A Retrospective Analysis of Multigene Panel Testing for Marfan Syndrome, Aneurysm, and Related Disorders: Diagnostic Yield and Cardiac Phenotypic Spectrum

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BACKGROUND

- Marfan syndrome (MFS) is caused by mutations in *FBN1* and is characterized by cardiovascular, skeletal, and ocular findings.[1]
- Diagnosis can be challenging due to phenotypic variability and overlap with related disorders.
- Thoracic aortic aneurysm and dissection (TAAD), in particular, is a life-threatening major component of MFS; however, it also occurs in other syndromes, and genetic causes of isolated TAAD have also been discovered. [1,2]
- Identifying a genetic cause of TAAD helps clarify risk and medical management, leading to improved prognosis.
- Here, we sought to determine the overall diagnostic yield and assess the cardiac phenotypic spectrum of individuals with a mutation identified on a panel of 10 genes associated with predisposition to MFS and TAAD.

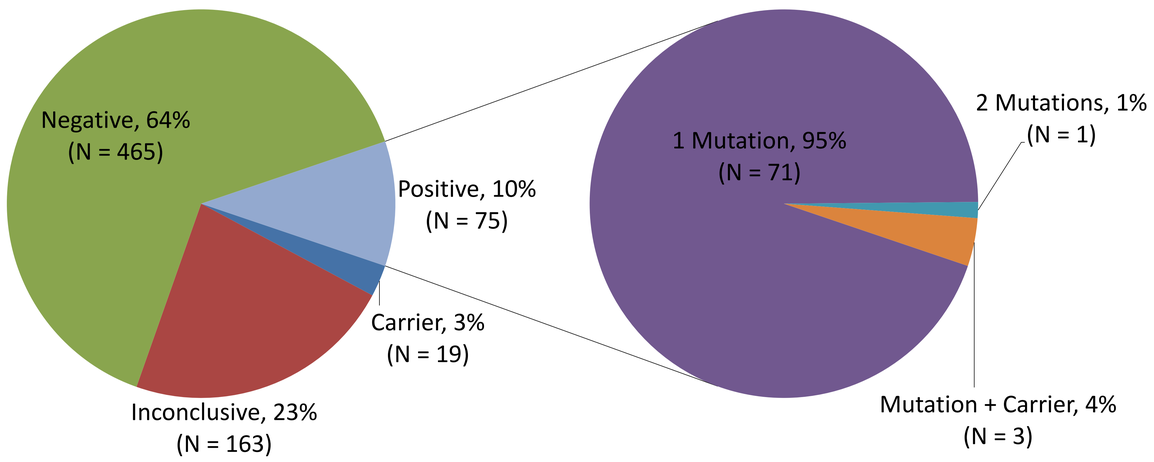
METHODS

- DNA samples from 722 individuals underwent multigene panel testing via next generation sequencing (NGS) at our clinical diagnostic laboratory from October 2011 through September 2014 for the following genes: *ACTA2, CBS, COL3A1, FBN1, FBN2, MYH11, SLC2A10, SMAD3, TGFBR1,* and *TGFBR2.*
- In 593 (82.1%) cases, all genes were analyzed concurrently, while the remaining 17.9% were approached in a stepwise way beginning with *FBN1* and reflexing to the remaining genes.
- Clinical histories were obtained from test requisition forms and supporting documents provided by healthcare providers.
- Familial co-segregation analyses were performed in some cases to help clarify clinical implications of variant(s) of unknown significance and to elucidate if inherited or *de novo*.

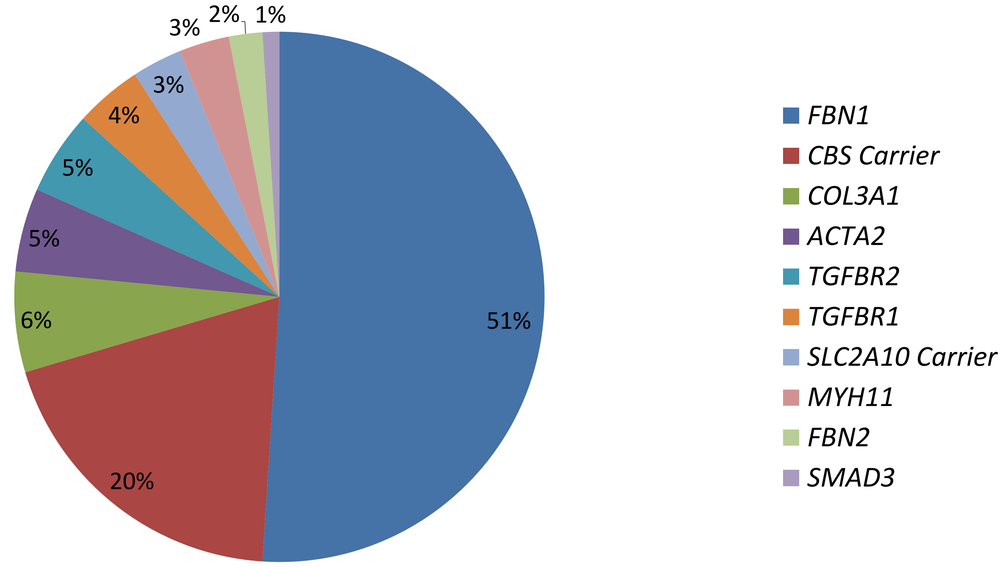
RESULTS

- A total of 98 pathogenic mutations or likely pathogenic variants (mutations) were identified in this cohort.
- There were mutations in all 8 genes with autosomal dominant (AD) inheritance (n=76), including one digenic case with pathogenic mutations in both *FBN1* and *FBN2*.
- While biallelic mutations in *CBS* and *SLC2A10* (characterized by autosomal recessive inheritance) were not identified, 3.05% (n=22) of individuals were carriers for a mutation in one of these genes.
- Full gene sequencing resulted in the detection of novel mutations which accounted for approximately 1 in 3 positives at the time of testing.
- Mitral valve prolapse was reported in 54 individuals and 13 had positive findings on panel testing.

Overall Report Classification



Mutation Distribution (N = 98)



DIAGNOSTIC YIELD

- A positive finding was identified in 10.39% (n=75) of individuals tested.
- Not surprisingly, the majority of positive findings (65.8%) were detected in *FBN1*, as the prevalence of MFS is the highest, approximately 1:5,000, whereas the prevalence estimates of the other gene conditions are lower or unknown.
- Mutations in the remaining 7 genes with AD inheritance accounted for an additional 34.2% of positive findings (n=26), thus contributing significantly to the overall diagnostic yield for this panel (p<0.001).
- Mutations in *MYH11*, a gene more recently associated with TAAD, were responsible for 11.5% (n=3) of non-*FBN1* positive findings.
- Variant(s) of unknown significance were identified in 24.9% (n=180) and no reportable findings (negative) were identified in 64.4% (n=465) of cases.

CARDIAC PHENOTYPES

- Reported cardiac phenotypes were compared between *FBN1* positive cases, other positive cases, and negative cases.
- Clinical information was provided for significantly more of the mutation positive (91%, n=68) than negative (79%, n=367) cases (p<0.017) for any gene.
- Of these cases, aneurysm or dissection of the aorta or other vessel was reported more frequently in the positive (85.3%; n=58) compared to negative (69.5%; n=255) cases (p=0.008).
- Non-aortic involvement was statistically more common in the mutation negative cases compared to mutation positive cases (p=0.036).
- Cases in which a family history of TAAD was reported were more likely to be in the positive rather than the negative cohort.
- Other cardiovascular features reported include mitral valve prolapse and bicuspid aortic valve, which lead to an increased risk for TAAD.
- Mitral valve prolapse was reported in 12 individuals with positive findings in *FBN1* and 1 individual with a positive finding in *TGFBR2*.
- Bicuspid aortic valve was reported in 17 individuals and 1 had a positive finding in *FBN1*.

TAKE-HOME POINTS

- Our data demonstrate that a panel based approach significantly improves diagnostic yield compared to testing for *FBN1* alone.
- Our data yielded a clearly positive finding in 1 in 10 individuals tested.
- Cases with reported personal and/or family history of aneurysm or dissection were more likely to test positive.
- Inclusion of gross deletion/duplication analysis and additional genes implicated in the expanding TAAD related phenotype are likely to maximize detection rates and may ultimately improve patient management and outcome.

REFERENCES

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