Hypertension is a major public health problem, and yet, the molecular mechanisms underlying hyperten-
sion are poorly understood in the majority of pa-
tients. 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. Among the most significant find-
ings 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. 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.

Although such work has greatly expanded our understand-
ing of molecular mechanisms underlying hypertension, path-
dways 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 genominc polymorphisms are linked genetically to
hypertensive phenotypes. Literally hundreds, if not thou-
sands, of such studies have been reported, but, unfortunately,
little real insight into underlying pathogenetic mechanisms
has been gleaned from such studies. 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; these loci are intriguing because they have
previously been linked to monogenic blood pressure disor-
ders as well. Nevertheless, no precise genetic polymor-
phism 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. 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 mem-
brane. The significance of this channel to renal sodium
conservation is demonstrated by the finding that patients
lacking this channel have Bartter syndrome type III, charac-
terized by salt-wasting and hypertension. 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. 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 approxi-
mately 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=0.0.011). 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 regula-
tion 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 hyper-
tensive 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
remember the high rate of false-positive results in single-nucleotide polymorphism association studies. 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. 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. 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. Furthermore, genomic control methods use independent marker loci to quantitatively assess the degree of stratification and adjust test statistics accordingly. Unfortunately, for studies such as this report by Jeck et al, where only borderline significance is achieved, the number of independent loci that must be genotyped to effectively rule out population stratification is large.

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-KbT481S 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-KbT481S variant on blood pressure.

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References

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David S. Geller

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