Mendelian Hypertension: Clinical Implications

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Valencia, ICHCA, 2018
Genetic Pathways Involved in Blood Pressure

- PHAECHROMOCYTOMA PARAGANGLIOMAS
- CONGENITAL ADRENAL HYPERPLASIA
- ALDOSTERONE PRODUCING ADENOMA
- PHACTR1 (FIBROMUSCULAR DYSPLASIA) GWAS LOCI
- PDE3 HYPERTENSION/BRACHYDACTYLY
- GORDON SYNDROME
- GITELMAN SYNDROME
- LIDDLE SYNDROME
- BARTER SYNDROME
When to Suspect Monogenic Hypertension

Before labelling HT as essential or primary, a very thorough search for secondary causes should be undertaken, particularly in the paediatric population. Monogenic HT is an important consideration for patients presenting with one-or more features described below:

- Early-onset HT
- Severe or refractory HT
- Family history of childhood HT (in autosomal dominant & autosomal recessive disorders) and history of consanguinity (in autosomal recessive disorders)
- Clues from physical examination, which may indicate an underlying genetic syndrome
- Specific biochemical and hormonal abnormalities

Arggarwal et al, Adv Chronic Kidney Dis 2017;24:372
### Characteristic physical examination findings suggestive of genetic disorder in a child with hypertension

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Monogenic Syndrome</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Café-au-lait spots, axillary, or inguinal freckling</td>
<td>Neurofibromatosis type 1</td>
<td>NF1</td>
</tr>
<tr>
<td>Hypomelanotic macules, facial angiofibroma, shagreen patch</td>
<td>Tuberous sclerosis complex</td>
<td>TSC2 &gt; TSC1</td>
</tr>
<tr>
<td>Female with short stature, webbed neck, widely spaced nipples, short 4(^{th}) metacarpal</td>
<td>Turner Syndrome</td>
<td>46, XO</td>
</tr>
<tr>
<td>Retinal angioma, spinal or cerebellar hemangioblastoma, adrenal or extra-adrenal pheochromocytoma</td>
<td>Von Hippel-Lindau Syndrome</td>
<td>VHL</td>
</tr>
<tr>
<td>Ambigious genitalia</td>
<td>Congenital adrenal hyperplasia (11β-hydroxylase deficiency or 17α-hydroxylase deficiency)</td>
<td>CYP11B1, CYP17A1</td>
</tr>
<tr>
<td>Short metacarpal bones, short stature</td>
<td>Autosomal dominant hypertension with brachydactyly syndrome</td>
<td>PDE3A</td>
</tr>
</tbody>
</table>

*Arrgarwal et al, Adv Chronic Kidney Dis 2017;24:372*
Genetic Pathways Involved in Blood Pressure

**PDE3**

**HYPERTENSION/BRACHYDACTYLY**

**PDE3**

**HYPERTENSION/BRACHYDACTYLY**

**BARTER SYNDROME**

**GORDON SYNDROME**

**GITELMAN SYNDROME**

**LIDDLE SYNDROME**
- mutations in 4 genes (*WNK1*, *WNK4*, *KLHL3*, *CUL3*)

- intronic deletions in *WNK1* increase *WNK1* expression in the cytoplasmic compartment of distal nephron cells

- missense mutations in *WNK4* cause loss of function of *WNK4* in the tight junctions

- All 4 mutations lead to overexpression of the NCC (sodium/chloride co-transporter) + increased Na reabsorption
cellular phenotype: over-activation of thiazide-sensitive Na/Cl cotransporter (NCC) $\rightarrow$ increased renal reabsorption of sodium, decreased availability of Na$^+$ for ENaC & decreased K$^+$ and H$^+$ excretion

clinical phenotype: hypertension, volume expansion, hyperkalemia, hyperchloremic metabolic acidosis

treatment: thiazides - correct the underlying pathophysiology and result in blood pressure lowering along with normalization of electrolyte balance
Liddle Syndrome (Pseudohyperaldosteronism)

- **genetic defect:** single mutations of the gene for β or γ subunits of ENaC
- **cellular phenotype:** alteration/deletion in the cytoplasmic tails of β or γ subunits → the channels are not internalized → remain activated on the cell surface → increased renal reabsorption of sodium

*Jeunemaitre et al, J Hypertens 1997;15:1091, Lifton et al, Cell 2001;104:545*  
*Luft FC, Clin Med Res 2003;291:291*
Liddle Syndrome (Pseudohyperaldosteronism)

- **clinical phenotype:** early onset hypertension, resistance to most of the classes of antihypertensive treatment, hypokalemic alkalosis, suppressed plasma renin activity, and low plasma aldosterone levels

- **treatment:** - amiloride – a natural antagonist of ENaC – corrects increased reabsorption of sodium through mutated ENaCs, lowers blood pressure and corrects hormonal disturbances as well as renal water and electrolyte handling

Genetic Pathways Involved in BP- Adrenal gland- cortex

- **ALDOSTERONE PRODUCING ADENOMA**
  - **GRA**
  - **ANG-II** → **ANG-I** → **AGT** → **REN** → **CONGENITAL ADRENAL HYPERPLASIA** → **CYP17A1** → **HSD3B2** → **CYP21A2** → **CYP11B1** → **CYP11B2** → **AME** → **HSD11B2**

- **ADRENAL CORTEX**
  - **FH** → **MALATE** → **α-KETO-GLUTARATE** → **SDH** → **SUCCHINATE**

- **RET** → **TMEM127** → **GFRαs** → **NF1** → **RAS** → **PI3K** → **TMEM127** → **AKT** → **mTOR** → **43BP1** → **HIF** → **HIF1A**

- **PARAGANGLIOMAS**
  - **PHD2** → **VHL**

- **PHAECHROMOCYTOMA**
  - **JMJD** → **HIF2A** → **VHL**

- **ALDOSTERONE PRODUCING ADENOMA**
  - **MC2R** → **ATP1A1** → **CACNA1D** → **ATP2B3** → **KCNJ5**
<table>
<thead>
<tr>
<th>Form</th>
<th>Age at Symptom Onset</th>
<th>Hypokalemia</th>
<th>PA in relatives</th>
<th>Particular Characteristics</th>
<th>Transmission</th>
<th>Gene</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH-1</td>
<td>Often &lt;20 yrs</td>
<td>+/-</td>
<td>+</td>
<td>Familial history of stroke &lt;40yrs, hybrid steroids in urine</td>
<td>AD</td>
<td>Chimeric CYP11B1/B2</td>
<td>Aldosterone Synthase</td>
</tr>
<tr>
<td>FH-II</td>
<td>Variable after &gt;20 yrs</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
<td>AD</td>
<td>Not known</td>
<td>Not Known</td>
</tr>
<tr>
<td>FH-III</td>
<td>&lt;20 years (but variable in moderate forms)</td>
<td>++ in severe forms</td>
<td>&lt;20 years (variable in moderate forms)</td>
<td>Bilateral adrenal hyperplasia</td>
<td>AD</td>
<td>KCNJ5</td>
<td>GIRK4</td>
</tr>
<tr>
<td>FH-IV*</td>
<td>&lt;10 years</td>
<td>+/-</td>
<td>+/-</td>
<td>Not Described</td>
<td>AD or de novo</td>
<td>CACNA1H</td>
<td>CAv3.2</td>
</tr>
</tbody>
</table>

AD: Autosomal dominant
* Only 1 report, of 5 patients, published to date

Zennaro et al, Annales d’Endocrinologic 2016;17:214
Unequal meiotic recombination between aldo synthase (CYP11B2) and 11β-hydroxylase (CYP11B1) genes leads to chimeric gene consisting of CYP11B2 sequences in the coding region and regulatory promoter segments of CYP11B1.

Glucocorticoid Remediable Aldosteronism
Familial Hyperaldosteronism Type I

**GRA Adrenal**

- Ang-II
- **AldoS**
- 11 beta hydrox
- Chimeric AldoS

**fasciculata**

**glomerulosa**

ACTH

**Cortisol + Aldosterone**

**Normal Adrenal**

- Ang-II
- **AldoS**

**glomerulosa**

ACTH

11 beta hydrox

**Cortisol**

**fasciculata**

**Aldo**
• phenotype: early-onset hypertension, resistance to standard antihypertensive treatment

• elevated plasma levels of aldosterone, low renin activity and hypokalemia

• high morbidity and mortality from early onset of hemorrhagic stroke and ruptured intracranial aneurysms

• dexamethasone is a treatment of choice i.e. perfect pharmacogenetics
Other mendelian forms (FHx), bilateral adrenal hyperplasia (BAH), aldosterone producing adenomas (APA), loss of heterozygosity (LOH)

*Zennaro and Jeunemaitre, Circ Res 2011*
Proposed mechanism underlying aldosterone-producing adenoma and Mendelian aldosteronism

Choi et al, Science 2011
Genetic Pathways Involved in BP- Adrenal gland-medulla

PHAEOMOCYTOMA
PARAGANGLIOMAS

GRA
ALDOSTERONE PRODUCING ADENOMA
Malignant phaeochromocytomas & paragangliomas

- 10% of phaeochromocytomas & 20% of paragangliomas are malignant with poor survival
- Genetic testing helps to predict tumour behaviour
- VHL & SDHB mutated tumours are associated with malignancy in 5% and 50% respectively
- Gene analysis should be done early in the diagnostic workup, especially in younger patients or those with (+)ve FHx

*Initial whole-body $^{123}$I-MIBG scintigraphy of a patient with malignant, metastatic phaeochromocytoma.*

Anderson et al, Cancer Treatment Reviews, 2011
# Hereditary neoplastic syndromes clustering with phaeochromocytoma

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Causative gene</th>
<th>Genetic analysis</th>
<th>Indication for genetic testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple endocrine neoplasia type 2 (MEN2A, MEN2B)</td>
<td>RET (rearranged during transfection) proto-oncogene</td>
<td>targeted mutation analysis, sequencing</td>
<td>recommended to family members of a proband</td>
</tr>
<tr>
<td>Von Hippel Lindau disease</td>
<td>VHL tumor suppressor</td>
<td>sequencing</td>
<td>recommended to family members of a proband</td>
</tr>
<tr>
<td>Neurofibromatosis 1 (vonRecklinghausen disease)</td>
<td>NF1 (neurofibromin) gene</td>
<td>sequencing</td>
<td>optional in family members</td>
</tr>
<tr>
<td>Paraganglioma syndromes</td>
<td>Succinate dehydrogenase subunits SDHB &amp; D</td>
<td>sequencing</td>
<td>recommended</td>
</tr>
</tbody>
</table>
Genetic testing in patients with apparently sporadic phaeochromocytoma

- From 12% to 24% patients with non-syndromic (apparently sporadic) pheochromocytoma carry a germline mutation in RET, VHL, SDHD, or SDHB
  
  Amar L et al, J Clin Oncol 2005;34:8812

- SDHB mutations - particularly predisposing to malignancy
  
  Amar L et al, J Clin Oncol 2005;34:8812

Genetic screening should be a part of routine diagnostic work-up in patients with sporadic pheochromocytoma in order to confirm or exclude predisposition to malignancies of hereditary syndromes
Hypertension and Brachydactyly (Bilginturan Syndrome)

- Autosomal dominant due to missense pathogenic variants in PDE3A on chr 12
- Mechanism of high BP – increase VSMC proliferation (medial hyperplasia)
- Increased cAMP hydrolysis causes PTHrP downregulation, dysregulation of chondrogenesis thus causing brachydactyly
- Clinical presentation in childhood, all affected individuals have high BP, some have strokes but no other organ damage
- Drugs that increase cGMP in VSMC might be of therapeutic potential in this syndrome

Mass, Luft at al, Nature Genetics, 2015; 47: 647-653
Examples of diagnostic and therapeutic applications in monogenic hypertension

- confirmation of rare causes of secondary hypertension
- identification of monogenic hypertension
- screening of families at risk of rare genetic disorders
- directed treatment in patients with several forms of monogenic hypertension

- hereditary neoplastic syndrome in patients with pheochromocytoma
- glucocorticoid-remediable aldosteronism (GRA)
- asymptomatic family members of hypertensive patients with autosomal-dominant polycystic kidney disease (ADPKD)
- Liddle syndrome – amiloride
  GRA – glucocorticoids
  Gordon syndrome – thiazide- & thiazide-like diuretics

www.genetics.org
Clinical Summary

• Hypertension is a common clinical feature of many genetic disorders and is the predominant feature in monogenic disorders

• Monogenic hypertension is an increasingly recognised cause of hypertension in children and young adults

• Genetics of monogenic forms of HT is an expanding field that provides insight into the pathophysiology of HT, helps to detect risk for disease, guide strategies for maintaining health, offer more accurate diagnosis, and guides treatment choices

Arggarwal et al, Adv Chronic Kidney Dis 2017;24:372
Thank you

www.stratmed.co.uk
Enzymatic blocks in steroidogenesis pathway causing hypertensive forms of congenital adrenal hyperplasia

Arggarwal et al, Adv Chronic Kidney Dis 2017;24:372
• epidemiologic data show that hypertension arises from a combination of genetic & environmental factors

• heritability = the fraction of BP variance contributed by genetic determinants is 30-50%

• sibling recurrence risk = relative risk of hypertension given that a sibling is affected is 2.5-3.5
WNK1 is a serine–threonine kinase, which regulates Na\(^+\), K\(^+\) and Cl\(^-\) handling in the distal nephron.

Large deletions of the first intron of the WNK1 gene lead to overexpression of L-WNK1 in the distal convoluted tubule, thereby triggering the development of pseudohypoaldosteronism type 2 (PHA2).

Hypertension in PHA2 patients is caused by increased activity of the thiazide-sensitive Na–Cl cotransporter, following L-WNK1 activation.

The mechanisms leading to hyperkalemia and hyperchloremic metabolic acidosis in PHA2 patients still remain to be defined.
Feasibility of identifying genetic variants by risk allele frequency and strength of genetic effect

Manolio et al, Nature 2009
Adrenal medulla and ganglia

Phaeochromocytoma/Paragangliomas

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