Conserved Synteny in Rat and Mouse for a Blood Pressure QTL on Human Chromosome 17

Heike Zimdahl, Thomas Kreitler, Claudia Gösele, Detlev Ganten, Norbert Hübner

Abstract—Evidence for blood pressure quantitative trait loci (QTLs) on rat chromosome 10 has been found in multiple independent studies. Analysis of the homologous region on human chromosome 17 revealed significant linkage to blood pressure. The critical segment on human chromosome 17 spans a large interval containing the genes \( \text{ITGA2B} \), \( \text{GFAP} \), and \( \text{ITGB3} \). Therefore, findings in the rat may help to refine the position of blood pressure–regulating loci, assuming a common molecular cause across species. However, it has recently been suggested that the gene order in human, rat, and mouse is not conserved in this region, leaving uncertainty about the overlap of the blood pressure–regulating region between human chromosome 17 and rat chromosome 10. We have performed a detailed comparative analysis among human, mouse, and rat, defining the segment in question, by obtaining gene structure information in silico and by radiation hybrid mapping. It is of interest that this region also contains \( \text{Wnk4} \), a gene previously identified to cause pseudohypoaldosteronism type II and human hypertension. Our results definitively show that the conserved synteny extends among human chromosome 17, rat chromosome 10, and mouse chromosome 11, demonstrating an overlap between previously localized blood pressure QTLs in humans and rats. (Hypertension. 2002;39:1050-1052.)

Key Words: rats ■ mice ■ human ■ hypertension, essential ■ genes ■ genetics

A major blood pressure quantitative trait locus (QTL) has been identified on rat chromosome 10 by linkage analysis in multiple independent studies (see Rapp 2000 for review). By construction of congenic lines, this QTL has been confirmed and narrowed down. Evidence has been presented that, in fact, multiple blood pressure QTLs may be operative on rat chromosome 10. The homologous region on human chromosome 17 has been shown to demonstrate significant linkage to blood pressure in several independent studies, presenting evidence for localization of this QTL to a critical segment of about 10 cM, with a peak logarithm of odds (LOD) score at marker D17S593. This interval on human chromosome 17 contains the genes \( \text{ITGA2B} \), \( \text{GFAP} \), and \( \text{ITGB3} \) (Figure).

Recently, Garrett et al have noted the importance of re-examining how closely rat blood pressure QTLs align with the human data on human chromosome 17 after improved QTL localization using congenic approaches in the rat. The marker order within this segment in the rat was theoretically inferred using mouse genetic maps. Cross-species comparison suggested that the marker order of this blood pressure–relevant segment was not conserved in the rat with respect to humans because of rearrangements of small chromosomal regions between species, thus preventing a definitive conclusion about whether these QTLs in humans and rodents are overlapping.

Here, we present evidence that the gene order in the discussed segment of human chromosome 17 is well conserved between human and rat. Thus, it can be concluded that the blood pressure QTL identified in multiple crosses overlaps with the blood pressure QTL on human chromosome 17. In our analysis we relied on the availability of high-throughput genomic sequence (htgs) data from human, mouse, and rat. To identify rat genes homologous to human \( \text{GFAP} \), \( \text{ITGA2B} \), \( \text{ITGB3} \), and \( \text{Wnk4} \), cDNA sequences were taken from the National Center for Biotechnology Information (NCBI) database (GenBank accession numbers: \( \text{Wnk4} \): NM_032387; \( \text{GFAP} \): XM_050159; \( \text{ITGA2B} \): NM_000419; \( \text{ITGB3} \): NM_000212). The exon-intron structures of the genes were identified/determined by alignment of the cDNA sequence alongside the corresponding genomic BAC clone, respectively. Exons for each gene were identified, and conserved splice sites were observed. Individual human exon sequences were blasted against the rat trace files of the Ensembl database (www.trace.ensembl.org) and the NCBI trace file server (www.ncbi.nlm.nih.gov/blast/nrtrace.html). Appropriate rat trace files were downloaded and aligned to the human exons to identify homologous rat exons, which were subsequently used for primer design. The physical order of the genes in mice was determined using mouse genomic sequence provided in the Celera database (www.celera.com) and mouse radiation hybrid mapping data (www.ncbi.nlm.nih.com).

The physical localization of the 4 genes in human and mouse showed a conserved order \( \text{Wnk4—ITGA2B—} \)
GFAP—ITGB3 within this chromosomal segment as depicted in the Figure. We experimentally verified the gene order in the rat by in silico analysis and radiation hybrid mapping and placed the genes on the radiation hybrid framework map in a 2-step process using the RHMAPPER 1.22 software package. In addition, we have mapped the genes Ppy and Mapt in a high resolution by radiation hybrid analysis. The results are represented in the Figure and indicate the same marker order identified in human and mouse.

In summary, we have shown that the blood pressure QTL regions on human chromosome 17 and rat chromosome 10 are syntenic. This chromosomal segment is conserved with respect to gene order between human, rat, and mouse. Our data indicate that it is possible to directly compare blood pressure susceptibility loci in rats and humans. This would locate the human blood pressure QTL on chromosome 10 directly between the 2 congenic lines defined by Garrett et al. Alternatively, it should be considered that quantitative trait locus mapping can be imprecise with respect to the exact chromosomal localization. Thus, the well-defined blood pressure regulating congenic segments identified in Dahl rats may in fact reflect the true human situation.

However, we believe that the latter explanation is less likely because several human studies using different approaches have consistently identified the same QTL region, making the possibility of a QTL placement artifact unlikely. Fine mapping approaches in humans and congenic experiments in different rat strains will provide a definitive answer in the future.

It is of interest that WNK4 is located within this blood pressure QTL region. Recently, mutations in this serine/threonine kinase have been determined to cause pseudohypoaldosteronism type II, a cause of human hypertension. These data further support the marked conservation between human, rat, and mouse within this region (Figure).

**Perspective**

Detailed genetic maps for blood pressure–associated chromosomal regions are essential for the identification of candidate genes. Comparative mapping approaches are based on the sequence conservation between species and allow the data generated in model organisms such as the rat to be related to the human genome. The cross-comparison of susceptibility loci for genetic hypertension thus becomes possible. Our analysis included the identification of exon-intron structures of homologous human genes, deriving rat exon sequences from high-throughput rat genomic sequence and radiation hybrid mapping of selected genes.

With the continued growth of genomic sequence data from different species within public databases, comparative mapping using bioinformatical tools becomes increasingly important in the identification of candidate genes within regions of interest. The use of sequence information from human,
mouse, and rat will significantly decrease the time and resources needed to identify positional candidate genes that might contribute to the susceptibility to common forms of hypertension. Comparative mapping will, therefore, help to triangulate physiology and genetics in humans, rats, and mice.

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References

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