Diagnostic Yield of Genetic Testing in an Unselected Cohort of Patients with Congenital Heart Disease

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Introduction

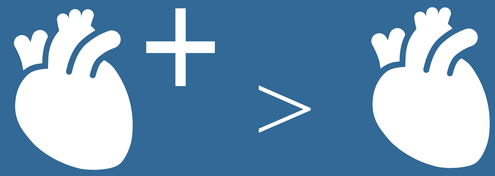
- Congenital heart disease (CHD) is the most common human birth defect (affecting 1%-2% of live births).
- Genetic testing results may guide medical management, prompt surveillance of extracardiac features, and identify at-risk relatives.
- Next generation sequencing (NGS) panels are not often pursued in CHD patients as the yield of testing is variable and relatively low; few studies have described genetic findings identified on panel testing.
- We evaluated the yield from NGS panel testing in a heterogeneous cohort of patients with CHD.

Methods

- Retrospective review of patients who underwent genetic testing of the targeted Congenital Structural Heart Disease panel at Blueprint Genetics. All patients had a suspected or confirmed CHD diagnosis per the information provided on the test requisition.
- Patients were considered to have a syndromic presentation if the clinical history described ≥ 1 extracardiac anomaly.
- Testing included both sequencing and copy number variant (CNV) analysis of 28, 62 or 114 genes associated with CHD, due to the evolution of the panel content over time
- Either 48 (in the case of the 62-gene panel) or 102 (in the case of the 114-gene panel) clinically relevant non-coding variants were included in the analysis. No clinically relevant non-coding variants were included in the 28-gene panel.
- A diagnostic test result was defined by the identification of pathogenic (P) or likely pathogenic (LP) variant(s) (classified using a modified ACMG/AMP variant classification scheme) that were consistent with the patient's reported phenotype and known disease inheritance.
- Chi-square analysis and Fisher's exact test were utilized to determine statistical significance where appropriate. A *P* value less than 0.05 was considered significant.

One in 7 patients undergoing next generation sequencing (NGS) panel testing for a congenital heart disease indication received a molecular diagnosis.

1 in 4 diagnostic variants were CNVs; 1 in 3 were **intragenic.**



20.7% yield in syndromic cases; 9.5% yield in non-syndromic cases (*P*=0.015)

Results

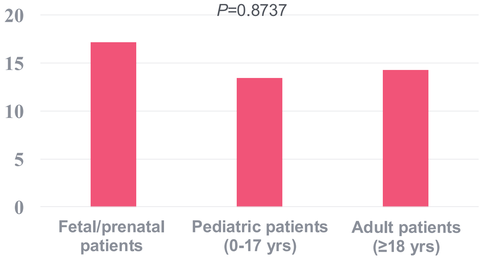
Table: Patient Demographics

Patient Demographics	Number of individuals (n=204)	Proportion of the cohort
Male sex	100	49.0%
Female sex	89	43.6%
Sex not reported	15	7.4%
Fetuses/prenatal cases	35	17.2%
Pediatric cases (0-17)	134	65.6%
Adult cases (≥ 18)	35	17.2%
Apparently syndromic cases*	82	40.2%
Apparently isolated cases*	115	56.4%
114-gene panel	117	57.4%
62-gene panel	71	34.8%
28-gene panel	16	7.8%

* n=7 patients did not have sufficient clinical information included on the test requisition to determine if their presentation was apparently isolated or syndromic.

- A total of 204 patients underwent CHD panel testing (see Table)
- A diagnostic (sequence or copy number) variant was identified in 14.2% of patients (n=29) in 17 genes.
- Variants in *TBX5* were most common (n=6, 2.9% of all patients), followed by *CHD7* (n=3, 1.5% of all patients), and *GATA4*, *GATA6*, *JAG1*, and *KMTD* (n=2, 1.0% respectively).
- Diagnostic CNVs were identified in 3.4% of all patients in the cohort.
- The diagnostic yield of genetic testing was not significantly different across age groups (see Figure).

Figure: Diagnostic yield of genetic testing (%) by age group at the time of testing



Conclusions

- The diagnostic yield of NGS panel testing in an unselected cohort of patients with CHD was 14.2% and comparable to what has been reported for patients undergoing exome or genome sequencing.[1]
- CNVs were present in 3.4% of all patients in the cohort.
- These data support the consideration of NGS targeted panel testing for patients with CHD.

Conflict of interest statement:
All authors are employed by Blueprint Genetics.

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References:
1. Reuter MS, Chaturvedi RR et al. The Cardiac Genome Clinic: implementing genome sequencing in pediatric heart disease. *Genet Med*. 2020;22(6):1015-1024.

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