DISTINCT QTL ARE LINKED TO CARDIAC LEFT VENTRICULAR MASS IN A SEX-SPECIFIC MANNER IN A NORMOTENSIVE INBRED RAT INTERCROSS

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Wistar-Kyoto (WKY) and WKY-derived hyperactive (WKHA) rats are two inbred strains that display differences in cardiac left ventricular mass (LVM) (WKHA > WKY) but no differences in arterial blood pressure. We had performed previously a partial genome scan of a F2 WKYxWKHA intercross that has led to the identification of a QTL on chromosome RNO5 (band 5q36) that was significantly linked to LVM in males, but not in female rats. We have thus undertaken a more extensive mapping using a larger number of either male or female rats originating from the same cross. A total of 351 males and 332 females have been genotyped with an initial set of 78 microsatellite markers. Calculation of LOD thresholds to be used for significance was performed on the basis of multiple permutations performed on the data set. In males, we detected (in addition to the locus on RNO5) one significant locus on RNO12 (LOD = 2.5, $p < 0.01$) and two loci on RNO17 (LOD = 3.6 and 3.2, respectively, $p < 0.01$). Contrary to the RNO5 locus, the RNO12 and RNO17 loci were transgressive since high LVM was associated with corresponding WKY alleles. In females we detected no linkage of LVM with any of the QTL found in the male progeny, but we found two new and different loci on RNO3 ($p < 0.01$) and RNO15 ($p < 0.05$) (LOD = 2.6 and 2.2, respectively). For the RNO5 locus, we had previously obtained evidence that natriuretic peptide precursor type A (*Nppa*) (that is contained within that locus) constituted a strong candidate gene. This gene codes for the precursor of atrial natriuretic peptide (ANP) that signals via the receptor NPRA, which is encoded by the *Npr1* gene. Since others have shown recently that inactivation of *Npr1* increased LVM in mice only in the presence of testosterone, we tested whether the presence of testosterone affected cardiomyocyte width (i.e. a trait that correlates closely with LVM) in males from the parental WKY and WKHA strains. We found that: 1) cardiomyocyte width was no different in male WKY and WKHA at 4 weeks of age, but that the difference appeared along with sexual maturation, and 2) cardiomyocyte width was not different in adult male WKY and WKHA that had been castrated at 6 weeks of age. Altogether, these results provide evidence that distinct genes may influence LVM of rats in a sex-dependent manner, and that the sex-specific effects could be explained in part (at least for the RNO5 locus) by interaction of the QTL with the sex steroid environment.

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