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Diagnostic yield from cardiogenomic panel testing for inherited cardiovascular diseases

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Introduction

Multiple organizations have issued practice guidelines and statements recommending genetic testing for heritable heart conditions. The American College of Medical Genetics and Genomics published a 2018 practice resource which recommended genetic testing using a 39 gene panel for patients with cardiomyopathy and at-risk relatives. The Heart Rhythm Society and European Heart Rhythm Association published a 2011 consensus statement which recommended a 9 gene panel for individuals with a suspected arrhythmic disorder. In a 2020 scientific statement on genetic testing, the American Heart Association reiterated the findings of the ClinGen Aortopathy Working Group which found definitive evidence associating 11 genes with heritable thoracic aortic aneurysms and dissections along with moderate/limited evidence for an additional 8 genes. Consequently, a retrospective analysis was conducted on the results from cardiogenomic testing in our laboratory to evaluate diagnostic yield.

Methods

Panel based testing included 10 genes for aortopathy and the *MED12* c.3020A>G variant, 29 genes for arrhythmia, and 48 genes for cardiomyopathy. Disease-associated variants (pathogenic and likely pathogenic) and variants of uncertain significance (VUS) were reported for all panels. Data included 1385 aortopathy panels, 596 arrhythmia panels, and 831 cardiomyopathy panels.

Results

- Disease-associated variants (pathogenic/likely pathogenic) were identified in 2% of aortopathy, 13% of arrhythmia, and 16% of cardiomyopathy panels.
- VUS were the most common variant interpretation identified including 83.8% of aortopathy, 76.9% of arrhythmia, and 87.1% of cardiomyopathy reportable variants (**Table 1**).
- One cardiomyopathy panel reported a single pathogenic *PKP2* gene variant along with seven VUS in the *DSP*, *MYH7*, *RYR2*, *SGCD*, and *TTN* genes.
- A majority of reportable variants were identified for the aortopathy panel in the *FBN1* (32%), *MYH11* (17%) and *COL3A1* (17%) genes (**Figure 1A**), for the arrhythmia panel in the *KCNQ1* (13%), *SCN5A* (11%) *RYR2* (11%) and *KCNH2* (11%) genes (**Figure 1B**), and for the cardiomyopathy panel in the *TTN* (37%), *ALMS1* (10%), *MYBPC3* (6%) and *MYH7* (6%) genes (**Figure 1C**).
- Only one cardiomyopathy sample had more than one disease-associated variant; a *FKTN* gene pathogenic variant and a likely pathogenic variant in the *DSP* gene.
- Only 1% of aortopathy panels had more than one reportable variant, but significantly more of such scenarios were seen in arrhythmia (12%) and cardiomyopathy (35%) testing. Nearly all such cases involved 1 one more VUS.

Conclusions

- The large proportion of VUS identified create result interpretation challenges. There is currently active debate in the field around the clinical utility of reporting such variants.
- These results reaffirm the diagnostic value of panel based, genetic testing for inherited cardiovascular diseases and illustrate testing challenges.

References

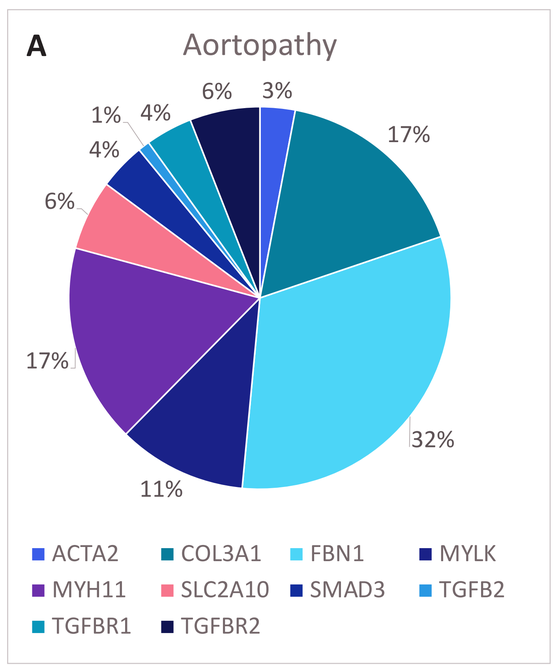
1. Hershberger RE, Givertz MM, Ho CY, Judge DP, Kantor PF, McBride KL, Morales A, Taylor MRG, Vatta M, Ware SM; ACMG Professional Practice and Guidelines Committee. Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2018 Sep;20(9):899-909. doi: 10.1038/s41436-018-0039-z. Epub 2018 Jun 14. Erratum in: *Genet Med*. 2019 Oct;21(10):2406-2409. PMID: 29904160.
2. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP; Heart Rhythm Society (HRS); European Heart Rhythm Association (EHRA). HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Europace*. 2011 Aug;13(8):1077-109. doi: 10.1093/europace/eur245. PMID: 21810866.
3. Musunuru K, Hershberger RE, Day SM, Klinedinst NJ, Landstrom AP, Parikh VN, Prakash S, Semsarian C, Sturm AC; American Heart Association Council on Genomic and Precision Medicine; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Genetic Testing for Inherited Cardiovascular Diseases: A Scientific Statement From the American Heart Association. *Circ Genom Precis Med*. 2020 Aug;13(4):e000067. doi: 10.1161/HCG.0000000000000067. Epub 2020 Jul 23. PMID: 32698598.
4. Renard M, Francis C, Ghosh R, Scott AF, Witmer PD, Adès LC, Andelfinger GU, Arnaud P, Boileau C, Callewaert BL, Guo D, Hanna N, Lindsay ME, Morisaki H, Morisaki T, Pachter N, Robert L, Van Laer L, Dietz HC, Loeys BL, Milewicz DM, De Backer J. Clinical Validity of Genes for Heritable Thoracic Aortic Aneurysm and Dissection. *J Am Coll Cardiol*. 2018 Aug 7;72(6):605-615. doi: 10.1016/j.jacc.2018.04.089. PMID: 30071989; PMCID: PMC6378369.

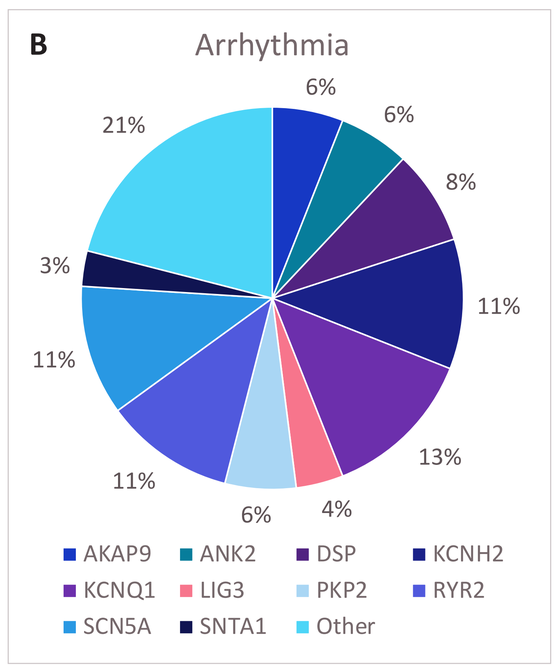
Figures

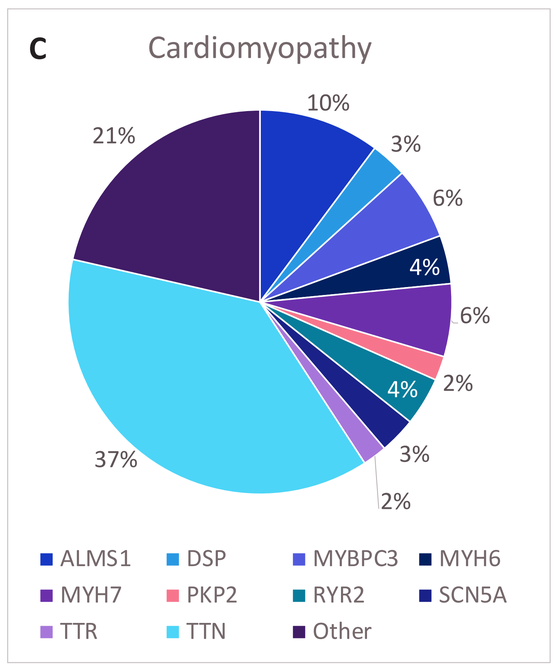
Table 1. Percent of each type of reportable variants identified for each cardiogenomic panel

Panel	Variant interpretation	% of Reportable variants identified
Aortopathy	Pathogenic	9.6%
	Likely pathogenic	6.6%
	VUS	83.8%
Arrhythmia	Pathogenic	15.3%
	Likely pathogenic	7.8%
	VUS	76.9%
Cardiomyopathy	Pathogenic	8.8%
	Likely pathogenic	4.1%
	VUS	87.1%

Figure 1. Frequency of reportable variants (pathogenic, likely pathogenic, and VUS) across the 10 most common genes in the aortopathy (A), arrhythmia (B), and cardiomyopathy (C) panels.







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