progeny of mice  
35 selected, respectively, for high and low body weight.

36 **Methods.** We measured weight of 5 hindlimb muscles; tibialis anterior (TA), extensor digitorum longus  
37 (EDL), gastrocnemius, soleus and quadriceps femoris (QF) in inbred, LG/J and SM/J male and female  
38 mice, in  $F_1$  and  $F_2$  intercrosses and in an advanced intercross (AI),  $F_{34}$ , between the two.  $F_2$  mice were  
39 genotyped using 162 SNPs throughout the genome;  $F_{34}$  mice were genotyped at 3,015 SNPs.

40 **Results.** A 2-fold difference in muscle mass between the LG/J and SM/J mouse strains was observed.  
41 Integrated genome-wide association analysis in the combined population of  $F_2$  and AI identified 22  
42 quantitative trait loci (QTL; genome-wide  $p < 0.05$ ) affecting muscle weight on Chr 2 (2 QTL), 4, 5, 6 (7  
43 QTL), 7 (4 QTL), 8 (4 QTL) and 11 (3 QTL). Among the QTL, two explained over 10% and five over 5% of  
44 phenotypic variance. The LG/J allele conferred greater muscle weight in all cases. The 1.5-LOD QTL  
45 support intervals ranged between 0.3 Mb and 13.4 Mb (median 3.7 Mb) restricting the list of candidates to  
46 between 5 and 97 genes.

47 **Conclusion.** Selection for body weight segregated the alleles affecting skeletal muscle, the most  
48 abundant tissue in the body. Combination of analyses in an  $F_2$  and AI was an effective strategy to detect  
49 and refine the QTL in a genome-wide manner. The achieved resolution facilitates further elucidation of the  
50 underlying genetic mechanisms affecting muscle mass.

## 51 ***Introduction***

52 Skeletal muscle is the most abundant tissue in the body and is critical for diverse functions, including  
53 locomotion, glucose homeostasis, thermoregulation and protection of bones and viscera. Muscle strength  
54 is an important factor of health and fitness as it inversely associated with the risk for coronary heart disease  
55 and stroke (33). Because of the world's growing geriatric population, age-related loss of strength and  
56 muscle mass (sarcopenia), is an increasingly pressing problem. Understanding the mechanisms  
57 underlying skeletal muscle mass and its function is therefore of increasing importance.

58 Genetic variation accounts for around half of the variation in strength in humans (1, 5, 11, 30, 32,  
59 34, 37), presumably reflecting various aspects of muscle structure and function. Discovery of the relevant  
60 gene variants affecting muscle mass may identify the biological pathways affecting skeletal muscle  
61 development and atrophy thereby facilitating identification of novel pharmacological targets. Nevertheless,  
62 very few specific genes underlying genetic variation in muscle mass have been identified to date (8, 25, 41,  
63 42).

64 Animal models such as mice (25, 35), sheep (6) and pigs (41) have been used to study the genetics  
65 of muscle mass. In these studies, traits that are largely monogenic have been examined, facilitating  
66 discovery of the underlying genes. However, variation in skeletal muscle phenotypes is a polygenic trait in  
67 all species and attempts to study the polygenic architecture of muscle variation have been initiated in mice  
68 (4, 20, 24), pigs (26, 43) and chicken (18, 27, 29, 40). A number of quantitative trait loci (QTL) have been  
69 mapped; however, refinement of these QTL and identification of the underlying genes is a challenging  
70 problem.

71 We used a classical  $F_2$  intercross and an advanced intercross (AI) population, which allows  
72 mapping of QTL to very small intervals (9), in an effort to accelerate progress in this area. By integrating  
73 studies of  $F_2$  and AI mice, we have combined the power of an  $F_2$  population and the resolution of an AI  
74 population. The inbred strains used to make this AI were divergently selected for body size (13, 22), and  
75 are thus ideally suited for this experiment. Studies in pigs (26, 43), sheep (8) and mice (19, 20) have  
76 demonstrated that genetic variation can exert muscle-specific effects. Therefore, we examined 5 different  
77 muscles in the hindlimb of mice in our populations.

## 78 **Methods**

### 79 Animals and phenotype

80 The study was carried out on males and females of the LG/J and SM/J inbred strains, LGSMF<sub>1</sub>, LGSMF<sub>2</sub>  
81 intercrosses and a population of the 34<sup>th</sup> filial generation of AI, LGSMF<sub>34</sub>, (see **Table 1** for details). This set  
82 of mice, recently described by Cheng and colleagues (7), was involved in a behavioral study prior to the  
83 analyses of muscle phenotypes. Animals were sacrificed at the age of 94 ± 4 days and their carcasses  
84 frozen. All procedures through sacrifice were conducted at the University of Chicago and approved by the  
85 Institutional Animal Care and Use Committee.

86 Carcasses were defrosted and tibialis anterior (TA), extensor digitorum longus (EDL),  
87 gastrocnemius (Gastroc), soleus and quadriceps femoris (QF) were dissected under a dissection  
88 microscope and weighed on a Mettler AE 50 balance (Mettler Toledo, OH) to the closest 0.1 mg.

89

### 90 Aggregate genetic effects

91 Broad sense heritability estimates,  $H^2$ , were obtained as follows;  $H^2 = (V_P - V_E)/V_P$  (10), where phenotypic  
92 variance,  $V_P$ , is variance of genetically mixed population (LGSMF<sub>2</sub> or LGSMF<sub>34</sub>) and environmental  
93 variance,  $V_E$ , is variance of LGSMF<sub>1</sub> population.

94

### 95 QTL mapping

96 Mice were genotyped using SNP markers that were approximately evenly distributed across the genome at  
97 162 (F<sub>2</sub>) SNPs or 3015 (AI) SNPs. We performed genome wide association analysis in the combined  
98 population of the F<sub>2</sub> and F<sub>34</sub> intercrosses using software developed at the University of Chicago (QTLRel;  
99 <http://www.palmerlab.org>); with some custom modifications. This software allowed us to account for the  
100 complex relationships (e.g. sibling, half-sibling, cousins) among the AI mice by using a mixed model as  
101 described by Cheng and colleagues (7). Because of sex differences in muscle mass and also the  
102 discovery of sex-specific QTL in other studies (19, 20) we explored genetic models where sex was included  
103 as either an additive or an interactive covariate.

104

## 105 Significance thresholds

106 Muscle-specific thresholds were derived using a gene dropping procedure, which generates genotypic data  
107 by simulating meiosis involving individuals in a pedigree, as described in Cheng et al (7). Briefly, a  
108 genotypic data set was simulated and a genome-wide scan was performed using the simulated genotypic  
109 data and the original phenotypic data and using the model for which a significance threshold was being  
110 sought. The maximum of the test statistic was recorded. This process was repeated 1000 times and the  
111 corresponding maxima of the test statistic were pooled to estimate the threshold at a given significance  
112 level. This procedure controls the false positive (type I) error rate while preserving correlations among  
113 phenotypes and genotypes. We used a similar procedure to calculate significance thresholds on a per-  
114 chromosome basis.

115 There is a substantial difference in muscle size between males and females. Also, a number of loci  
116 affecting skeletal growth in a sex-specific manner were reported in this lineage (28). Therefore, to test for  
117 the sex-specific effects on muscle weight we compared the model with QTL-by-sex interaction (alternative  
118 hypothesis) and the model without the interaction (null hypothesis). The testing procedure was the same  
119 as described above and the testing method was also gene dropping.

120 In instances of multiple peaks on the chromosome the following criteria were used to discriminate  
121 between linked QTL; the peak must be above the genome-wide  $p < 0.05$  threshold and must drop by 3 LOD  
122 on each side of that peak (except for the end of the chromosome).

123 We defined the confidence interval for each QTL as the 1.5-LOD drop off on either side of the peak  
124 marker. This interval was expressed in physical map position (Mb) by using the nearest genotyped SNP  
125 that flanked the support interval.

126

## 127 Database analyses

128 Mouse phenome database (3) was used to identify non-synonymous SNPs in the QTL regions. The SNP  
129 genotypes of the LG/J and SM/J strains were selected from the CGD1 imputed data set  
130 (<http://phenome.jax.org/pub-cgi/phenome/mpdcgi>) (36).

131 PolyPhen web based tool (31) was utilized to predict the possible effects of amino acid substitution  
132 on the function of a protein (<http://genetics.bwh.harvard.edu/pph/>). These predictions are based on  
133 multiple sequence alignments, functional and structural characterization of the substitution site.

134 Mouse genome informatics (MGI) database (<http://www.informatics.jax.org/>) and gene expression  
135 omnibus (<http://www.ncbi.nlm.nih.gov/geo/>) were used to examine tissue expression of the genes. The  
136 MGI database was also utilized to search for transgenic models influencing skeletal muscle.

137

### 138 Other statistical analyses.

139 Muscle weight phenotypes approximated normality in both F<sub>2</sub> and F<sub>34</sub> populations. Strain effect on muscle  
140 weight in progenitors was assessed using 2-way ANOVA (strain and sex as independent factors).

141 Pearson's product-moment correlations were calculated between different muscle weights within males  
142 and females. First principal component (PC1) was extracted from the five muscles and used as additional  
143 phenotype in the QTL analysis.

144

## 145 **Results**

### 146 Phenotypic analyses

147 There was a more than 2-fold difference in muscle weight between the LG/J and SM/J strains ( $p < 0.0001$ ;  
148 **Table 1**) indicating that selection for body size at 60 days of age (13, 22) resulted in segregation of alleles  
149 affecting skeletal muscle weight at 90 days. Phenotypic correlations (within-sex) between weights of  
150 various muscles were comparable in the LGSMF<sub>2</sub> and LGSMF<sub>34</sub> populations and ranged between 0.70-  
151 0.90 (all  $p < 0.01$ ) in males and 0.69-0.91 ( $p < 0.01$ ), in females.

152 Broad sense heritability ranged between 0.60 and 0.82, was similar among the 5 muscles and  
153 tended to be somewhat higher in males than females (**Table 2**). Heritability estimates derived from the  
154 LGSMF<sub>34</sub> variances were comparable with those based on the LGSMF<sub>2</sub>.

155

### 156 QTL analysis

157 Multiple linked QTL emerged as a characteristic feature of the genetic architecture of muscle weight in the  
158 cross of LG/J and SM/J strains. Association analysis of individual muscles and of PC1 in the integrated

159 LGSMF<sub>2</sub> and LGSMF<sub>34</sub> population mapped 22 QTL (genome-wide p<0.05) to Chromosomes 2 (2 loci), 4, 5,  
160 6 (7 loci), 7 (4 loci), 8 (4 loci) and 11 (3 loci) (**Figure 1**). Characteristics of the genetic architecture of  
161 muscle weight are summarized in **Table 3**. Size of the QTL effect did not differ between males and  
162 females statistically significantly. Among the QTL, two (*Skmw28*, *Skmw37*) explained over 10% of  
163 phenotypic variance and ten loci explained 5% or more of phenotypic variation in one or more muscles  
164 and/or in PC1. The LG/J allele always conferred greater muscle weight. The QTL support interval (1.5-  
165 LOD drop-off) of individual traits ranged between 0.3 Mb and 13.4 Mb (median 3.7 Mb).

166 Consistent with the positive phenotypic correlation between different muscles, the majority of the  
167 QTL exerted pleiotropic effects on more than one muscle. Weight of the TA muscle was affected by 12  
168 (together accounting for 54% of phenotypic variance; based on single QTL model estimates), EDL by 12  
169 (45%), gastrocnemius by 7 (42%), soleus by 9 (19%) and quadriceps femoris by 6 (39%) QTL. The  
170 genetic architecture of the PC1 largely overlapped with that of the individual muscles. In addition, PC1  
171 analysis permitted refinement of three additional loci (**Table 3**). A total of 14 QTL were identified for PC1.

172

### 173 Candidate genes

174 The mapping resolution provided by our analyses guided us to a manageable number of genes in many  
175 loci, for instance, *Skmw27* and *Skmw30* harbored fewer than ten genes and three loci, *Skmw23*, *Skmw32*  
176 and *Skmw40*, harbored less than twenty. The SNP analysis of all QTL identified approximately thirty genes  
177 with nonsense polymorphisms between the two strains that were clustered within ten QTL regions. We  
178 examined these genes using the PolyPhen tool (<http://genetics.bwh.harvard.edu/pph/>) which relies on the  
179 sequence, phylogenetic and structural information characterizing the substitution (31). Most of these  
180 polymorphisms were predicted to have no effect of the protein function, however, polymorphisms in the  
181 zinc finger protein 341, *Zfp341*, (*Skmw21*); lipopolysaccharide binding protein, *Lbp*, phospholipase  $\gamma$  1,  
182 *Plcg1* (*Skmw22*); tubulin tyrosine ligase-like family member 3, *Ttll3*, interleukin 17 receptor C, *Il17rc*,  
183 Fanconi anemia complementation group D2, *Fancd2*, interleukin-1 receptor-associated kinase 2, *Irak2*  
184 (*Skmw29*); and WD repeat containing protein 17, *Wdr17* (*Skmw38*) genes are predicted to alter protein  
185 function. Based on the available microarray data transcripts of all eight genes are detected in mouse

186 skeletal muscle (GDS2840, GDS2698) providing support for further scrutiny of the candidacy of these  
187 genes.

188 We examined available transgenic models for possible effects on muscle tissue using the MGI  
189 database and found that allelic variations (due to spontaneous or induced mutations) in a number of genes  
190 from the QTL regions can affect the skeletal muscle (summarized in **Table 3**). There were no non-  
191 synonymous polymorphisms between the two strains in these genes. However polymorphisms causing  
192 expression variation could be the underlying mechanism of the QTL effects.

193

## 194 ***Discussion***

195 We carried out the genome-wide mapping of QTL affecting skeletal muscle mass in an F<sub>2</sub> and AI  
196 population of mice derived from strains selected for high and low body weight at 60 days of age. We  
197 hypothesized that such selection would have segregated alleles affecting skeletal muscle weight, the most  
198 abundant tissue in the body. Indeed, the LG/J and SM/J strains exhibited a 2-fold difference in weight of 5  
199 hindlimb muscles and heritability estimates ranged between 0.60 and 0.88 for the weight of different  
200 muscles. We mapped 22 QTL affecting weight of one or more muscles. The LG/J allele conferred an  
201 increasing effect in all QTL. The analyses in the integrated F<sub>2</sub> and AI population permitted us to achieve a  
202 genome-wide fine mapping of the loci to median resolution of 3.7 Mb. In four muscles, the aggregate effect  
203 of the identified QTL accounted for between 38% and 59% of phenotypic variation and somewhat less,  
204 19%, in soleus. The underlying mechanism of this contrast between soleus and other muscles is not clear  
205 but could be partially due to the fiber type composition differences. Mouse soleus consists of a mixture of  
206 type I and IIA fibers whereas four other tested muscles predominantly consist of type IIA and IIB fibers (47,  
207 49).

208 Analyses of body and organ weights as well as skeleton and body growth have proven the LG/J x  
209 SM/J lineage a suitable model for studying the mechanisms underlying variation in body size components  
210 (17, 44). Because of the contribution of muscle tissue to body size and growth some overlap between QTL  
211 affecting muscle weight and integrative phenotypes was expected. In accordance with this assumption  
212 muscle weight QTL mapped to the similar genomic regions on Chr 2, 4, 6, 7, 8 and 11 to those implicated  
213 in body weight and growth traits (17, 44). The comparison with the genetic architecture of the long bone

214 (28) indicated possible muscle/bone pleiotropy of six loci scattered through chromosomes 2 (*Skmw21*,  
215 *Smw22*), 6 (*Skmw25*, *Skmw31*), 7 (*Skmw33*) and 8 (*Skmw36*). Several scenarios can be offered to explain  
216 the pleiotropy. Considering a single causative gene per QTL, variation in muscle mass could be secondary  
217 to that in bone length. Alternatively, it can be a result of a concomitant influence on both tissues.  
218 However, it is also possible that pleiotropy is an outcome of the effects of different genes influencing  
219 muscle and bone phenotypes. Identification of the causative genes will be required for understanding of  
220 the underlying mechanisms of pleiotropy.

221 We were able to refine nine loci to <3 Mb size. The strength of the classical QTL mapping in an F<sub>2</sub>  
222 intercross lies in its ability to identify the entire genetic architecture contributing to phenotypic variation.  
223 The refinement of the QTL, however, poses a significant hurdle. Typically, the fine mapping is carried out  
224 via congenic strain approach on a locus by locus basis aiming to narrow down the region of interest to a  
225 manageable list of candidate genes (38). An advanced intercross is an appealing alternative, particularly  
226 for the phenotype with rich genetic architecture, because it allows screening of the entire genome in one  
227 study (9). However, the power to detect QTL in AI appeared more limited than in F<sub>2</sub>s. For instance, none  
228 of the QTL affecting TA weight on Chr 6, 7 or 8 in LGSMF<sub>2</sub> intercross was replicated in a separate analysis  
229 within the LGSMF<sub>34</sub> population (**Figure 2**). We hypothesize that this is an outcome of the partitioning of  
230 QTL into several linked loci. The effect size of fractioned QTL might have been beyond detection power of  
231 the available sample size. Partitioning of the QTL has been reported previously (45) and suggested as a  
232 possible cause of replication failure in addition to the false positives and the Beavis effect (2). A QTL scan  
233 in the integrated F<sub>2</sub> and AI population of the same lineage offers a superior strategy of data analysis by  
234 increasing the sample size, combining the detection power of the former and accuracy of the latter. To  
235 illustrate the aspect of accuracy, we continue an example presented in **Figure 2**. A 1.5-LOD drop off  
236 interval of the TA weight QTL on Chr 6 spanned between 54.1 and 104.8 Mb (50.7 Mb long) in the LGSMF<sub>2</sub>  
237 population. The QTL broke down into six smaller loci in the combined analysis of the LGSMF<sub>2</sub> and  
238 LGSMF<sub>34</sub> populations (**Supplemental Table 1**). The size of the refined loci ranged between 0.3 and 5.4  
239 Mb, a more than 10-fold reduction. Importantly, three out of six loci were outside of the LGSMF<sub>2</sub> 1.5-LOD  
240 drop off interval and thus, candidacy of the genes within those regions would not even be considered in the  
241 analysis of solely F<sub>2</sub> population.

242 Mapping resolution led us to a manageable list of the candidate genes in most of the loci. Among  
243 them we identified eight genes, *Zfp341*, *Lbp*, *Plcg1*, *Ttll3*, *Il17rc*, *Fancd2*, *Irak2* and *Wdr17*, with non-  
244 synonymous polymorphisms which are likely to influence function of the proteins between the two strains.  
245 These genes are expressed in muscle tissue and thus are good candidates for follow-up analysis. Several  
246 other genes in the QTL regions are likely functional candidates as well. For instance, mutation in  
247 mitochondrial protease Omi coding gene, *Htra2* (*Skmw26*), leads to muscle wasting (16), overexpression of  
248 caveolin-3, *Cav3*, gene results in fiber phenotypes resembling Duchenne muscle dystrophy (12), and  
249 disruption of type 1 IGF receptor gene, *Igf1r* (*Skmw32*), causes severe suppression of muscle growth (21).  
250 Whereas *Tead1* (*Skmw34*) (39), *Tead4* (*Skmw30*) (48) and *Mef2a* (*Skmw32*) (48) genes are transcription  
251 factors abundantly expressed in skeletal muscle. The genomic sequence of the LG/J and SM/J strains and  
252 the transcriptome analysis will provide additional leverage for further nomination of candidate genes  
253 underlying those QTL.

254 The overall genetic architecture was richer than that of any individual muscle indicating that not all  
255 muscles were affected (or at least were not affected equally) by the same locus. Six out of 22 loci were  
256 found influencing only EDL (three loci), soleus (two loci) or TA (one locus) muscle. Specificity of the  
257 *Skmw22* and *Skmw42* loci to soleus might be related to the distinct fiber type composition of this muscle (a  
258 mixture of type 1 and type 2A fibers) compared to the other examined muscles (predominantly a mixture of  
259 type 2A and type 2B fibers) as well as its function (soleus is a frequently used postural muscle). The  
260 effects specific to EDL (*Skmw23* and *Skmw24* loci) but not, for instance, to its synergist TA were also  
261 reported in the intercross between the C57BL/6J and DBA/2J strains (19, 20) although the underlying  
262 mechanisms of the specificity between muscles of similar type remain unclear. Specificity of the loci  
263 affecting TA (*Skmw27*) and EDL (*Skmw36*) muscles most likely is an artifact arising from inability to  
264 discriminate between the linked loci according to the selected criteria, i.e., 3 LOD drop between the peaks,  
265 in other muscles (**Figure 1**). Muscle-specific effects were observed earlier in various species (15, 19, 20,  
266 23, 26, 43) and a gene underlying variation of such nature was recently identified in sheep (46).  
267 Identification of the genes and pathways affecting different muscles in a variable manner will help in  
268 understanding of myopathies which often affect some but not all muscles (14).

269 In conclusion, we identified and refined the genetic architecture consisting of 22 QTL affecting  
270 variation in muscle weight in the LG/J x SM/J lineage. The resolution and effect size of the QTL are  
271 favorable for a fruitful pursuit of the underlying genes.

272

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277

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282 **Table 1.** Phenotypes of the LG/J and SM/J strains and their intercross populations (mean  $\pm$  SD).  
283

|                     | Sex       | Age (days)     | TA, mg         | EDL, mg        | Gastroc, mg      | Soleus, mg     | QF, mg           |
|---------------------|-----------|----------------|----------------|----------------|------------------|----------------|------------------|
| LG/J                | ♂ (n=18)  | 93.9 $\pm$ 2.6 | 68.5 $\pm$ 4.3 | 12.7 $\pm$ 1.0 | 164.8 $\pm$ 9.8  | 10.1 $\pm$ 0.9 | 321.0 $\pm$ 18.6 |
|                     | ♀ (n=19)  | 95.1 $\pm$ 1.7 | 56.7 $\pm$ 3.0 | 10.0 $\pm$ 0.5 | 122.3 $\pm$ 7.1  | 8.0 $\pm$ 0.8  | 241.4 $\pm$ 12.4 |
| SM/J                | ♂ (n=15)  | 90.5 $\pm$ 0.9 | 31.2 $\pm$ 2.2 | 6.4 $\pm$ 0.6  | 80.8 $\pm$ 5.7   | 4.8 $\pm$ 0.5  | 150.2 $\pm$ 9.2  |
|                     | ♀ (n=10)  | 90.7 $\pm$ 0.9 | 26.6 $\pm$ 2.0 | 5.1 $\pm$ 0.5  | 64.1 $\pm$ 5.8   | 3.8 $\pm$ 0.5  | 117.0 $\pm$ 11.0 |
| LGSMF <sub>1</sub>  | ♂ (n=11)  | 93.2 $\pm$ 1.2 | 58.9 $\pm$ 2.9 | 10.2 $\pm$ 0.6 | 138.1 $\pm$ 7.0  | 8.1 $\pm$ 0.5  | 255.3 $\pm$ 12.8 |
|                     | ♀ (n=5)   | 91.4 $\pm$ 1.3 | 46.5 $\pm$ 3.4 | 8.1 $\pm$ 0.6  | 100.1 $\pm$ 6.0  | 5.9 $\pm$ 0.5  | 184.4 $\pm$ 13.3 |
| LGSMF <sub>2</sub>  | ♂ (n=252) | 95.3 $\pm$ 2.5 | 49.4 $\pm$ 6.5 | 9.2 $\pm$ 1.2  | 122.8 $\pm$ 14.4 | 7.0 $\pm$ 1.1  | 227.8 $\pm$ 27.9 |
|                     | ♀ (n=245) | 95.6 $\pm$ 2.2 | 38.3 $\pm$ 5.9 | 7.0 $\pm$ 1.0  | 87.3 $\pm$ 11.2  | 5.2 $\pm$ 0.8  | 166.6 $\pm$ 22.4 |
| LGSMF <sub>34</sub> | ♂ (n=254) | 93.0 $\pm$ 5.4 | 51.8 $\pm$ 6.8 | 9.7 $\pm$ 1.3  | 128.2 $\pm$ 15.8 | 7.7 $\pm$ 1.3  | 233.9 $\pm$ 29.3 |
|                     | ♀ (n=238) | 94.1 $\pm$ 4.4 | 40.4 $\pm$ 5.6 | 7.3 $\pm$ 1.0  | 92.4 $\pm$ 12.8  | 5.9 $\pm$ 1.0  | 172.8 $\pm$ 23.1 |

285 **Table 2.** Broad sense heritability of muscle weight in males and females.  
286

|                     |         | TA   | EDL  | GAST | Sol  | QF   |
|---------------------|---------|------|------|------|------|------|
| LGSMF <sub>2</sub>  | males   | 0.80 | 0.76 | 0.76 | 0.82 | 0.79 |
|                     | females | 0.67 | 0.62 | 0.79 | 0.60 | 0.65 |
| LGSMF <sub>34</sub> | males   | 0.82 | 0.81 | 0.80 | 0.88 | 0.81 |
|                     | females | 0.63 | 0.62 | 0.78 | 0.73 | 0.67 |

287

**Table 3.** Summary of the genetic architecture of muscle weight in the LG/J and SM/J strains.

| Trait <sup>†</sup> | Chr     | Start <sup>**</sup> | End     | Size   | %var <sup>†</sup> |      | Candidate genes <sup>**</sup>  | QTL <sup>†††</sup>               | Locus <sup>‡</sup> |
|--------------------|---------|---------------------|---------|--------|-------------------|------|--|----------------------------------|--------------------|
|                    |         |                     |         |        | Low               | High |  |                                  |                    |
| P                  | 2       | 153.445             | 156.369 | 2.9    | -                 | 2.9  | <i>Ncoa6</i> <sup>TM</sup> , <i>Zfp341</i> <sup>NS</sup>   | <i>Lbn2.2</i>                    | <i>Skmw21</i>      |
| S                  |         | 157.958             | 162.160 | 4.2    | -                 | 1.6  | <i>Slc32a1</i> <sup>TM</sup> , <i>Lbp</i> <sup>NS</sup> , <i>Plcg1</i> <sup>NS</sup>   | <i>Bdlng7</i> ,<br><i>Lbn2.2</i> | <i>Skmw22</i>      |
| E                  | 4       | 53.650              | 55.833  | 2.2    | -                 | 3.5  | <i>Fktn</i> <sup>TM</sup> , <i>Tmem38b</i> <sup>TM</sup>   | N/A                              | <i>Skmw23</i>      |
| E                  | 5       | 69.173              | 82.557  | 13.4   | -                 | 2.3  | <i>Corin</i> <sup>TM</sup> , <i>Sgcb</i> <sup>TM</sup> , <i>Pdgfra</i> <sup>TM</sup> , <i>Kdr</i> <sup>TM</sup> , <i>Hopx</i> <sup>TM</sup>  | N/A                              | <i>Skmw24</i>      |
| T,G,S,P            | 6       | 49.942              | 53.809  | 3.9    | 1.9               | 5.9  | <i>Hoxa1</i> <sup>TM</sup> , <i>Hoxa2</i> <sup>TM</sup> , <i>Hoxa3</i> <sup>TM</sup>   | <i>Lbn6.1b</i>                   | <i>Skmw25</i>      |
| T,E,G,S,Q          |         | 79.491              | 83.038  | 3.5    | 2.8               | 9.7  | <i>Htra2</i> <sup>SP</sup>   | N/A                              | <i>Skmw26</i>      |
| T                  |         | 92.586              | 93.829  | 1.2    | -                 | 5.0  | N/A  | N/A                              | <i>Skmw27</i>      |
| T,E,S,Q,P          |         | 94.796              | 100.209 | 5.4    | 3.6               | 12.3 | <i>Foxp1</i> <sup>TM</sup>   | N/A                              | <i>Skmw28</i>      |
| P                  |         | 110.596             | 113.993 | 3.4    | -                 | 6.9  | <i>Cav3</i> <sup>TM</sup> , <i>Mtmt14</i> <sup>TM</sup> , <i>Vhl</i> <sup>TM</sup> , <i>Ttll3</i> <sup>NS</sup> , <i>Il17rc</i> <sup>NS</sup> , <i>Fancd2</i> <sup>NS</sup> , <i>Irak2</i> <sup>NS</sup> | N/A                              | <i>Skmw29</i>      |
| T,E,G,Q            |         | 127.916             | 128.186 | 0.3    | 3.6               | 4.9  | N/A  | N/A                              | <i>Skmw30</i>      |
| T,E,S,P            |         | 136.083             | 138.966 | 2.9    | 2.5               | 5.5  | N/A  | <i>Lbn6.2</i>                    | <i>Skmw31</i>      |
| T,E,G,Q,P          |         | 7                   | 73.789  | 75.508 | 1.7               | 2.5  | 6.1  | <i>Igf1r</i> <sup>TM</sup>       | N/A                |
| E,P                | 90.115  |                     | 96.666  | 6.6    | 2.9               | 5.6  | <i>Fes</i> <sup>TM</sup> , <i>Fzd4</i> <sup>TM</sup>   | <i>Lbn7.1</i>                    | <i>Skmw33</i>      |
| T,E,S,Q,P          | 118.012 |                     | 122.071 | 4.1    | 2.5               | 5.7  | <i>Mrv1</i> <sup>TM</sup> , <i>Tead</i> <sup>TM</sup>  | N/A                              | <i>Skmw34</i>      |
| P                  | 135.755 |                     | 141.073 | 5.3    | -                 | 3.8  | <i>Ate1</i> <sup>TM</sup> , <i>Bub3</i> <sup>TM</sup> , <i>Fgfr2</i> <sup>TM</sup> , <i>Hmx3/Hmx2</i> <sup>TM</sup> , <i>Plekha1</i> <sup>GT</sup>   | N/A                              | <i>Skmw35</i>      |
| E                  | 8       | 10.522              | 15.505  | 5.0    | -                 | 5.1  | N/A  | <i>Lbn8.2</i>                    | <i>Skmw36</i>      |
| T,G,Q,P            |         | 31.960              | 38.083  | 6.1    | 7.6               | 10.7 | <i>Nrg1</i> <sup>TM</sup>  | <i>Bdywt</i> ,<br><i>Lbn7</i> ,  | <i>Skmw37</i>      |
| E,G,S,P            |         | 48.755              | 55.272  | 6.5    | 2.6               | 5.8  | <i>Hand2</i> <sup>TM</sup> , <i>Wdr17</i> <sup>NS</sup>  | N/A                              | <i>Skmw38</i>      |
| T,E,G,P            |         | 85.897              | 87.972  | 2.1    | 1.6               | 4.7  | <i>Gipc1</i> <sup>GT</sup> , <i>Cacna1</i> <sup>SP, TM</sup> , <i>Calr</i> <sup>TM</sup> , <i>Dnase2a</i> <sup>TM</sup>  | N/A                              | <i>Skmw39</i>      |
| T,S                | 11      | 6.827               | 9.697   | 2.9    | 1.6               | 2.8  | <i>Igfbp3</i> <sup>TM</sup>  | <i>Bglq8</i>                     | <i>Skmw40</i>      |
| T,G,Q,P            |         | 28.239              | 29.465  | 1.2    | 2.0               | 3.3  | <i>Efemp1</i> <sup>TM</sup>  | <i>W6q3</i>                      | <i>Skmw41</i>      |
| S                  |         | 31.225              | 35.337  | 4.1    | -                 | 1.7  | <i>Hba-a1</i> <sup>TM</sup> , <i>Kcnmb1</i> <sup>TM</sup>  | <i>W6q3</i>                      | <i>Skmw42</i>      |

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291 \* abbreviations used for different phenotypes T, TA; E, EDL; G, GAST; S, SOL; Q, QF muscles; P, first  
292 principal component.

293 \*\* physical map position (Build 37.1) and size of 1.5-LOD drop off interval in Mbp. Position of the  
294 overlapping interval is given for the loci affecting multiple phenotypes. Characteristics of individual trait  
295 QTL are presented in **Supplemental Table 1**.

296 † percent of phenotypic variance explained by the locus across sex. The lowest (Low) and highest (High)  
297 estimates are presented for multi-trait loci.

298 †† effects of listed genes on skeletal muscle were documented in targeted (<sup>TM</sup>), spontaneous (<sup>SP</sup>) or gene  
299 trapping (<sup>GT</sup>) mutation models ([www.informatics.jax.org](http://www.informatics.jax.org)); non-synonymous polymorphisms (<sup>NS</sup>) between the  
300 LG/J and SM/J strains are likely to affect function of these genes. N/A, not available.

301 ††† body/organ weight, body length, growth, or bone length QTL ([www.informatics.jax.org](http://www.informatics.jax.org)) overlapping with  
302 skeletal muscle weight (*Skmw*) locus.

303 † locus name assigned to QTL.

**Supplemental Table 1.** Characteristics of muscle weight QTL in the lineage of LG/J and SM/J strains.

| Phenotype | Chr | Position and size of 1.5-LOD drop off, bp (Build 37) |             |            | Locus effect |      |      | Locus         |
|-----------|-----|--|-------------|------------|--------------|------|------|---------------|
|           |     | lower  | upper       | size, bp   | a/SD         | d/SD | %var |               |
| PC1       | 2   | 153,444,570  | 156,368,950 | 2,924,380  | -1.4         | -0.2 | 2.9  | <i>Skmw21</i> |
| SOL       | 2   | 157,957,996  | 162,160,118 | 4,202,122  | 1.6          | 0.6  | 1.6  | <i>Skmw22</i> |
| EDL       | 4   | 53,649,562   | 55,833,085  | 2,183,523  | 2.2          | 1.0  | 3.5  | <i>Skmw23</i> |
| EDL       | 5   | 69,173,468   | 82,557,190  | 13,383,722 | 1.6          | 1.8  | 2.3  | <i>Skmw24</i> |
| TA        | 6   | 49,942,003   | 53,808,619  | 3,866,616  | 2.1          | 0.7  | 4.3  | <i>Skmw25</i> |
| GAST      | 6   | 49,942,003   | 53,808,619  | 3,866,616  | 2.5          | 1.1  | 5.3  |               |
| SOL       | 6   | 49,942,003   | 53,808,619  | 3,866,616  | 1.8          | -0.4 | 1.9  |               |
| PC1       | 6   | 49,035,227   | 53,928,667  | 4,893,440  | -2.4         | 0.1  | 5.9  |               |
| GAST      | 6   | 76,065,781   | 83,062,445  | 6,996,664  | 3.3          | 1.3  | 7.5  |               |
| SOL       | 6   | 76,065,781   | 83,062,445  | 6,996,664  | 2.4          | 0.3  | 2.8  |               |
| EDL       | 6   | 76,437,152   | 83,062,445  | 6,625,293  | 2.8          | 0.6  | 5.4  |               |
| PC1       | 6   | 79,491,203   | 83,038,237  | 3,547,034  | -3.2         | -0.1 | 9.7  |               |
| QF        | 6   | 76,437,152   | 83,062,445  | 6,625,293  | 3.2          | 0.1  | 7.0  |               |
| TA        | 6   | 79,432,382   | 83,062,445  | 3,630,063  | 2.9          | -0.1 | 5.3  |               |
| TA        | 6   | 92,586,287   | 93,829,424  | 1,243,137  | 2.6          | 0.3  | 5.0  | <i>Skmw27</i> |
| EDL       | 6   | 94,795,564   | 100,209,455 | 5,413,891  | 3.3          | 1.7  | 7.4  | <i>Skmw28</i> |
| QF        | 6   | 94,795,564   | 100,209,455 | 5,413,891  | 3.7          | 1.5  | 8.7  |               |
| TA        | 6   | 94,795,564   | 100,209,455 | 5,413,891  | 3.6          | 1.3  | 8.4  |               |
| SOL       | 6   | 94,795,564   | 100,982,494 | 6,186,930  | 2.7          | 0.5  | 3.6  |               |
| PC1       | 6   | 94,554,523   | 104,813,397 | 10,258,874 | -3.7         | -1.3 | 12.3 |               |
| PC1       | 6   | 110,595,862  | 113,992,607 | 3,396,745  | -2.6         | 0.4  | 6.9  |               |
| EDL       | 6   | 127,916,001  | 128,186,433 | 270,432    | 2.2          | 1.7  | 3.6  | <i>Skmw30</i> |
| QF        | 6   | 127,916,001  | 129,001,312 | 1,085,311  | 2.7          | 1.4  | 4.9  |               |
| TA        | 6   | 127,916,001  | 128,186,433 | 270,432    | 2.1          | 1.4  | 3.6  |               |
| GAST      | 6   | 127,916,001  | 128,186,433 | 270,432    | 2.5          | 1.3  | 4.7  |               |
| TA        | 6   | 134,394,713  | 138,966,204 | 4,571,491  | 1.8          | 2.1  | 2.7  |               |
| EDL       | 6   | 134,720,099  | 140,261,660 | 5,541,561  | 2.2          | 1.9  | 3.3  |               |
| SOL       | 6   | 136,082,535  | 141,494,615 | 5,412,080  | 2.2          | 1.3  | 2.5  |               |
| PC1       | 6   | 133,563,062  | 141,518,241 | 7,955,179  | -2.3         | -1.0 | 5.5  |               |
| EDL       | 7   | 71,646,592   | 75,507,975  | 3,861,383  | 2.2          | 1.2  | 3.6  | <i>Skmw32</i> |
| GAST      | 7   | 71,646,592   | 75,507,975  | 3,861,383  | 1.5          | 0.6  | 2.5  |               |
| QF        | 7   | 71,646,592   | 75,894,127  | 4,247,535  | 2.5          | 1.2  | 4.5  |               |
| TA        | 7   | 73,789,451   | 75,507,975  | 1,718,524  | 2.3          | 2.0  | 4.2  |               |
| PC1       | 7   | 71,646,592   | 75,507,975  | 3,861,383  | -2.5         | -0.7 | 6.1  |               |
| EDL       | 7   | 87,372,042   | 96,666,054  | 9,294,012  | 2.0          | 1.1  | 2.9  | <i>Skmw33</i> |
| PC1       | 7   | 90,115,093   | 96,666,096  | 6,551,003  | -2.4         | -0.7 | 5.6  |               |
| QF        | 7   | 112,702,939  | 123,174,561 | 10,471,622 | 2.7          | -0.7 | 4.7  | <i>Skmw34</i> |
| EDL       | 7   | 113,957,643  | 122,071,240 | 8,113,597  | 2.3          | -0.5 | 3.8  |               |
| SOL       | 7   | 116,422,737  | 122,071,240 | 5,648,503  | 2.0          | -0.6 | 2.5  |               |
| TA        | 7   | 118,011,780  | 122,071,240 | 4,059,460  | 2.3          | -1.4 | 3.9  |               |
| PC1       | 7   | 118,011,780  | 122,071,240 | 4,059,460  | -2.3         | 0.6  | 5.7  |               |
| PC1       | 7   | 135,754,842  | 141,073,215 | 5,318,373  | -1.6         | 0.4  | 3.8  |               |
| EDL       | 8   | 10,521,727   | 15,504,807  | 4,983,080  | 2.5          | 2.2  | 5.1  |               |
| TA        | 8   | 28,327,939   | 38,082,699  | 9,754,760  | 3.6          | 1.8  | 8.5  | <i>Skmw37</i> |
| QF        | 8   | 29,225,710   | 42,876,689  | 13,650,979 | 3.1          | 2.3  | 7.6  |               |
| GAST      | 8   | 31,960,208   | 42,876,689  | 10,916,481 | 3.6          | 2.0  | 10.0 |               |
| PC1       | 8   | 29,193,796   | 47,665,361  | 18,471,565 | -3.2         | -1.8 | 10.7 |               |
| SOL       | 8   | 48,676,640   | 60,253,347  | 11,576,707 | 2.5          | -0.3 | 3.1  |               |
| EDL       | 8   | 48,755,167   | 60,253,347  | 11,498,180 | 1.7          | 0.8  | 2.6  |               |
| GAST      | 8   | 48,755,167   | 60,253,347  | 11,498,180 | 2.6          | 0.6  | 5.2  |               |
| PC1       | 8   | 48,271,310   | 55,272,450  | 7,001,140  | -2.2         | -0.7 | 5.8  |               |
| GAST      | 8   | 80,975,290   | 90,718,893  | 9,743,603  | 2.1          | -0.3 | 4.7  | <i>Skmw39</i> |

|      |    |            |            |           |      |      |     |               |
|------|----|------------|------------|-----------|------|------|-----|---------------|
| TA   | 8  | 85,896,590 | 87,971,600 | 2,075,010 | 1.8  | -0.8 | 2.8 |               |
| EDL  | 8  | 85,896,590 | 87,971,600 | 2,075,010 | 1.1  | -0.7 | 1.6 |               |
| PC1  | 8  | 80,186,930 | 89,624,886 | 9,437,956 | -1.5 | -0.2 | 4.1 |               |
| TA   | 11 | 6,410,429  | 9,696,776  | 3,286,347 | 1.8  | 0.6  | 2.8 | <i>Skmw40</i> |
| SOL  | 11 | 6,826,771  | 9,696,776  | 2,870,005 | 1.7  | 0.2  | 1.6 |               |
| GAST | 11 | 24,326,311 | 30,813,598 | 6,487,287 | 1.5  | -0.1 | 2.2 | <i>Skmw41</i> |
| TA   | 11 | 24,633,366 | 29,464,549 | 4,831,183 | 2.0  | -0.2 | 2.9 |               |
| QF   | 11 | 24,633,366 | 30,813,598 | 6,180,232 | 1.4  | -0.3 | 2.0 |               |
| PC1  | 11 | 28,239,128 | 29,926,033 | 1,686,905 | -1.6 | 0.1  | 3.3 |               |
| SOL  | 11 | 31,225,432 | 35,337,492 | 4,112,060 | 1.6  | 0.8  | 1.7 | <i>Skmw42</i> |

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a/SD, d/SD – standardized additive and dominance effects.  
%var – variance explained by the locus.

307 **Figure legends**

308

309 **Figure 1.** LOD plots of chromosomes harboring muscle weight QTL identified by genome-wide association  
310 analyses of five hindlimb muscles and the first principal component (PC1) in integrated population of  
311 LGSMF<sub>2</sub> and LGSMF<sub>34</sub> mice. Horizontal lines represent genome-wide muscle-specific thresholds ( $p < 0.05$ ).

312

313 **Figure 2.** LOD plots of chromosomes 6, 7 and 8 of QTL analyses carried out on TA muscle weight in the  
314 integrated population of the F<sub>2</sub> and F<sub>34</sub> intercrosses and separately. Horizontal line represents empirically  
315 determined genome-wide 5% thresholds for integrated, F<sub>2</sub> and F<sub>34</sub> populations.

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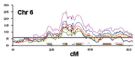
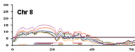
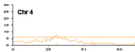
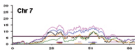
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— TA — GAST — QF  
— EDL — SOL — PC1

LOD

