What Have We Learned from the Genetics of Hypertension?

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KEYWORDS

- Genetics • Blood pressure • Hypertension • Mendelian
- Genomewide association studies

KEY POINTS

- Twin studies show that about half the risk of hypertension development is inherited.
- Mendelian hypertension has elucidated astounding basic pathways contributing to hypertension over (presumably) dietary salt intake or directly through increased peripheral vascular resistance.
- The Mendelian mutations exercise large effects on blood pressure. The genetics of hypertension-producing tumors underscores the point. Inversely, studying the entire human genome for sources signaling blood pressure has yielded many signals with small effects.
- Thus far, few loci have been validated or translated into targets. Both genetic strategies are necessary, and much remains to be done.

INTRODUCTION

Beginning titles with questions is risky. A weakness is that the readership could quickly conclude: "It's a question! So evidently not much has been learned." A debate ensued early on in the 20th century involving Mendelian (1 or few genes) genetic inheritance or multifactorial genetic inheritance of blood pressure.[1] We need not pick up on the winners and losers of that argument here.[2] We know since the first studies in monozygotic and dizygotic twins that the genetic components influencing blood pressure lie by about 50% (genetic variance), largely including the mechanistic components of blood pressure control.[3] The residual (other half) could be attributed to environment, behavior, and the vicissitudes of life.[4] This figure has changed but little. Many genetic mechanisms are responsible for hypertension in most hypertensive individuals.[5] The arguments between Platt[1] and Pickering[2] seem mundane today but they nevertheless

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Med Clin N Am 101 (2017) 195–206
http://dx.doi.org/10.1016/j.mcna.2016.08.015 **medical.theclinics.com**

pursue us and still have a major impact on how resources are distributed.[6] The entire debate would remain an academic exercise were it not for molecular biological methods that allow both ideas to be tested.

THE PLATTONISTS

The clinician/scientist Robert Platt believed that blood pressure was heritable as a Mendelian (autosomal-dominant) trait.[1] He drew his conclusions from studying families. In his day, he could not go further. In comparison, Platt's modern followers have matters relatively easy. And they have found numerous genes that have major (20–50 mm Hg) influences on arterial blood pressure. The affected individuals have a substantial risk of hypertensive complications. This line of pursuit has resulted in a mechanistic bonanza.

Lifton and colleagues[7] found that a chimeric 11 β-hydroxylase/aldosterone synthase gene (*CYP11B1/CYP11B2*) causes glucocorticoid-remediable aldosteronism and human hypertension. The regulatory region of the chimeric gene is influenced by adrenocorticotropic hormone; however, the product is the mineralocorticoid aldosterone. This condition had been recognized years earlier and the genetics appreciated, but the mechanism was unknown. As a result of this work, mineralocorticoid-induced hypertension was elucidated. Moreover, because the mechanism clearly involved increased sodium reabsorption, the genetics of "salt-sensitive" hypertension seemed to be more established. Next was the observation that a mutation truncating the carboxy terminus of the γ subunit of the epithelial sodium channel (ENaC) is the cause of Liddle's syndrome.[8] The truncated subunit activates channel activity, as channel degradation (ubiquitination) does not occur.[9] ENaC subunits are ubiquitinated by the NEDD4. Failure of this process can also result in salt-sensitive hypertension through hyperactivity of ENaC in the distal nephron. The finding clarified the genetic salt-sensitive hypertension first described by Grant Liddle years earlier.[8] Moreover, through the careful molecular studies of Rossier and colleagues[10] and researchers worldwide, a vista on sodium transport was opened. Thereafter came the finding that an activating mineralocorticoid receptor mutation in a woman with hypertension caused much worse hypertension during pregnancy. This novel finding implicated the mineralocorticoid receptor directly in the development of genetic hypertension.[11]

White[12] drew attention to inherited forms of mineralocorticoid-associated hypertension that appeared already in childhood. Deficiencies of steroid 11 β-hydroxylase or 17 α-hydroxylase are types of congenital adrenal hyperplasia, the autosomal recessive inability to synthesize cortisol. These 2 defects often cause hypertension because of cortisol-precursor overproduction. The precursors are then metabolized to agents activating the mineralocorticoid receptor. Such disorders result from mutations in the *CYP11B1* and *CYP17* genes. Apparent mineralocorticoid excess results from loss of functional ligand specificity of the mineralocorticoid receptor caused by a deficiency of the renal 11 β-hydroxysteroid dehydrogenase-2 (11-β HSD2) isozyme. This enzyme normally metabolizes cortisol to cortisone to prevent cortisol from occupying the mineralocorticoid receptor.[13] Phenotypically, these forms of genetic hypertension featured low plasma renin activity, hypokalemia, and a degree of metabolic alkalosis. The phenotype is mimicked by licorice gluttony.

A genetic syndrome also known years earlier and described in part by Gordon features hypertension, mild metabolic acidosis, and hyperkalemia.[14] The condition is perhaps more appropriately termed *pseudohypoaldosteronism type II*. Initially, 2 genes were found causing this condition, both encoding with-no-lysine kinases (WNKs). *WNK1* and *WNK4* both encode members of the WNK serine-threonine kinase