

A Genetic Predisposition to Hypertension?

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Hypertension is a major public health problem, and yet, the molecular mechanisms underlying hypertension are poorly understood in the majority of patients. A complex disorder, both environmental and genetic factors predispose individuals to hypertension. Whereas we know much about environmental factors, such as salt intake and exercise, that affect blood pressure, we know less about genetic factors that predispose individuals to hypertension. In recent years, there has been great progress in elucidating the molecular basis of monogenic disorders with primary effect on blood pressure, and this work has clarified many aspects of blood pressure regulation.¹ Among the most significant findings from this work has been that all known single-gene disorders with primary effect on blood pressure act via a single final common pathway—alteration of renal sodium reabsorption. These studies mirror what has been observed in acquired forms of hypertension, which uniformly feature increased sodium reabsorption as well. The sum of these findings is consistent with a large body of physiological work and animal studies drawing on the pioneering work of Arthur Guyton, who proposed that sustained hypertension ultimately required the active participation of the kidney.² The finding that all known inherited and acquired forms of hypertension ultimately operate via the same common pathway has led to the proposal that common forms of hypertension will feature perturbations in this pathway as well.¹

Although such work has greatly expanded our understanding of molecular mechanisms underlying hypertension, pathways determining this genetic predisposition to hypertension in the general population remain unknown. In recent years, there has been much effort expended in this area. One area of investigation has focused on association studies, in which various genomic polymorphisms are linked genetically to hypertensive phenotypes. Literally hundreds, if not thousands, of such studies have been reported, but, unfortunately, little real insight into underlying pathogenetic mechanisms

has been gleaned from such studies.³ Frequent problems with such studies include, but are not restricted to, issues with population stratification, insufficient sample size, and a lack of replication in independent populations or in family based transmission disequilibrium studies. Genome-wide linkage studies have also been performed, and these have linked regions on chromosome 12p and 17q to hypertension in large cohort studies;^{4,5} these loci are intriguing because they have previously been linked to monogenic blood pressure disorders as well.^{6–8} Nevertheless, no precise genetic polymorphism affecting blood pressure has been identified at these sites to date, and so the link between genetic polymorphism and sustained rise in blood pressure remains elusive.

In the June issue of *Hypertension*, Jeck et al assessed a possible association between essential hypertension and the common T481S variant in the CIC-Kb channel.⁹ In contrast to studies in which random single-nucleotide polymorphisms in genes thought relevant to hypertension are screened, this polymorphism was carefully chosen for its potential effect on renal sodium reabsorption. CIC-Kb is central to renal sodium reabsorption in the loop of Henle and distal-convoluted tubule, providing the route by which the transport partner of sodium, chloride, exits the cell through the basolateral membrane. The significance of this channel to renal sodium conservation is demonstrated by the finding that patients lacking this channel have Bartter syndrome type III, characterized by salt-wasting and hypotension.¹⁰ Intriguingly, the T481S substitution examined by Jeck et al is present in 20% to 40% of the population and induces a 7-fold increase in Cl⁻ transport by this channel in *Xenopus* oocytes.¹¹ The authors therefore ask whether the T481S variant might increase distal renal sodium reabsorption and thereby increase blood pressure in humans. Interestingly, they found that age-adjusted mean arterial pressure in a German study group is approximately 4 mm Hg higher in carriers of the T481S allele than in wild-type individuals ($P=0.015$); furthermore, they found that the prevalence of hypertension (defined as blood pressure >140/90) is significantly higher in T481S carriers than in wild-type individuals ($P=0.0011$). They thus propose that the T481S variant leads to increased renal salt retention and consequent elevation of blood pressure.

If this suggestion proves correct, it would be an important step forward in our understanding of blood pressure regulation in the general population. Physiologically, it would suggest that sodium transport in the loop of Henle and distal-convoluted tubule is rate-limited in part by basolateral chloride transport. Clinically, one might expect that hypertensive carriers of the T481S variant would derive particular benefit from thiazide or loop diuretics, which could override the effects of an overactive CIC-Kb channel.

Before we can recommend genotyping all hypertensive patients for the T481S allele, however, it is important to

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remember the high rate of false-positive results in single-nucleotide polymorphism association studies.¹² Although the study by Jeck et al does avoid 1 common pitfall of this type of association study, the problem of multiple associations testing, the authors have not effectively ruled out another common problem in this sort of analysis, the problem of population stratification. Population stratification occurs when unidentified ethnic subpopulations within the study group are responsible for the differences observed, providing a relatively trivial explanation for the study's findings.¹³ The authors have tried to limit the probability of population stratification within their study by noting that there is no evidence for stratification at the multidrug resistance 1 (*MDR1*) locus, but recent data suggest that ruling out population stratification is difficult even in well planned studies and requires much more thorough analysis.¹³ This is especially relevant in studies in which only borderline statistical significance is achieved, as is the case here. Methods exist to detect and correct for population stratification. For example, multilocus genotypes can be generated to identify individuals with different ancestries, providing a method to adjust for ancestry in the association analysis.^{13,14} Furthermore, genomic control methods use independent marker loci to quantitatively assess the degree of stratification and adjust test statistics accordingly.^{13,15} Unfortunately, for studies such as this report by Jeck et al,⁹ where only borderline significance is achieved, the number of independent loci that must be genotyped to effectively rule out population stratification is large.¹³

The identification of genetic factors that predispose individuals to hypertension remains an important goal as we seek improved methods to diagnose and treat hypertension and its coincident morbidities. The demonstration by Jeck et al that the CIC-Kb^{T481S} polymorphism cosegregates with high blood pressure is an intriguing preliminary finding, but the use of the word "preliminary" is essential for now. It will be necessary to replicate this result in large independent populations to clarify the effect of the CIC-Kb^{T481S} variant on blood pressure.

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