Chromosomal Assignment and Linkage Analysis of the Rat Mevalonate Pyrophosphate Decarboxylase Gene on Rat Chromosome 19.

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The stroke-prone spontaneously hypertensive rat (SHRSP) has been reported to show a lower serum cholesterol level compared to the Wistar-Kyoto rat (WKY). In addition, it has also been reported that an enzyme activity of mevalonate pyrophosphate decarboxylase (MPD), one of the key enzymes involved in cholesterol synthesis, is lower in SHRSP than that in WKY, suggesting that the gene encoding MPD may underlie mechanisms which genetically regulate serum cholesterol levels in rats. We previously performed a genome scan in the F2 population derived from SHRSP and WKY, and obtained preliminary results that at least two loci—on rat chromosomes 5 and 15—influence the phenotype. In the present study we thus investigated relevance of the rat MPD gene first by linkage mapping and then by studying cosegregation with the phenotype in the F2 population mentioned above.

[Methods] Sequence comparison of the rat MPD cDNA between the two strains was done to find a base substitution polymorphism, and a set of PCR primers were designed from the cDNA sequences to flank the detected polymorphism. Amplified PCR products contained additional intron sequences, where 17 bp tandem repeats were located. These tandem repeats were polymorphic between the two strains and used for characterization of the rat MPD locus in 125 male F2 rats. After it was mapped to a region on rat chromosome 19, the position of this gene relative to other 9 markers on the same chromosome was further determined. Cosegregation analysis was performed between the markers above and serum cholesterol levels with one way analysis of variance.

[Results] We newly developed a genetic marker of the rat MPD gene and determined its chromosome position. In the linkage map spanning 89.1 cM, in total, on rat chromosome 19, MPD was assigned to the position which was 22.0 cM away from the D19Mit7 locus. No significant linkage was found between the MPD locus and serum cholesterol levels. Although the D19Mit2 locus has been reported to be linked to the HDL2 cholesterol level, the corresponding region, which appeared somewhat distant from MPD on rat chromosome 19, showed no effects on the total cholesterol level in the population studied.

[Conclusions] We investigated whether or not the rat MPD gene was involved in the pathophysiological mechanisms of lower cholesterol levels in SHRSP rats. The rat MPD gene was precisely localized to a region on rat chromosome 19 by linkage mapping and showed no evidence in favour of linkage with serum total cholesterol levels. However, considering the reported locus regulating HDL2 cholesterol levels on the same chromosome, further investigation of the MPD gene locus in relation to other lipid phenotypes seems to be interesting.