Otago Spotlight Series
Child Health Research

Congenital Heart Disease
How much of it is genetic?

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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)

J. Obstet. Gynaecol. Can. 28, 680–689 (2006).

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

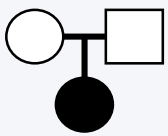
Recurrence risk of non-syndromic CHD in offspring with one affected parent

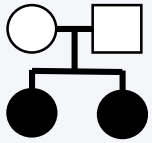
Type of defect	If mother affected (%)	If father affected (%)
Overall	2–20	1–5
VSD	9–10	2–3
ASD	6	1–2
Aortic coarctation	4	2–3
Aortic stenosis	15–20	5
Pulmonary stenosis	6–7	2
Tetralogy of Fallot	2–3	1–2

Data from Nora, J. J. *et al*. (1991)

Recurrence risk of non-syndromic CHD in siblings with two healthy parents

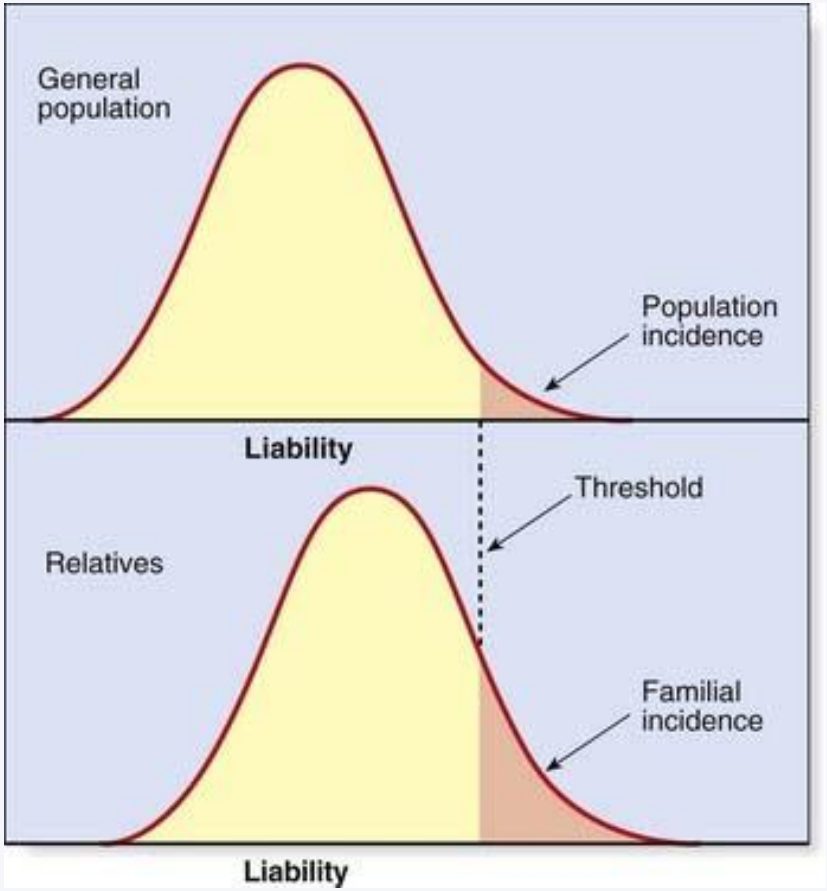
Type of defect	Recurrence risk when one child is affected (%)	Recurrence risk when two children are affected (%)
Overall	1–6	3–10
VSD	3	10
ASD	2–3	8
AVSD	3–4	NR
Ebstein anomaly	1	3
Aortic coarctation	2	6
Aortic stenosis	2	6
Pulmonary stenosis	2	6
Tetralogy of Fallot	2–3	8
Hypoplastic left heart	3	10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





Nora, J. J. *et al*. (1991); Calcagni, G. *et al*. (2007)

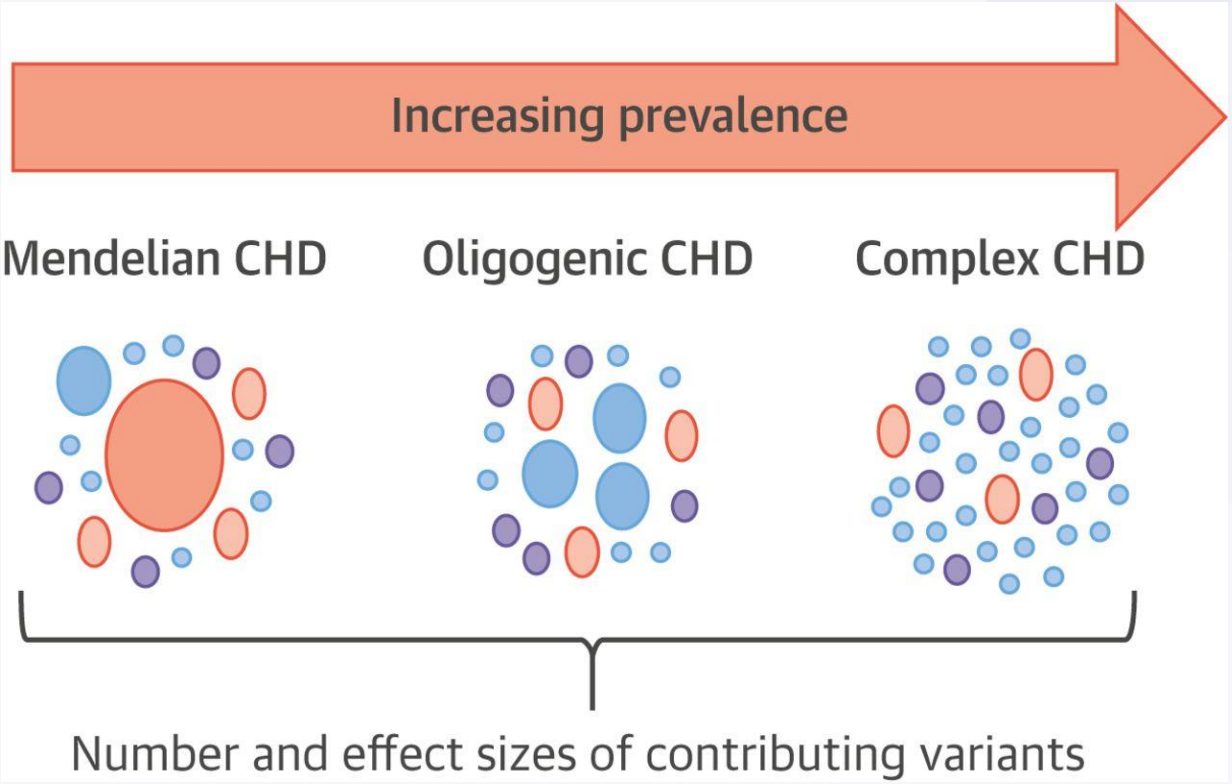
Liability Threshold Model - Does it apply?



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?



High
Intermediate
Low

Penetrance of variants

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:

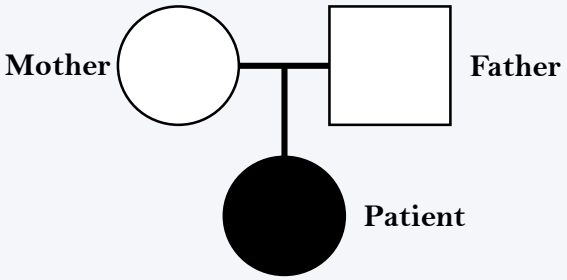
- Heterotaxy presentations
- Left sided heart defects
- Tetralogy of Fallot (*de novo* in 10% ToF cases)
- Atrioventricular Canal Defects
- All defects when associated with extracardiac anomalies especially developmental delay

Overall

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

Soemedi et al AJHG 2012

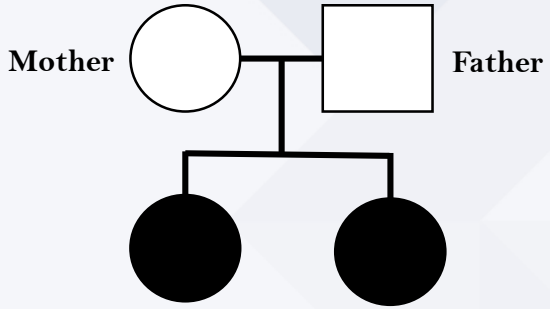
The logic around whole genome sequencing



Trio design

Good for discovering new (de novo) mutations

Search space - 1-2 new coding mutations/individual



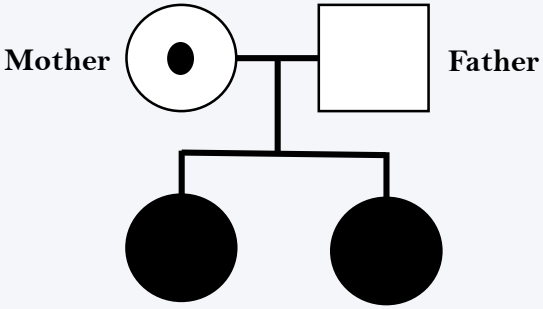
Sib recurrence

? 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 proarryhthmia)

Blue et al., (2014) Jia et al., (2015)

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)

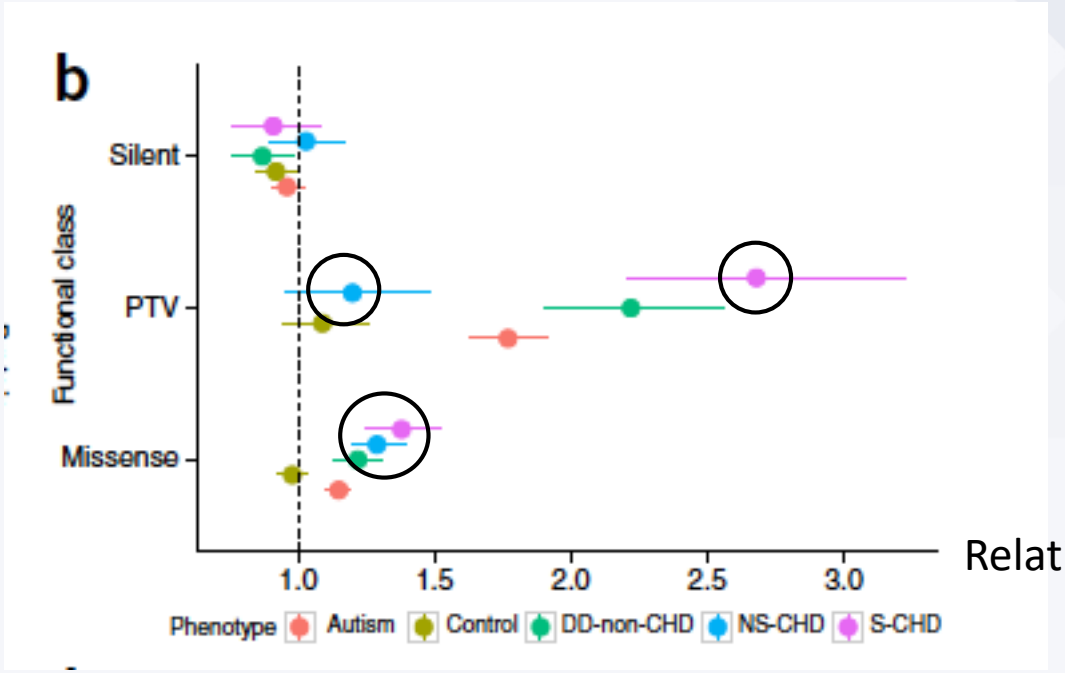
(Li et al, 2017)

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)

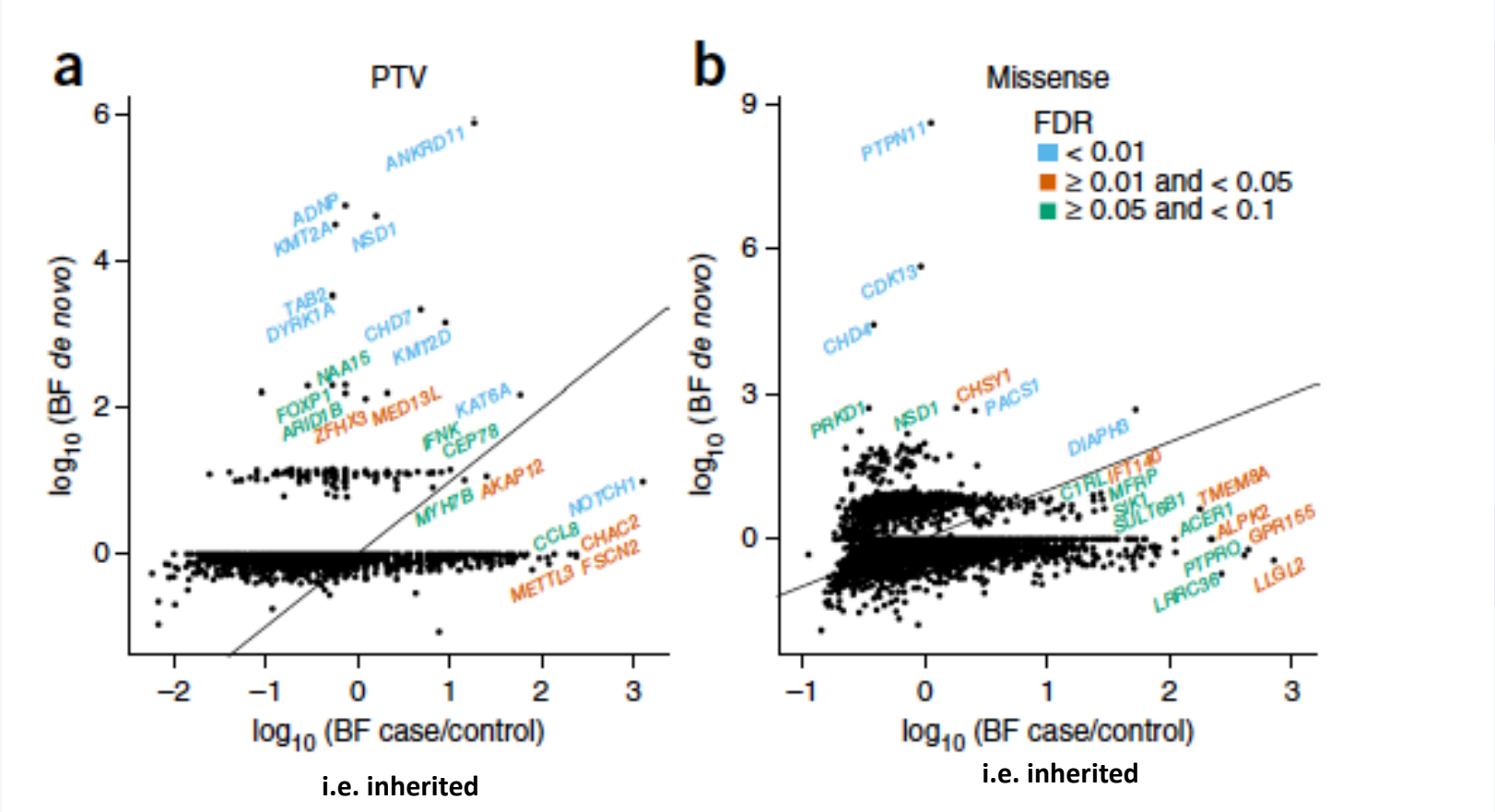
De Novo Variation



Relative excess

Sifrim et al 2017

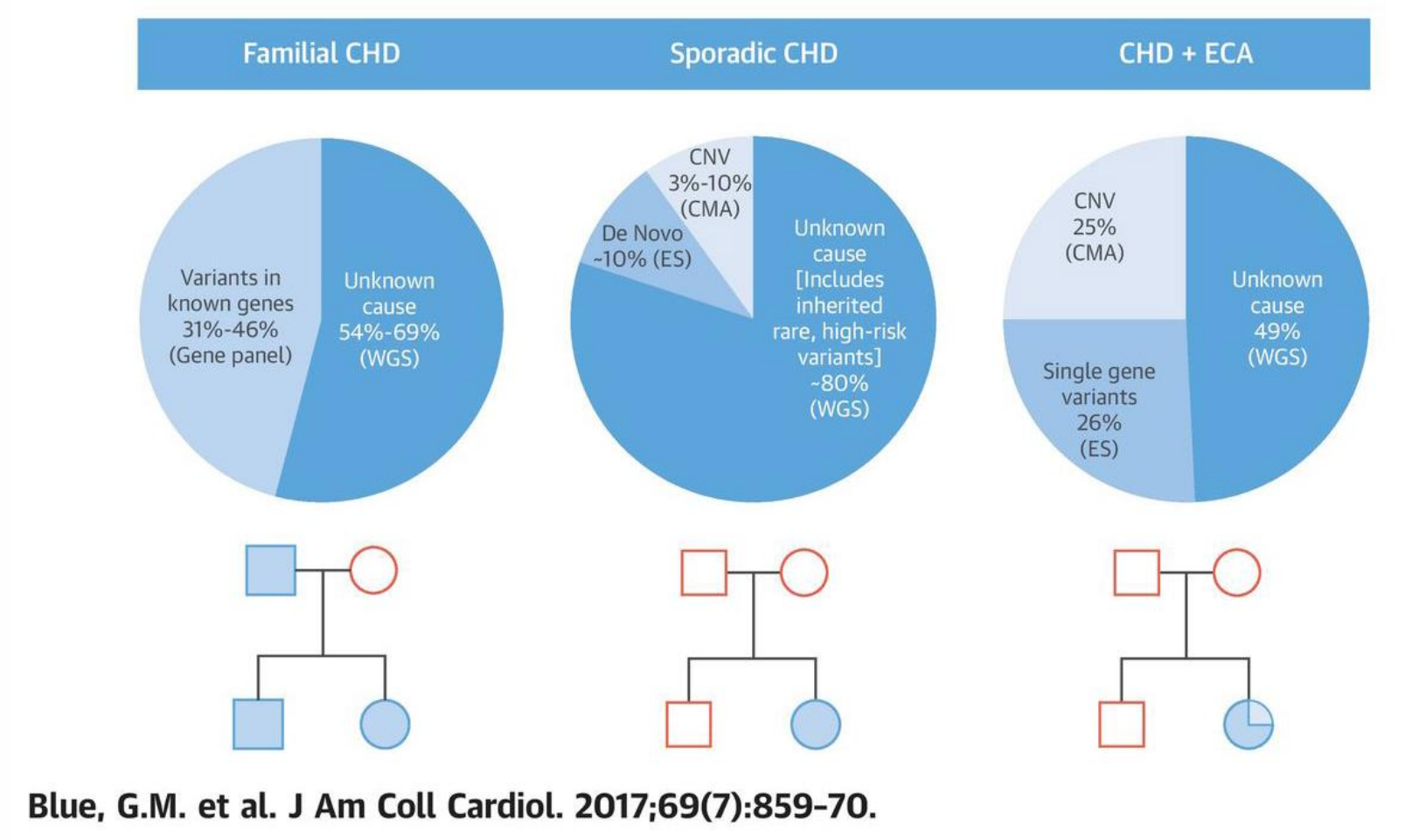
Inherited variation in non-syndromic congenital heart disease



i.e. inherited

i.e. inherited

Differing Genetic Approaches to the molecular diagnosis of CHD



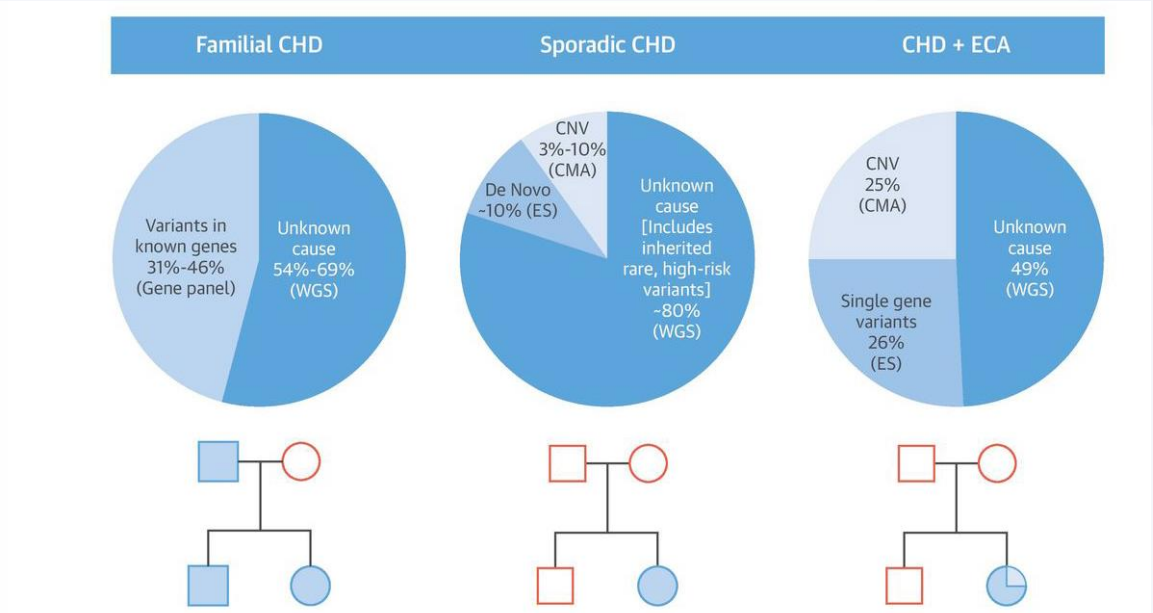
Blue, G.M. et al. J Am Coll Cardiol. 2017;69(7):859-70.

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
- Non-syndromic - unrewarding pickup with current gene panels - need comprehensive non-biased datasets for interpretation. Current panels under-powered.



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