

Monogenic Hypertension Associated with a Pathogenic STX16 Mutation

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Hypertension is the most important modifiable risk factor for death worldwide. Finding novel model mechanisms for blood-pressure (BP) regulation is an important goal and Mendelian syndromes have been very helpful in that regard.

Pseudohypoparathyroidism type 1B (PHP1B) is an example in which affected individuals are invariably hypertensive for unknown reasons.

We encountered a 48 year-old woman with severe, five-drug-resistant, hypertension. Her father and two aunts were also severely hypertensive. Her two young sons have developed drug-dependent hypertension before age 20 years. We measured 24-h ambulatory blood pressure and excluded all known secondary causes. However, the proband's sons and their grandfather have the PHP1B phenotype, while our index patient and her two hypertensive aunts do not. The blood pressure phenotype in this pedigree suggested autosomal dominant inheritance. The Syntaxin 16 (STX16) gene encodes a snare protein and mutations cause PHP1B. Mutated STX16 causes methylation defects of Guanine Nucleotide Binding Protein, Alpha Stimulating (GNAS), a G protein regulator. Since GNAS is an imprinted gene, only inheritance from the mother causes the PHP1B phenotype. Subsequently, we sequenced STX16 in our kindred. We found a heterozygous deletion involving exons 5 and 6. We were also able to show complete loss of methylation in GNAS exon 1A. All hypertensive persons in our kindred have the STX16 mutation and are hypertensive. However, only those with maternal inheritance show the PHP1B phenotype. The methylation target region influenced by STX16 encompasses 7 genes. Our candidate is endothelin-3 encoded by EDN3. Our data separate the hypertension-PHP1B phenotypes. We imply separate mechanisms are involved. We suggest new targets of blood pressure-raising relevance, and have successfully treated these affected individuals with endothelin antagonists.