Review

Genetic Analysis of Cardiovascular Risk Factor Clustering in Spontaneous Hypertension

(insulin resistance / dyslipidemia / hypertension / SHR-4 congenic strain / Cd36 / Cd36-transgenic rats)

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Abstract. The SHR is the most widely studied animal model of hypertension. In this strain, as in many humans with essential hypertension, increased blood pressure has been reported to cluster with other risk factors for cardiovascular disease, including insulin resistance and dyslipidemia. However, the genetic mechanisms that mediate this clustering of risk factors for cardiovascular disease or the hypertension "metabolic syndrome" remain poorly understood. In the current studies, we have demonstrated (1) that a gene or genes responsible for a whole spectrum of cardiovascular risk factors mapped to a limited segment of the centromeric region of rat chromosome 4, (2) that a spontaneous deletion in the gene for Cd36 that encodes a fatty acid transporter and is located directly at the peak of QTL linkages on chromosome 4 has been indirectly linked to the transmission of insulin resistance, defective fatty acid metabolism, and increased blood pressure, and (3) based on complementation analysis in two transgenic lines expressing wild-type Cd36 on the genetic background of the SHR strain harboring the deletion variant of Cd36, we have established that defective Cd36 can be a determinant of disordered fatty acid metabolism, glucose intolerance, and insulin resistance in spontaneous hypertension.

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Abbreviations: BN – Brown Norway, BP – blood pressure, HDL – high-density lipoproteins, NIH – National Institutes of Health, QTL – quantitative trait loci, SHR – spontaneously hypertensive rat.

Association of insulin resistance, dyslipidemia, and hypertension: a role for genetic factors

Insulin resistance and dyslipidemia have been reported to be common findings in patients with essential hypertension, and both increased blood pressure (BP) and disordered carbohydrate and lipid metabolism are important risk factors for cardiovascular disease (Reaven et al., 1996). However, despite extensive research, the basis for the association of insulin resistance, dyslipidemia, and hypertension remains a mystery. The lack of insulin resistance and dyslipidemia in patients with some forms of secondary hypertension, together with observations of disordered carbohydrate and lipid metabolism in cultured cells from hypertensive animals, indicate that the endocrine-metabolic disturbances are not simply a consequence of increased BP (Sowers et al., 1993). The abnormalities in insulin-stimulated glucose transport observed in isolated cells from hypertensive animals also indicate that the association of insulin resistance with high BP is not simply related to reduced skeletal muscle mass in the setting of hypertension. Increased BP and defective carbohydrate and lipid metabolism are highly complex phenotypes and there are many possible scenarios that could contribute to the association of these multifactorial disorders. Although there is considerable evidence of a role for genetic factors in the pathogenesis of insulin resistance, dyslipidemia, and hypertension, the genetic mechanisms that underlie this association remain poorly understood. The spontaneously hypertensive rat (SHR) is the most widely studied genetic model of human essential hypertension. The SHR displays many of the metabolic features of human syndrome X, including defective insulin action on glucose metabolism, reduced catecholamine action on lipolysis in fat cells, and dyslipidemia (Reaven et al., 1991). Thus, the SHR provides a potentially useful model for investigating the genetic

basis for the association between insulin resistance, dyslipidemia, and hypertension.

Mapping genes regulating hypertension, insulin resistance, and dyslipidemia in the SHR

We have used linkage mapping in recombinant inbred strains derived from the SHR to map quantitative trait loci (QTL) for complex traits including BP (Pravenec et al., 1995), defective insulin action and fatty acid metabolism in isolated adipocytes (Aitman et al., 1997), and dyslipidemia (Bottger et al., 1996). In these linkage studies, QTL for hypertension, high-density lipoproteins (HDL) phospholipids, and for defects of insulin action and fatty acid metabolism in isolated adipocytes mapped all to the same segment of the centromeric region of chromosome 4 (Fig. 1).

Development and characterization of the SHR-4 congenic strain

To investigate the hypothesis that genes influencing insulin resistance, dyslipidemia, and BP exist on chromosome 4, we determined the hemodynamic and metabolic effects of replacing a region of chromosome 4 in the SHR with the corresponding region from the normotensive and insulin-sensitive Brown Norway (BN) rat. The SHR.BN-Il6/Npy congenic strain (hereafter referred to as SHR-4) was derived using a selective breeding protol in which a segment of chromosome 4 between Il6 and Npy markers from the BN strain was transferred onto the genetic background of the SHR. The size of the transferred chromosome segment is approximately 35 cM (Fig. 2).

Arterial BP and heart rates were measured continuously in unanesthetized, unrestrained male SHR progenitor rats and SHR-4 congenic rats (N10 generation) using radiotelemetry (Fig. 3). We found that transfer of the target region of chromosome 4 from the BN rat into the SHR significantly attenuated hypertension in the SHR strain (Pravenec et al., 1999).

The SHR progenitor strain is glucose intolerant and has elevated plasma insulin levels relative to glucose when compared to certain other normotensive rat strains (Reaven et al., 1991). Fructose feeding greatly exacerbates the insulin resistance in SHR (Hwang et al., 1987). To investigate whether genes affecting systemic glucose metabolism have been isolated in the SHR-4 congenic strain, we first performed glucose tolerance testing in SHR progenitor and SHR-4 congenic rats fed a high-fructose diet for 13 days. There were no differences in

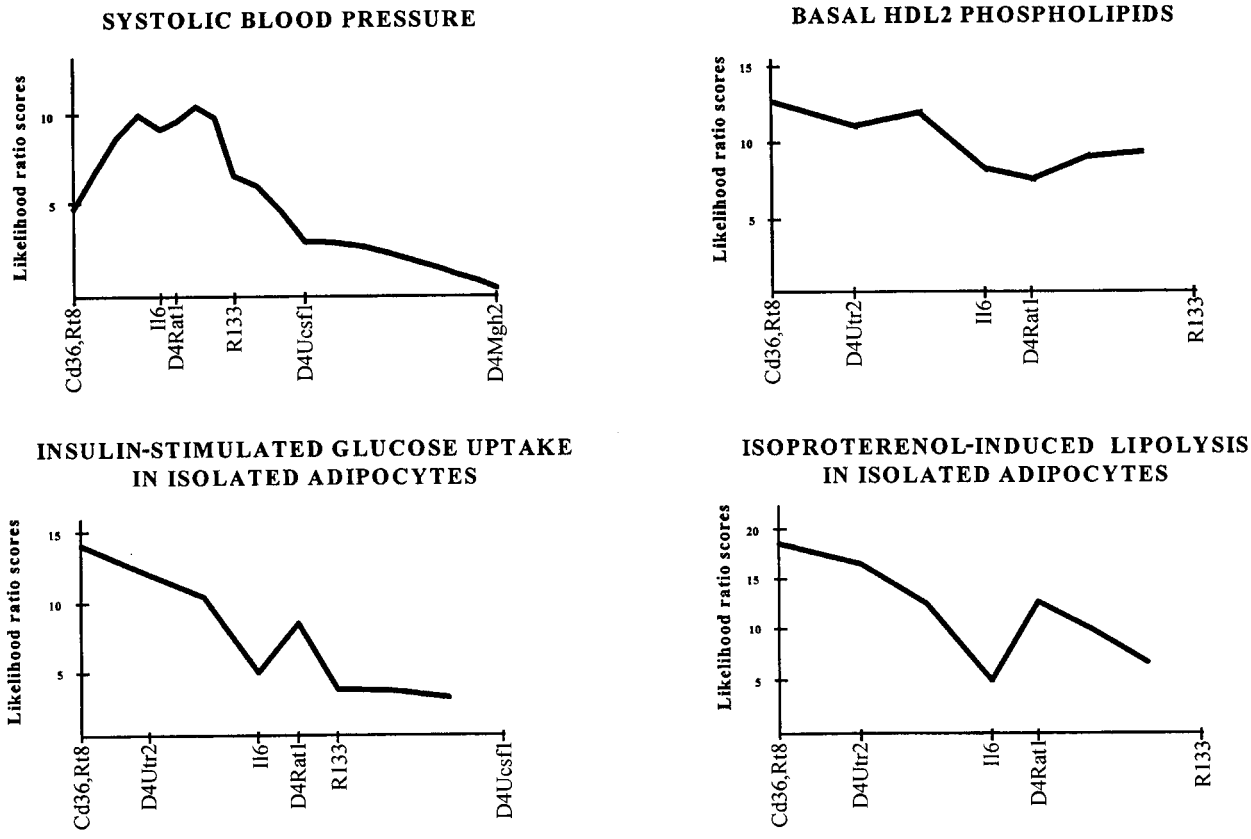

Fig. 1. Interval mapping of QTL associated with hemodynamic and metabolic phenotypes. Likelihood ratio statistics from the Map Manager QT linkage analysis are plotted across chromosome 4. Estimated distances between markers are in centiMorgans determined with the Haldane map function. To convert likelihood ratio statistics to lod scores, divide by 4.6.