Association of Blood Pressure With Genetic Variation in WNK Kinases in a White European Population

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Mutations in a recently discovered family of protein kinases are responsible for an autosomal-dominant form of inherited hypertension, known as Gordon’s syndrome or pseudohypopaldosteronism type II (PHAII). The phenotype also includes hyperkalemia and hyperchloremic metabolic acidosis. The name of this kinase family is WNK (with no lysine [K]) because of the absence of a lysine in subdomain II of the enzymes. WNK1 and WNK4, located in human chromosomes 12 and 17, respectively, are predominantly expressed in the distal convoluted tubules and the collecting ducts of the kidney.

In vitro, wild-type WNK4 inhibits the thiazide-sensitive sodium chloride cotransporter (NCCT) and the renal outer medullary potassium ion channel (ROMK), but increases paracellular chloride permeability. Some WNK4 mutations identified in PHAII behave as a loss of function for the NCCT inhibition but as a gain of function for the inhibition of ROMK, and further stimulate paracellular chloride transport. These effects of WNK4 mutations fit well with the proposed mechanisms for the development of hypertension and electrolyte abnormalities in PHAII. Furthermore, in vitro, WNK1 counteracts the inhibition of NCCT by WNK4 and activates the serum- and glucocorticoid-inducible protein kinase (SGK1), which in turn stimulates the epithelial sodium channel (ENaC). The observation that heterozygous WNK1-deficient mice had lower blood pressure than wild-type control animals further supports the role of WNK1 in blood pressure regulation. The evidence from studies in patients with PHAII, cell models, and genetically engineered animals makes WNK1 and WNK4 strong candidates possibly involved in the pathogenesis of essential hypertension. However, previous case-control and population-based studies of various single nucleotide polymorphisms (SNPs) in WNK1 and WNK4 yielded inconsistent results.

The study published by Tobin and colleagues in this issue of Circulation may herald a breakthrough in unraveling the putative association between blood pressure and genetic variation in the WNK kinases. The authors recruited via family practitioners a family-based sample of nuclear families consisting of both parents and 2 offspring, which was representative of the general population of Leicestershire, UK. A history of hypertension was not among the inclusion criteria. The researchers employed 24-hour ambulatory monitoring to measure the blood pressure phenotypes. Compared with conventional blood pressure measurement, ambulatory monitoring is characterized by high reproducibility, is not subject to digit preference and observer bias, and avoids the so-called white coat effect, which is the transient rise in a subject’s blood pressure in response to the clinical surroundings or the presence of an observer. The authors discarded the first 2 hours of each ambulatory recording to avoid any alerting response. In addition to the precision of the phenotype, Tobin and colleagues extensively genotyped 9 SNPs in WNK1, 8 of which were sufficient to predict the common haplotypes. They also measured 1 intronic SNP in WNK4, which is frequent among white Europeans. The heritability of the 24-hour systolic and diastolic blood pressure was around 65%. The authors found statistically significant associations of mean 24-hour systolic and/or diastolic blood pressures with several common SNPs and haplotypes in WNK1. The mean estimated effect sizes for single SNPs approximately ranged from a 2-mm Hg reduction to a 1-mm Hg increase. In contrast, there was no association between blood pressure and the SNP in WNK4. All findings remained consistent after adjustment for sex, age, body mass index, smoking, alcohol intake, history of hypercholesterolemia, and education level. The demonstration that common variants in WNK1, a gene causing a rare monogenic form of hypertension, contributes to the blood pressure variation in the general population is a genuine breakthrough.

Whereas the study by Tobin and colleagues lifts a corner of the veil surrounding the WNK paradigm, it also leaves several questions unanswered. First, the authors did not measure serum concentration or 24-hour excretion of electrolytes, nor the circulating components of the renin-angiotensin system. WNKs are widely expressed in epithelia. Their study therefore does not prove with absolute certainty that the association with blood pressure was renally mediated, although the latter hypothesis is most likely in view of the previous evidence. Second, the genetic epidemiological findings are not underpinned by in vitro studies proving functionality of the WNK1 haplotypes in renal tubular cells. Third, the findings by Tobin et al are at variance with another recent report published by the same investigators.

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Indeed, family-based association tests involving 712 severely hypertensive families in the British Genetics of Hypertension (BRIGHT) Study showed significantly positive associations of systolic \((z=2.241, P=0.025)\) and diastolic \((z=1.992, P=0.046)\) blood pressures with the rs1468326 SNP in WNK1, and a negative association of systolic \((z=-2.300, P=0.017)\) blood pressure with the WNK1 haplotype h10 AGCTTCCC. In the present study, these associations had an opposite sign and did not reach statistical significance. This was also the case for the common WNK1 haplotype h4 CACCCCCG, which was positively correlated with systolic pressure \((z=1.912, P=0.053)\) in the BRIGHT study but negatively with systolic and diastolic pressures during daytime and over 24 hours \((z\leq-2.142; P\leq0.032)\). These contradictory results require clarification. Fourth, Tobin and colleagues did not investigate the possible interaction between genetic variation in the WNKs and salt intake in relation to blood pressure. The European Project on Genes in Hypertension highlighted that phenotype–genotype relationships strongly depend on lifestyle, in particular salt intake, as reflected by 24-hour urinary excretion of sodium. Ignoring such interaction may explain the aforementioned inconsistencies.

Irrespective of its limitations, the present study is the first study that demonstrates that common genetic variants of WNK1 contribute to blood pressure variation in a general white population. If these findings are confirmed by other epidemiological studies and if they are supported by experimental evidence for functionality, then they may have wide-ranging implications. WNK kinases may become novel targets for pharmaceutical intervention and lead to the development of diuretic agents without the metabolic side effects of thiazides. Moreover, further studies should address the question to what extent genetic variation in the WNKs influences salt sensitivity and the response to antihypertensive drugs and whether they can predict the incidence of hypertension and cardiovascular morbidity and mortality. Thus, the article by Tobin and colleagues is a significant step forward, but the onward journey to the possible clinical applications of the WNK paradigm remains long.

References

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