Genetics of Hypertension

Morris Brown
University of Cambridge
Where are the genes for hypertension?
Methods for detecting genes for hypertension

- Linkage (family-based) vs Association (population-based)
- Candidate (hypothesis-based) vs Genome-wide (non-hypothesis-based)
Is hypertension ‘just’ the skewed end of the normal BP distribution?

Health Survey of England < 60 yrs
British Genetics of Hypertension (BRIGHT) study
Monogenic Syndromes of Hypertension are due to molecular variants of the Na+ channels inhibited by the diuretics

Na⁺-Cl⁻

Thiazide sensitive

Na⁺ 60%

Na⁺-K⁺, H⁺

Amiloride sensitive

Na⁺-K-2Cl⁻

Bumetanide sensitive

Na⁺ 30%

K⁺ 2%

Bumetanide sensitive

1%

ROMK
Monogenic Syndromes of Hypertension are due to molecular variants of the Na+ channels inhibited by the diuretics.

- **Na\(^+\)-Cl\(^-\)**
  - Thiazide sensitive
  - 60%
  - Na\(^+\) K\(^+\)
  - 7%

- **Na\(^+\)-K\(^+\), H\(^+\)**
  - Liddle’s syndrome
  - 2%
  - Na\(^+\)-K-2Cl\(^-\)
  - ROMK
  - 30%

- **Amiloride sensitive**
  - 1%

- **Bumetanide sensitive**
  - 1%
Monogenic Syndromes of Hypertension are due to molecular variants of the Na+ channels inhibited by the diuretics.

**Principal pathways and disorders altering sodium reabsorption in the nephron**

- **Na**⁺-Cl⁻: Thiazide sensitive
- **Na⁺-K⁺-Cl⁻** (ROMK): Bumetanide sensitive
- **Na⁺-K⁺**: Gitelman’s syndrome
- **Na⁺**: 60%
- **K⁺**: 2%

**Disorders**

- **Gitelman’s syndrome**
- **Thiazide sensitive**
- **Mineralocorticoid receptor**
- **Glucocorticoid Remediable Aldosteronism (GRA)**
- **Apparent Mineralocorticoid Excess (AME)**
- **Geller’s syndrome**
- **Liddle’s syndrome**
- **Pseudohypoaldosteronism type-I**
- **Amiloride sensitive**
- **Bumetanide sensitive**
- **Spironolactone**
- **Na⁺ -K⁺, H⁺**

**Diuretics**

- Thiazide sensitive
- Amiloride sensitive
- Bumetanide sensitive

**Molecular Variants**

- Monogenic Syndromes of Hypertension are due to molecular variants of the Na⁺ channels.
Monogenic Syndromes of Hypertension are due to molecular variants of the Na+ channels inhibited by the diuretics.
Liddle’s syndrome: how genetic truncation causes gain of function

Loss of C-terminus prevents internalisation & so causes constitutive activation
Apparent Mineralocorticoid Excess

Cortisol ± Liquorice (Mineralocorticoid receptor)

Na⁺ (in exchange for K⁺ or H⁺)

Loss of an inactivating enzyme gives cortisol access to mineralocorticoid receptor
**Low K⁺, low renin, low aldosterone = ? liquorice**

<table>
<thead>
<tr>
<th>D.O.B.</th>
<th>24/08/53</th>
<th>Location:</th>
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<tbody>
<tr>
<td>Specimen</td>
<td>24/01/06 at: 1519</td>
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<table>
<thead>
<tr>
<th>U/E</th>
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<tr>
<td>Serum Sodium</td>
<td>144</td>
<td>135-145</td>
</tr>
<tr>
<td>Serum Potassium</td>
<td>3.2 L</td>
<td>3.4-5.0</td>
</tr>
<tr>
<td>Bicarb</td>
<td>37 H</td>
<td>22-30</td>
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<tr>
<td>Creatinine</td>
<td>80</td>
<td>35-125</td>
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</table>

<table>
<thead>
<tr>
<th>Plasma Renin (mass)</th>
<th></th>
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<tbody>
<tr>
<td>Renin (immunoassay)</td>
<td>4.0</td>
<td>µU/L</td>
</tr>
</tbody>
</table>

In 271 hypertensive patients taking neither β-blockers or ACE inhibitors the 5th and 95th centile for renin mass were 3.9 and 78µU/L. Plasma Renin is affected by posture, volaemic status, dietary sodium, serum potassium and antihypertensive medication. Please contact the lab for more details.

Renin: Calculated activity 0.22 pmol/mL/hr

The calculated renin activity from the 5th and 95th centiles are 0.22 and 4.3 pmol/mL/hr

Aldosterone Less than 100 pmol/L
Syndrome of Hypertension and Hyperkalemia with Normal Glomerular Filtration Rate

*Hypertension* 1986, 8:93-102
doi: 10.1161/01.HYP.8.2.93

Richard D. Gordon

**Diagram:**
- Deficiency of any natriuretic or chloruretic factor (e.g., atrial natriuretic peptide or renal natriuretic prostaglandins)
- Dietary salt loading
- Sodium chloride volume overload → Hypertension
- Chronically suppressed renin and angiotensin
- Aldosterone hyporesponsive to hyperkalemic stimulus
Syndrome of Hypertension and Hyperkalemia with Normal Glomerular Filtration Rate

*Hypertension* 1986, 8:93-102  
doi: 10.1161/01.HYP.8.2.93  
Richard D. Gordon

**Figure 1. Pathophysiological mechanisms in Gordon's syndrome**

- Aldosterone hyporesponsive to hyperkalemic stimulus
- Resistance to aldosterone
- Failure to excrete $K^+$, $H^+$
- Membrane defect
- Hyperkalemia and acidaemia
Human Hypertension Caused by Mutations in WNK Kinases

Frederick H. Wilson,1 Sandra Disse-Nicodème,2*
Keith A. Choate,1* Kazuhiko Ishikawa,1* Carol Nelson-Williams,1
Isabelle Desitter,2 Murat Gunel,1 David V. Milford,3
Graham W. Lipkin,4 Jean-Michel Achard,5 Morgan P. Feely,6
Bertrand Dussol,7 Yvon Berland,7 Robert J. Unwin,8
Haim Mayan,9 David B. Simon,1 Zvi Farfel,9 Xavier Jeunemaitre,2
Richard P. Lifton1†

SCIENCE VOL 293 10 AUGUST 2001
Human Hypertension Caused by Mutations in WNK Kinases
Mutations in kelch-like 3 and cullin 3 cause hypertension and electrolyte abnormalities


Figure 3 | KLHL3 expression in the kidney

Novel mutations for Gordon’s syndrome identified by whole exome sequencing
From monogenic to complex: the numbers game

THE NEW ENGLAND JOURNAL OF MEDICINE Oct. 20, 1994

LINKAGE OF THE ANGIOTENSINOGEN GENE TO ESSENTIAL HYPERTENSION

To the Editor: To find linkage between the angiotensinogen gene and essential hypertension in one underpowered study and its subgroups requires good fortune; to present a second with still less power demands fortitude.
From monogenic to complex: the numbers game

THE NEW ENGLAND JOURNAL OF MEDICINE  Oct. 20, 1994

LINKAGE OF THE ANGIOTENSINOGEN GENE TO ESSENTIAL HYPERTENSION

.......... hundreds or even thousands of sibling pairs will be required in order to detect the degree of linkage that we might realistically expect to observe with a polygenic disease.

Morris J. Brown, M.Sc.
Cambridge CB2 2QQ, United Kingdom

David Clayton, M.A.
Addenbrookes Hospital
Genome-wide mapping of human loci for essential hypertension

Mark Caulfield, Patricia Munroe, Janine Pembroke, Nilesh Samani, Anna Dominiczak, Morris Brown, Nigel Benjamin, John Webster, Peter Ratcliffe, Suzanne O’Shea, Jeanette Papp, Elizabeth Taylor, Richard Dobson, Joanne Knight, Stephen Newhouse, Joel Hooper, Wai Lee, Nick Brain, David Clayton, G Mark Lathrop, Martin Farrall, John Connell, for The MRC British Genetics of Hypertension Study

Lancet 2003; 361: 2118-23

<table>
<thead>
<tr>
<th>Chromosomal location</th>
<th>Maximum lod score</th>
<th>Nearest marker</th>
<th>Interval size (cM)</th>
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<tr>
<td>2q</td>
<td>1.76</td>
<td>D2S142</td>
<td>25</td>
<td>0.042</td>
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<tr>
<td>5q</td>
<td>1.85</td>
<td>D5S2019</td>
<td>27</td>
<td>0.035</td>
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<tr>
<td>6q</td>
<td>3.21</td>
<td>D6S281</td>
<td>16</td>
<td>0.043</td>
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<tr>
<td>9q</td>
<td>2.24</td>
<td>D9S290</td>
<td>25</td>
<td>0.017</td>
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</table>

Table 2: Summary of genome-wide screen results on 1599 families
Genome-wide association study identifies eight loci associated with blood pressure

### Table 2  Loci associated with blood pressure

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Genes nearby</th>
<th>BP Trait</th>
<th>Beta (s.e.)</th>
<th>$P$</th>
<th>$N$ total</th>
<th>Coded allele freq</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p36</td>
<td>MTHFR, CLCN6, NPPA, NPPB, AGTRAP</td>
<td>SBP</td>
<td>$-0.85 (0.11)$</td>
<td>$2 \times 10^{-13}$</td>
<td>82,973</td>
<td>0.16</td>
</tr>
<tr>
<td>10q24</td>
<td>CYP17A1, AS3MT, CNNM2, NT5C2</td>
<td>SBP</td>
<td>$1.16 (0.12)$</td>
<td>$7 \times 10^{-24}$</td>
<td>132,552</td>
<td>0.91</td>
</tr>
</tbody>
</table>
‘Manhattan plot’ showing genetic complexity of hypertension

Nature : 478,: 103–109: (06 October 2011)
Relative Risk from GWAS loci

![Relative Risk from GWAS loci](image-url)
Breadth of loci of genetic association

CYP17A1
Breadth of loci of genetic association

GNAS

EDN3
Somatic mutations of the adrenal: the commonest cause of hypertension

Microarray, qPCR and KCNJ5 sequencing shows different profiles for zona glomerulosa (ZG) and fasciculata (ZF) tumors

Elena Azizan, Brian Lam, Gary Hoffman, Rhoda Kuc, Steve Newhouse, Morris Brown.

Azizan et al. J Clin Endocrinol Metab. (in press)
Conn’s Adenoma

K⁺ Channel Mutations in Adrenal Aldosterone-Producing Adenomas and Hereditary Hypertension

Murim Choi,¹ Ute I. Scholl,¹ Peng Yue,²* Peyman Björklund,³,4* Bixiao Zhao,¹*
Carol Nelson-Williams,¹ Weizhen Ji,¹ Yoonsang Cho,⁵ Aniruddh Patel,¹ Clara J. Men,¹ Elias Lolis,⁵
Max V. Wisgerhof,⁶ David S. Geller,⁷ Shrikant Mane,⁸ Per Hellman,⁴ Gunnar Westin,⁴
Göran Åkerström,⁴ Wenhui Wang,² Tobias Carling,³ Richard P. Lifton¹†

Choi et al, Science 2011; 331:768-772
Conn’s Adenoma

K⁺ Channel Mutations in Adrenal Aldosterone-Producing Adenomas and Hereditary Hypertension

Choi et al, Science 2011; 331:768-772
Are KCNJ5 mutations common and does their finding influence clinical management?

Sequencing of Conn’s Syndrome adrenals revealed 20/46 (43%)(95% CI[29,53]) APAs with a somatic mutation of KCNJ5

Azizan et al. J Clin Endocrinol Metab (in press)
KCNJ5 genotype:phenotype I

- ADR044T (L168R) CYP17A1 FC=1.30
- ADR082T (Wild-type) CYP17A1 FC=0.21

Graph showing the relationship between age at surgery, APA diameter, genotype (Mutant vs. Wild-type), and gender (Female vs. Male).
• Wild-type APAs are smaller because they have smaller, ZG-like cells.
Wild-type APAs are smaller because they have smaller, ZG-like cells. They cause resistant hypertension in older patients because overlooked or ignored.
Early diagnosis of APA by $^{11}$C-metomidate PET CT

Early diagnosis of APA by PET CT

• 50-year old man with hypertension, requiring 4 drugs
• Diagnosed as Conn’s in 2007, because suppressed renin and low potassium on diuretic
• Tiny nodule on CT, and poor lateralisation on adrenal vein sampling
Early diagnosis of APA by PET CT

• 50-year old man with hypertension, requiring 4 drugs
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6 weeks post op: BP on 2 drugs 138/86 mmHg
Summary

• Hypertension can be caused by mutations in single genes

• Inherited susceptibility to hypertension is most likely due to many hundred of genes with small effects

• However the KCNJ5 story illustrates how hypertension can be due to a molecule with nothing to do with normal BP control

• Much of hypertension could yet be due to uncommon variants whose phenotype is less obvious than low K⁺ or low renin