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X, Y AND AUTOSOMAL DETERMINANTS OF GENETIC ARCHITECTURE OF FAST- AND SLOW-TWITCH SKELETAL MUSCLE WEIGHT IN 500-DAY OLD MICE OF THE C57BL/6J AND DBA/2J LINEAGE

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The aim of the study was to explore the genetic basis for variation in muscle weight between C57BL/6J (B6) and DBA/2J (D2) strains at 500 days of age. The parental strains and two derivative populations, BXD recombinant inbred strains (BXD RIs) and B6D2F2 were used in the study. Paralleling the findings in 200-day old mice (Lionikas et al. 2003), the raw weight of the slow-twitch soleus, the mixed gastrocnemius and the fast-twitch tibialis anterior (TA) and extensor digitorum longus (EDL) muscles was 13 – 22% greater in B6 than in D2. The narrow sense heritability for different muscles ranged from 0.41 to 0.52. The distribution of BXD RI strain means indicated that the genetic influence of muscle weight (strain effect $p<0.001$) was of polygenic origin and the effect of the genetic factors varied between males and females (strain by sex interaction $p<0.05$ for soleus and $p<0.01$ for TA). Linkage analyses in the B6D2F2 population identified an association between the residuals of EDL weight (muscle weight adjusted for body length) and the origin of Y chromosome (B6 < D2, $p<0.001$), as well as a statistically significant quantitative trait loci (QTL) on Chr 2 (TA, EDL), 7 (TA), 9 (TA, EDL; males) and an interaction between regions of Chr 6 and Chr 9 affecting adjusted muscle weights. Correlations of strain means within muscles at 200- and 500-days among BXD RIs indicated a partial commonality of the factors affecting muscle weight at the two ages. Linkage analyses in the combined 200- and 500-day B6D2F2 data set identified QTL on Chr 1 (TA), 2 (EDL, gastrocnemius), 4 (soleus), 5 (soleus), 6 (gastrocnemius), 7 (TA) and 9 proximal (TA, EDL) and distal (TA), and linkages with the X (soleus) and Y (EDL) chromosomes in males. The effects of QTL were not muscle type (fast-/slow-twitch) or function (flexor/extensor) related. The present results support and extend our previous observations that the variation in hind limb muscle weight in B6/D2 lineage is due to a polygenic system. Effects of the genetic factors vary among muscles, i.e. some of the QTL appeared to be muscle-specific whereas others acted pleiotropically; however none of the QTL affected all four muscles. The genetic architecture in the F2 intercross, containing autosomal, X- and Y-linked effects, is independent of type of muscle (fast- or slow-twitch) and may vary between sexes. Several linkages that were unidentified at 200 days of age emerge at the age of 500 days, including sex-chromosomes-linked ones, whereas others were present across the age, e.g. QTL on Chr 2. This pattern is in accordance with the observation in the BXD RI strains indicating that only part of the factors influence muscle weight at both 200 and 500 days of age, others are switched on or off at different ages. The availability of the DNA sequence of both B6 and D2 strains facilitates the nomination of candidate genes and may help to verify their effects in future studies.