Great strides have recently been made in our understanding of human hypertension at the level of discrete genetic mutations. We now understand the pathophysiology of glucocorticoid-remediable aldosteronism (1), Liddle’s syndrome (2), and the apparent mineralocorticoid excess syndrome (3). In each of these syndromes, inappropriate renal Na⁺ retention with subsequent hypertension occurs through the agency of unusual mineralocorticoids, or in the case of Liddle’s syndrome (“pseudoadosteronism”), an apparent mineralocorticoid effect due to mutations which constitutively activate the amiloride-sensitive epithelial Na⁺ channel. In each of these examples (1–3), the functional effects of these mutations have been confirmed in various expression systems.

These successes have relied on the candidate gene approach and clinical insights into the underlying pathophysiology. These successes are notable, but failures of the candidate gene approach go unheralded. At the same time, positional cloning efforts have been quite fruitful in identifying numerous loci of interest in hypertensive inbred rat strains. As a rule, these efforts have identified promising chromosomal intervals which contain genes of specific interest (e.g., inducible nitric oxide synthase), but precise mutational derangements have not yet been described. While these efforts hold great promise for identifying new candidate genes for human hypertension, considerable effort will be required to extend these findings to Precise pathophysiologic understanding of human disease.

The report herein of Tripodi et al. (4) provides an important demonstration of the functional effects of mutations in accessory proteins which appear to regulate transepithelial Na⁺ transport. Previous work from this group demonstrated that missense mutations in the α and β adducin subunits accounted for some of the blood pressure difference between the Milan hypertensive and normotensive strains of inbred rat strains. As a rule, these effects have identified promising chromosomal intervals which contain genes of specific interest (e.g., inducible nitric oxide synthase), but precise mutational derangements have not yet been described. While these efforts hold great promise for identifying new candidate genes for human hypertension, considerable effort will be required to extend these findings to Precise pathophysiologic understanding of human disease.

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