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Genes that "really" cause hypertension

Cardiovascular disease is the commonest cause of death worldwide and hypertension is the primary driving risk factor. Twin studies have shown that about half of blood pressure is influenced by genetic variance. However, aside from rare Mendelian syndromes, what could this mean to practical hypertension in the clinic? I led one from 1993 until 2010 and I would like to show you some of my patients. We begin with a patient with primary hyperaldosteronism; perhaps 5% of patients have this condition. We have learned that somatic (sometimes germline) mutations in 3 ion channel genes commonly are responsible. We had a patient with Cushing's disease. We now know that a ubiquitin hydrolase is commonly responsible. Pheochromocytoma causes hypertension in about 1% of patients. However, a panoply of genes is responsible mostly involved in oxidative energy metabolism. Even fibromuscular hyperplasia is regulated by the phosphatase-and-actin regulator-1 gene. Mendelian syndromes involving salt transport are common and can be confused with licorice gluttony. These salt-sensitive syndromes all cause moderate to severe (20-50 mm Hg) increases in blood pressure. Then, "our" syndrome, a Mendelian hypertension invariably associated with short fingers (brachydactyly) has garnered our attention. We have worked on this problem for >20 years. The hypertension features salt-resistance, rather than sensitivity to salt, and abnormal baroreflex blood pressure buffering. We identified gain of function mutations in phosphodiesterase (PDE) 3A. This mechanism involves a direct increase in peripheral vascular resistance. A linkage study in Chinese hypertensive patients (without short fingers) coincides with our locus and four genome-wide association studies also have identified PDE3A, as important to blood pressure. Our mutations, now in 12 families, suggest mechanisms. We have generated animal models that are currently under investigation. Our studies could lead to intracellular micro-domain-directed therapies. We suggest that clinical medicine is "not-so-bad" in finding hypertension-causing genes that are really important.