

R E V I E W

Monogenic hypertension

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Summary. Hypertension is a significant public health problem. Thirty percent of cases are caused by a single genetic mutation. Hypertension is the predominant and usually the only manifestation in monogenic hypertension. Monogenic hypertension may involve mineralocorticoid-dependent or -independent increase in Na⁺ transport. Diagnosis is based on routine physical examination, blood pressure measurement and laboratory analysis of renin, aldosterone, cortisol and potassium. Genetic testing is useful for confirming diagnosis and for differential diagnosis. Monogenic hypertension has autosomal dominant or autosomal recessive inheritance. (www.actabiomedica.it)

Key words: hypertension, apparent mineralocorticoid excess, hyperaldosteronism, congenital adrenal hyperplasia, Liddle syndrome, pseudohypoaldosteronism

Hypertension is a significant public health problem and is defined as average systolic and/or diastolic blood pressure $\geq 95^{\text{th}}$ percentile for gender, age and height on at least three occasions (1). It is considered a multifactorial disorder, but approximately 30% of cases are caused by a single genetic mutation. Hypertension is the predominant and usually the only manifestation in monogenic hypertension. Three mechanisms are recognised to explain the physiopathology of monogenic hypertension: increased sodium reabsorption leading to plasma volume expansion, excessive aldosterone synthesis, and deficiencies of enzymes that regulate adrenal steroid hormone synthesis and deactivation (2).

Monogenic hypertension may involve: a) increased Na⁺ transport induced by a mineralocorticoid effect, including apparent mineralocorticoid excess (AME) syndromes, glucocorticoid-remediable aldosteronism and congenital adrenal hyperplasia due to 11 β -hydroxylase or 17 α -hydroxylase deficiency; or b) increased Na⁺ transport independent of mineralocorticoids, including Liddle's and Gordon's syndromes.

Apparent mineralocorticoid excess is a rare disorder arising from impaired activity of 11-beta-hydroxysteroid dehydrogenase type II (HSD11B2). This enzyme is responsible for converting active cortisol to inactive cortisone at aldosterone binding sites. In AME patients, the persistence of cortisol leads to increased mineralocorticoid activity due to higher cortisol affinity for the mineralocorticoid receptor. The consequences are hypokalemia, metabolic alkalosis, low plasma renin activity and low plasma aldosterone levels (3).

Glucocorticoid-remediable aldosteronism is a rare disorder caused by unequal crossover of two adjacent genes, *CYP11B1* and *CYP11B2* (coding for 11-hydroxylase and aldosterone synthase, respectively). The chimeric gene encodes a hybrid protein that stimulates aldosterone production, independent of renin, resulting in upregulation of Na⁺ reabsorption and K⁺ secretion. Although plasma renin is low, plasma concentrations of aldosterone may be normal. Patients show mild hypokalemia and metabolic alkalosis (1).

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Congenital adrenal hyperplasia presents with hypertension and may be due to deficiency of 11 β -hydroxylase or 17 α -hydroxylase. Excess production of steroid intermediaries with mineralocorticoid effects lead to hypernatremia, hypokalemia and low-renin HT.

Liddle syndrome (pseudo-hyperaldosteronism) is a rare disorder due to an epithelial Na⁺ channel gain of function. Enhanced epithelial Na⁺ channel activity causes increased Na⁺ reabsorption, increased in-

travascular volume, suppression of renin activity and reduction of aldosterone levels. Additional abnormalities include metabolic alkalosis and hypokalemia (4). Patients respond well to K-sparing diuretics such as triamterene and amiloride, but spironolactone is ineffective for blood pressure control in patients with this syndrome.

Gordon syndrome (pseudo-hypoaldosteronism type II) is caused by gain-of-function pathogenic variants in four genes that regulate Na-K-Cl cotrans-

Table 1. Genes associated with various forms of monogenic hypertension

Gene	OMIM gene	Disease	OMIM disease	Inheritance	Function
<i>CYP11B1</i>	610613	HALD1, congenital adrenal hyperplasia	103900, 202010	AD, AR	Drug metabolism, synthesis of cholesterol, steroids, other lipids
<i>KLHL3</i>	605775	PHA2D	614495	AD, AR	Regulator of ion transport in the distal nephron
<i>CUL3</i>	603136	PHA2E	614496	AD	Role in late endosome maturation
<i>NR3C2</i>	600983	PHA1A	177735	AD	Receptor for aldosterone, corticosterone, cortisol
<i>SCNN1B</i>	600760	LIDLS1, PHA1B	177200, 264350	AD, AR	Essential role in electrolyte and blood pressure homeostasis
<i>SCNN1G</i>	600761	LIDLS2, PHA1B	618114, 264350	AD, AR	Essential role in electrolyte and blood pressure homeostasis
<i>WNK1</i>	605232	PHA2C	614492	AD	Regulation of electrolyte homeostasis and cell signaling, survival, and proliferation. Activator of sodium-coupled chloride cotransporters, inhibitor of potassium-coupled chloride cotransporters
<i>WNK4</i>	601844	PHA2B, PHA2A	614491, 145260	AD, AR	Regulation of electrolyte homeostasis and cell signaling, survival, and proliferation. Activator of sodium-coupled chloride cotransporters, inhibitor of potassium-coupled chloride cotransporters
<i>PDE3A</i>	123805	HTNB	112410	AD	Regulation of vascular smooth muscle contraction and relaxation
<i>HSD11B2</i>	614232	AME	218030	AR	Conversion of cortisol to the inactive metabolite cortisone
<i>CYP17A1</i>	609300	Congenital adrenal hyperplasia	202110	AR	Catalysis of reactions involved in drug metabolism; synthesis of cholesterol, steroids, other lipids
<i>SCNN1A</i>	600228	PHA1B	264350	AR	Electrolyte and blood pressure homeostasis

AD=autosomal dominant; AR=autosomal recessive; HALD=familial hyperaldosteronism; PHA=pseudohypoaldosteronism; LIDLS=Liddle syndrome; HTNB=hypertension and brachydactyly syndrome; AME=apparent mineralocorticoid excess.

porter activity in the distal convoluted tubules of the kidney, with overexpression of Na-Cl cotransporters at the apical surface of the cells, causing increased Na⁺ reabsorption (5). Affected individuals show early-onset hyperkalemia, normal Na⁺ levels, hyperchloremia, metabolic acidosis and hypercalciuria. Plasma renin activity is suppressed and aldosterone levels are inappropriately low in relation to hyperkalemia. Thiazides are recommended to correct electrolyte abnormalities and blood pressure.

Diagnosis is based on routine physical examination, blood pressure measurement and laboratory analysis of renin, aldosterone, cortisol and potassium. Genetic testing is useful for confirming diagnosis and for differential diagnosis. Differential diagnosis should consider hypertension secondary to renal parenchymal disease, renal artery stenosis, adrenal gland neoplasia, hyperthyroidism, alcohol abuse and excessive dietary salt intake.

The estimated global age-standardized prevalence of hypertension in adults aged ≥ 20 years was 32.6% in the period 2009-2012. Genetic factors are thought to contribute to 30-60% of blood pressure variations, although known genetic factors explain only 3% of blood pressure variability (6).

Monogenic hypertension has autosomal dominant or autosomal recessive inheritance (Table 1). Pathogenic variants may be missense, nonsense, splicing or small indels. Large deletions/duplications have also been reported in *CYP11B1*, *CYP11B2*, *NR3C2*, *SCNN1B*, *WNK1*, *HSD11B2*, *CYP17A1* and *SCNN1A*.

We use a multi-gene NGS panel to detect nucleotide variations in coding exons and flanking introns of the above genes, and MLPA to detect duplications and deletions in *CYP11B1*, *CYP11B2*, *NR3C2*, *SCNN1B*, *WNK1*, *HSD11B2*, *CYP17A1* and *SCNN1A*.

Worldwide, 10 accredited medical genetic laboratories in the EU and 13 in the US, listed in the Orphanet (7) and GTR (8) databases, respectively, offer genetic tests for monogenic hypertension. The guidelines for clinical use of genetic testing are described in Genetics Home Reference (9).

Conclusions

We created a NGS panel to detect nucleotide variations in coding exons and flanking regions of all the genes associated with cardiac disorders. When a suspect of hypertension is present, we perform the analysis of all the genes present in this short article. In order to have a high diagnostic yield, we developed a NGS test that reaches an analytical sensitivity (proportion of true positives) and an analytical specificity (proportion of true negatives) of $\geq 99\%$ (coverage depth $\geq 10x$).

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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