Congenital Heart Disease
How much of it is genetic?

Stephen Robertson
Curekids Professor of Paediatric Genetics
Dunedin School of Medicine
University of Otago

otago.ac.nz/child-health-research
Congenital Heart Disease

- The most common survivable birth defect: 0.5-0.8% of live births
- Possible rising incidence over previous decades
- Now birth prevalence decreasing due to prenatal diagnosis
The Aetiology of CHD
The Traditional View

- 15% have an ascribable cause
- 8-10% chromosomal or CNV (e.g. trisomies, 22q11del)
- Single genes - mutations in single genes (most associated with syndromic presentations) - clues from clinical evaluation
- Non-syndromic - 2% of all CHD have an environmental cause - DM, PKU, obesity, alcohol
- Multivitamin supplements may be protective against the development of congenital cardiovascular defects (OR 0.61 or 0.78)

Methods of Evaluation
Copy number evaluation

Recurrent microdeletion syndromes
- 22q11 - “Di George”/ Velocardiofacial Syndrome
- 7q11 - Williams Syndrome
- 20p12 - Alagille syndrome

Non-syndromic recurrent CNVs
- 8p23 - atrioventricular canal defects
- 1q21 - left sided outflow tract anomalies
The Traditional View: Point Mutations

- Predominantly non-syndromic, therefore familial aggregation the key to consider testing
- Mutations in *TBX20* result in ASDs and valvular abnormalities
- Mutations in *NKX2-5* commonly ASDs with or without conduction abnormalities
- Mutations in *GATA4* - septal heart defects
- Inherited left sided disease (BiAV, HLH) - defects in NOTCH signaling
- X-linked heterotaxy - *ZIC3*

The frustration of rarities without a clear view of whom to test
Recurrence risk of non-syndromic CHD in offspring with one affected parent

<table>
<thead>
<tr>
<th>Type of defect</th>
<th>If mother affected (%)</th>
<th>If father affected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>2–20</td>
<td>1–5</td>
</tr>
<tr>
<td>VSD</td>
<td>9–10</td>
<td>2–3</td>
</tr>
<tr>
<td>ASD</td>
<td>6</td>
<td>1–2</td>
</tr>
<tr>
<td>Aortic coarctation</td>
<td>4</td>
<td>2–3</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>15–20</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
<td>6–7</td>
<td>2</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>2–3</td>
<td>1–2</td>
</tr>
</tbody>
</table>

Data from Nora, J. J. et al. (1991)
Recurrence risk of non-syndromic CHD in siblings with two healthy parents

<table>
<thead>
<tr>
<th>Type of defect</th>
<th>Recurrence risk when one child is affected (%)</th>
<th>Recurrence risk when two children are affected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1–6</td>
<td>3–10</td>
</tr>
<tr>
<td>VSD</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>ASD</td>
<td>2–3</td>
<td>8</td>
</tr>
<tr>
<td>AVSD</td>
<td>3–4</td>
<td>NR</td>
</tr>
<tr>
<td>Ebstein anomaly</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Aortic coarctation</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>2–3</td>
<td>8</td>
</tr>
<tr>
<td>Hypoplastic left heart</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Tricuspid atresia</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary atresia</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>TGA</td>
<td>1–2</td>
<td>5</td>
</tr>
<tr>
<td>ccTGA</td>
<td>5–6</td>
<td>NR</td>
</tr>
</tbody>
</table>

Nora, J. J. et al. (1991); Calcagni, G. et al. (2007)
Liability Threshold Model - Does it apply?

Possibly not

- RR rises with number of affected siblings to 10%
- Affected mothers confer additional RR (2.5:1)
An Explanatory Genetic Architecture for CHD?

Blue et al., (2017)
Options for testing

- Microarray - detection of chromosomal microdeletions and microduplications
- Panels (pre-specified genes relating to a pathology)
- Whole exome or whole genome sequencing
New data on comprehensive microarray analysis

Rare CNVs over-represented in CHD - OR 1.8

Rare ("private") Copy Number Variants are over-represented in:

- Heterotaxy presentations
- Left sided heart defects
- Tetralogy of Fallot (de novo in 10% ToF cases)
- Atrioventricular Canal Defects
- All defects when associated with extracardiac anomalies especially developmental delay

Overall

- 5% of CHD cases have a de novo CNV - (cf. controls 2%)
- Uncertainty with regards to penetrance

Soemedi et al AJHG 2012
The logic around whole genome sequencing

**Trio design**
Good for discovering new (de novo) mutations
Search space - 1-2 new coding mutations/individual

**Sib recurrence**
? recessive = 25% recurrence risk
Requires searching for two mutations (one from each parent)
Search space - extensive
Epidemiology indicates this unlikely

**Non-penetrant parent**
Dominant inheritance
Ongoing sib and offspring recurrent risk
Search space huge but can confine focus to known genes
Familial Congenital Heart Disease
The (rare) sweet spot for genomics

• Gene panel approaches
• Pre-specified genes
• 31-46% diagnosis rate
• Surprising mixes of inherited liability but also excess “extra” mutational burden (? explains variable expressivity / incomplete penetrance)
• No excess of private CNVs
• Management implications for some genes (\(NKX2-5\), \(TBX5\) and proarrythmia)

**de novo (new) Variants**

The evidence so far

- Whole-exome sequencing of 362 parent-offspring trios with an affected CHD proband.
- *de novo* point mutations /insertion/deletion mutations in *over 200 genes* collectively contribute to *~10% of sporadic CHD*
- carriers of LOF variants in candidate genes had higher odds of having CVM (OR = 4.0)

(Li et al, 2017)
Syndromic vs non-syndromic CHD
A clinically useful distinction

• Given a clinical presentation of CHD that is sporadic in the context of extra cardiac anomalies or an isolated presentation, what is the significance of finding:
  • A missense vs a protein truncating variant
  • A variant that is de novo vs inherited
  • The relative likelihoods (and therefore diagnostic yield) of finding either of these combinations?

• N = 1891 probands (+ their parents); 610 syndromic, 1281 non-syndromic

(Sifrim et al. 2017)
De Novo Variation

Relative excess

Sifrim et al 2017
Inherited variation in non-syndromic congenital heart disease
Differing Genetic Approaches to the molecular diagnosis of CHD

Summary of Recent Data

• The relative contributions of DNVs and incompletely penetrant variants differ markedly between NS-CHD and S-CHD.

• A major role for de novo mutations in S-CHD.

• CHD is often not fully penetrant in S-CHD disorders, but a diagnosis rate of ~50% is possible. Predicting deleterious missense mutations is a problem.

• Inherited high-risk variants predominate in NS-CHD but causative highly penetrant variants are hard to define confidently. Current studies underpowered.

• Very large cohorts (~30,000 individuals) will be needed to define most dominant CHD-associated genes (~400?).
A Clinical approach: Familial vs Syndromic vs Non-Syndromic presentations

• Familial - Gene panels; Microarrays probably unfulfilling in non-syndromic presentations

• Syndromic - Gene panels or whole exome approaches + microarray. Interpret in context with parental information
