Bioinformatics re-analysis of genome sequencing data increases the genetic testing diagnostic yield of inherited heart disease

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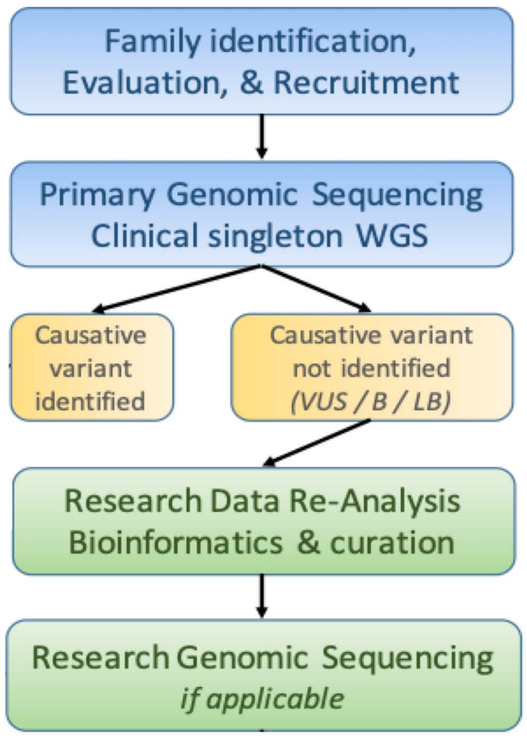
Introduction

Australian Genomics informs the integration of genomic medicine into mainstream healthcare.

The Cardiac Genetic Diseases Flagship aims to demonstrate the clinical utility and cost-effectiveness of genomic testing approaches in genetic heart disease.

Methods



First Tier Analysis

- Clinical genome sequencing
- Established disease genes
- Clinical report feedback

Second Tier Analysis

- Research-based analysis
- 573 disease-associated genes
- Deep intronic variant analysis
- Mitochondrial genome analysis
- Copy number variant analysis
- Clinical curation of variants
- Causative variant identified
- Research report feedback

Figure 1. Australian Genomics Cardiac Flagship Workflow

Aim

Evaluate the additional benefits of a wider genetic analysis in inherited heart diseases

Results

To date, we have analysed 234 participants with inherited heart disease. 78 participants have primary arrhythmia disease and 156 participants have inherited cardiomyopathy.

123 cases have no genetic cause found after the First Tier Analysis.

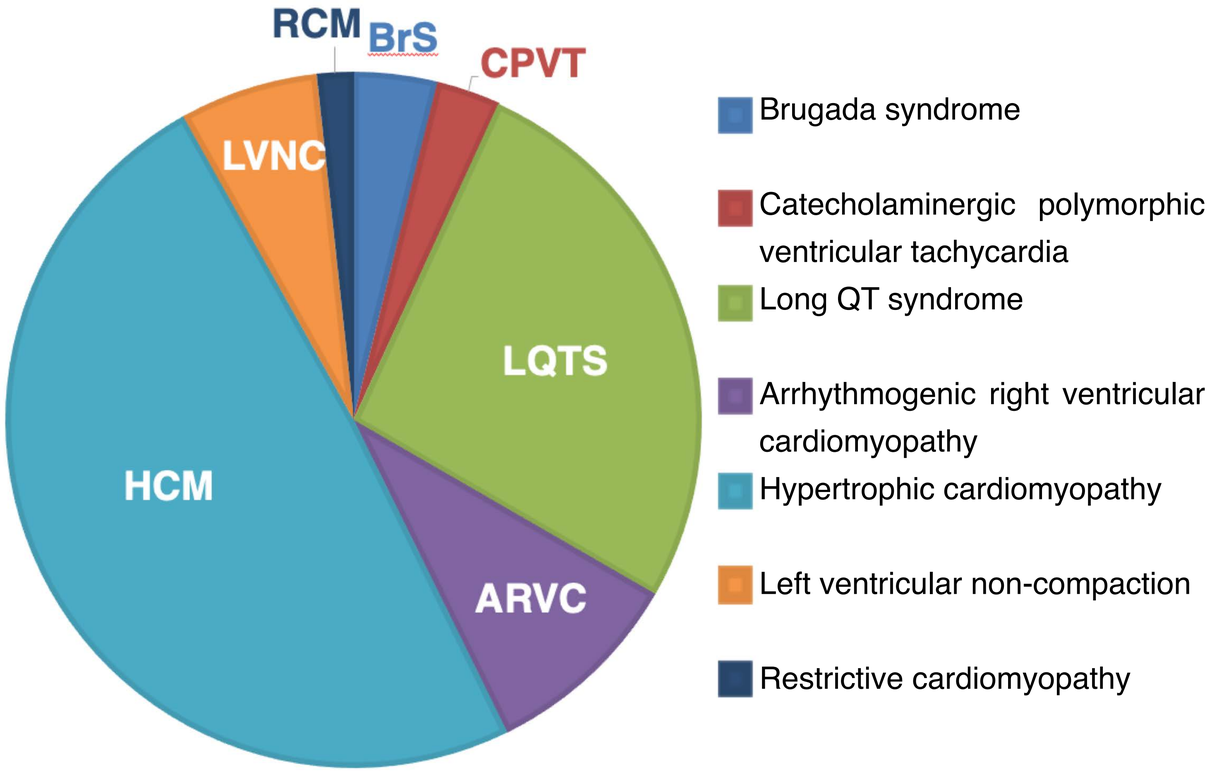


Figure 2. Participants' clinical diagnosis

Results

We have found a likely pathogenic or pathogenic variant in 5/123 participants who did not have a genetic cause of disease identified following clinical genetic testing (Table 1).

Table 1. Genetic causes of disease identified following Tier 2 analysis

Diagnosis	Tier 1	Tier 2	Variant	Tier 2 classification
LVNC	indeterminate	MT-TI	m.4300A>G	Pathogenic
LVNC	indeterminate	TTN	Arg27806Ter	Likely Pathogenic
LVNC	indeterminate	TBX20	Ser125Ter	Likely Pathogenic
LVNC	indeterminate	PRDM16	Arg1091Ter	Likely Pathogenic
*HCM	MYBPC3 Pro186Leu	MYBPC3	NM_000256.3: c.1224-33G>A	Likely Pathogenic

Ten additional participants have candidate pathogenic variants awaiting clinical classification or functional assessment.

Two patients have incidental genetic findings possibly related to clinically relevant cardiac phenotypes (Table 2).

Table 2. Cases with incidental genetic findings on Tier 2 analysis

Diagnosis	Tier 1	Tier 2	Variant	Tier 2 classification
**LQTS	KCNQ1 Leu2666Pro	TTN	p.Ile30515Argfs*2	VUS
CPVT	RYR2 Leu4105Phe	KCNQ1	Arg583His	VUS

VUS - variant of uncertain clinical significance.

Two case presentations

* A 14 year-old male with hypertrophic cardiomyopathy and no family history of disease had a deep intronic splice-gain variant in *MYBPC3* found on Tier 2 analysis. Functional studies confirmed abnormal splicing of *MYBPC3* transcripts.

A 16 year-old female with long QT syndrome had a **pathogenic *KCNQ1* variant identified on Tier 1 analysis. Tier 2 bioinformatics reanalysis of her genome identified a *TTN* frameshift variant that may explain early onset atrial fibrillation in her family (Figure 3).

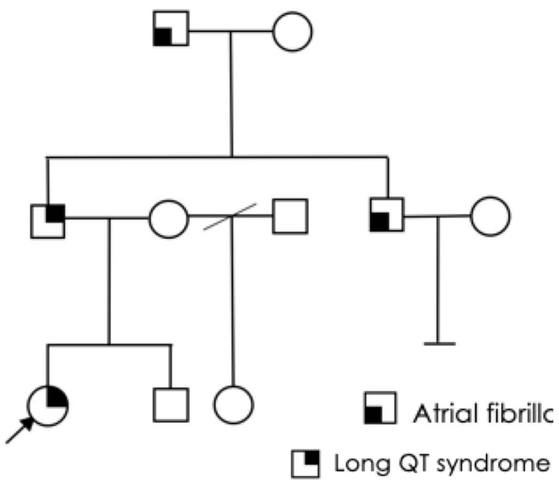


Figure 3. Pedigree of family with incidental finding possibly related to early onset atrial fibrillation

Conclusion

Secondary bioinformatics analysis increases the genetic testing diagnostic yield of inherited heart diseases

Acknowledgements

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