

Genetic basis of blood pressure and hypertension

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Human primary or essential hypertension is a complex, polygenic trait with some 50% contribution from genes and environment. Richard Lifton and colleagues provided elegant dissection of several rare Mendelian forms of hypertension, exemplified by the glucocorticoid remediable aldosteronism and Liddle's syndrome. These discoveries illustrate that a single gene mutation can explain the entire pathogenesis of severe, early onset hypertension as well as dictating the best treatment.

The dissection of the much more common polygenic hypertension has proven much more difficult. Early studies used a single polymorphic marker such as the I/D polymorphism in the ACE gene and small numbers of cases and controls. Candidate gene studies have been largely non-informative and non-reproducible. These were followed by linkage studies, which used approximately 300 microsatellite markers distributed across the genome. These studies resulted in large peaks covering regions with 50-100 genes, with no easy way to quickly focus on a few genes of causal relevance. The real breakthrough came with the initiation of the genome wide association studies (GWAS) characterised by a much more thorough coverage of the genome with thousands single nucleotide polymorphisms (SNPs). Typically 500,000 – 2,500,000 SNPs have been used for the big, collaborative GWAS for hypertension. These studies resulted in several "hits" or signals with a genome-wide significance and a high level of reproducibility between studies. These "hits" have been used successfully to calculate genetic risk scores for cardiovascular complications such as left ventricular hypertrophy, stroke and coronary artery disease. Intragenic signals, such as for example Uromodulin, are being used to