

Identification of the *UBP1* Locus as a Critical Blood Pressure Determinant Using a Combination of Mouse and Human Genetics

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Abstract

Hypertension is a major health problem of largely unknown genetic origins. To identify new genes responsible for hypertension, genetic analysis of recombinant inbred strains of mice followed by human association studies might prove powerful and was exploited in our current study. Using a set of 27 recombinant BXD strains of mice we identified a quantitative trait locus (QTL) for blood pressure (BP) on distal chromosome 9. The association analysis of markers encompassing the syntenic region on human chromosome 3 gave in an additive genetic model the strongest association for rs17030583 C/T and rs2291897 G/A, located within the *UBP1* locus, with systolic and diastolic BP (rs17030583: 1.3 ± 0.4 mmHg $p < 0.001$, 0.8 ± 0.3 mmHg $p = 0.006$, respectively and rs2291897: 1.5 ± 0.4 mmHg $p < 0.001$, 0.8 ± 0.3 mmHg $p = 0.003$, respectively) in three separate studies. Our study, which underscores the marked complementarities of mouse and human genetic approaches, identifies the *UBP1* locus as a critical blood pressure determinant. *UBP1* plays a role in cholesterol and steroid metabolism via the transcriptional activation of *CYP11A*, the rate-limiting enzyme in pregnenolone and aldosterone biosynthesis. We suggest that *UBP1* and its functional partners are components of a network controlling blood pressure.

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