Genetic findings in a cohort of over 2,300 individuals with clinically suspected heritable thoracic aortic disease

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Introduction

Heritable thoracic aortic disease (HTAD) is associated with high morbidity and mortality; sudden death due to aortic dissection may be the first presenting feature. Genetic testing for individuals with suspected HTAD is a published guideline recommendation.[1,2] Genetic test results can directly affect the management of individuals and their at-risk family members, including prompting surveillance for the extracardiac manifestations associated with certain genes and the screening of family members after the sudden death of an affected relative. The yield of genetic testing in individuals with HTAD has been described, but the genes and cohort inclusion criteria in past studies have varied. In this study, we reviewed the genetic findings in a large heterogeneous cohort of individuals with suspected HTAD to further assess the value of genetic testing in this population.

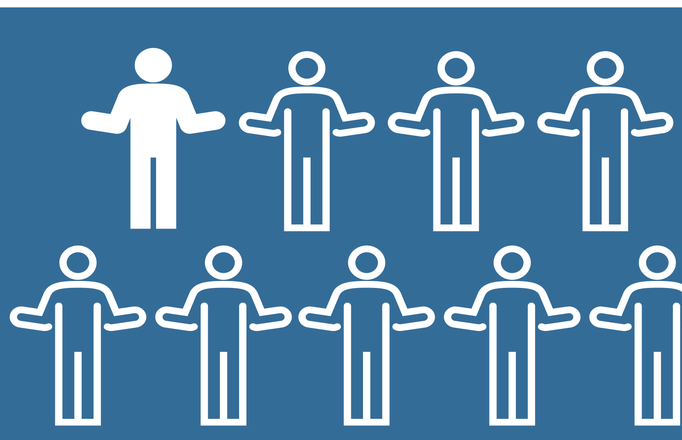
Methods

We performed a retrospective review of de-identified data from consecutive individuals who underwent genetic testing for a panel of genes associated with HTAD and related syndromes. Test requisition forms were searched for the terms “deceased” and “death” to identify individuals who were deceased at the time of testing. Sequencing and copy number variant (CNV) analysis was performed by next-generation sequencing (NGS) for up to 53 genes associated with HTAD, as well as up to 62 noncoding variants in these genes catalogued as disease-associated by HGMD and/or ClinVar. Gene content varied due to the addition of genes to the panel over time. Variant interpretation was performed in accordance with modified ACMG/AMP guidelines. An informative result was defined as the identification of a pathogenic (P) or likely pathogenic (LP) variant(s) consistent with the individual’s reported phenotype and disease inheritance. Chi-square analyses determined statistical significance (α=.05).

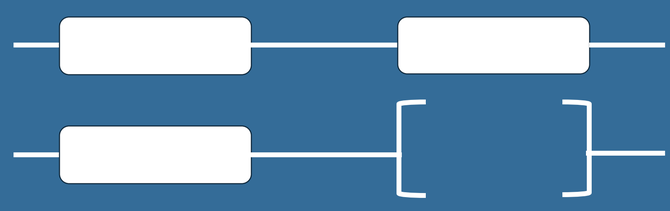
Results

A total of 2,358 presumably unrelated individuals were tested with the panel; 88.1% (2,077/2,358) were adults (≥18 years of age) at the time of testing, 63.1% (1,489/2,358) were male, and 1.4% (34/2,358) were deceased at the time of testing. The median age at the time of testing was 53 years (range: prenatal to 91). In all, 11.8% (278/2,358) of individuals received an informative test result. A total of 282 LP/P variants were identified; 6.0% (17) of these were CNVs. The most common LP/P CNV was a duplication involving the *ABCC6* and *MYH11* genes (29.4% [5/17] of all CNVs). Overall, 98.6% (278/282) of LP/P variants identified were in genes associated with extracardiac features in addition to HTAD.

The yield of genetic testing in deceased individuals (23.5% [8/34]) was significantly higher than in living individuals (11.6% [270/2,324], $P<.05$, $\chi^2=4.57$). The yield of testing was similar for children (12.5% [35/281]) and adults (11.7% [243/2,077], $P>.05$, $\chi^2=0.14$) (Table 1). Among individuals who received an informative result, an LP/P variant in *FBN1* was the most common finding for both children (48.6% [17/35]) and adults (43.6% [106/243]) (Figures 1 and 2). After *FBN1*, the most common LP/P variants identified were in *ACTA2* (9.4% [26/278]), *SMAD3* (9.0% [25/278]), *COL3A1* (7.2% [20/278]), *TGFBR2* (5.4% [15/278), *TGFB2* (4.3% [12/278]), *TGFBR1* (3.6% [10/278]), and *FLNA* (2.5% [7/278]) (Figures 1 and 2). Two LP/P variants in different autosomal dominant genes in the same individual were identified in 0.13% (3/2,358) of individuals in the cohort.



1 in 9 patients in the cohort received an informative result.



LP/P CNVs accounted for ~6% of all informative variants in the cohort.

Table 1. Patient demographics

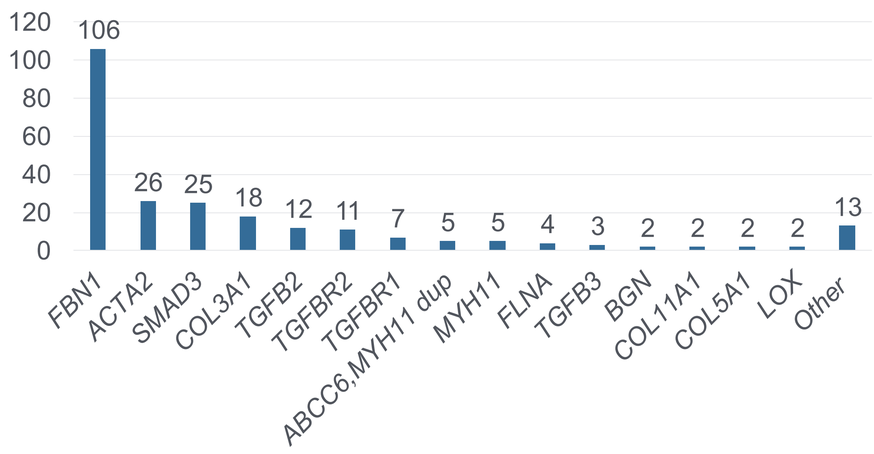
Demographic	% of cohort (# of patients)	% with informative result (# of patients)
Male[1]	63.1% (n=1,489)	11.3% (n=169)
Female[1]	36.6%(n=863)	12.7% (n=110)
Adult (≥18 yrs)	88.1% (n=2,077)	11.7% (n=243)[2]
Pediatric (<18 yrs)	11.9% (n=281)	12.5% (n=35)[2]
Living	98.6% (n=2,324)	11.6% (n=270)[3]
Deceased	1.4% (n=34)	23.5% (n=8)[3]

1. Sex not reported in n=6.
2. Compared for statistical significance, not significant at $P>.05$, $\chi^2=0.14$.
3. Compared for statistical significance, significant at $P<.05$, $\chi^2=4.57$.

Table 2. LP/P CNVs identified in the cohort

Event	Size	Count
Duplication	>1000 kb	2
Duplication	100-1000kb	5
Deletion	100-1000kb	4
Deletion	1-99kb	5
Deletion	<1kb (single exon)	1

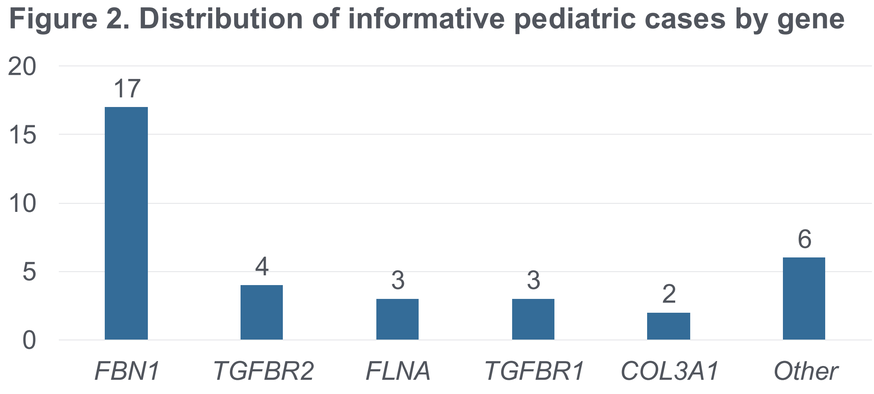
Figure 1. Distribution of informative adult cases by gene



Other (n=1, respectively):

7q11.3 dup; *ABL1*; *CBS*; *COL1A1; COL2A1*; *COL3A1+COL5A2* del; *ELN*; *FBN2*; Mosaic 45X;*MYLK*; *SLC2A10; TGFBR1/BGN*; *TGFBR2/SMAD3*

Figure 2. Distribution of informative pediatric cases by gene



Other (n=1, respectively):

ACTA2; *COL1A2; COL2A1; ELN; FBN1/BGN; TGFB3*

Conclusion

The overall yield of genetic testing in this cohort of individuals with suspected HTAD was 11.8%, and CNVs accounted for 6% of all LP/P variants; the yield of testing was similar in children and adults but was higher in deceased individuals compared to living individuals.

Nearly all individuals with an informative result had an LP/P variant(s) in a gene associated with extracardiac features.

This work further demonstrates the importance of comprehensive genetic testing in individuals with suspected HTAD, especially in those with relevant findings on autopsy, to inform management for at-risk family members.

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

References:

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