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Clinical Validity of Genes for Heritable Thoracic Aortic Aneurysm and Dissection

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ABSTRACT

BACKGROUND Thoracic aortic aneurysms progressively enlarge and predispose to acute aortic dissections. Up to 25% of individuals with thoracic aortic disease harbor an underlying Mendelian pathogenic variant. An evidence-based strategy for selection of genes to test in hereditary thoracic aortic aneurysm and dissection (HTAAD) helps inform family screening and intervention to prevent life-threatening thoracic aortic events.

OBJECTIVES The purpose of this study was to accurately identify genes that predispose to HTAAD using the Clinical Genome Resource (ClinGen) framework.

METHODS We applied the semiquantitative ClinGen framework to assess presumed gene–disease relationships between 53 candidate genes and HTAAD. Genes were classified as causative for HTAAD if they were associated with isolated thoracic aortic disease and were clinically actionable, triggering routine aortic surveillance, intervention, and family cascade screening. All gene-disease assertions were evaluated by a pre-defined curator-expert pair and subsequently discussed with an expert panel.

RESULTS Genes were classified based on the strength of association with HTAAD into 5 categories: definitive (n = 9), strong (n = 2), moderate (n = 4), limited (n = 15), and no reported evidence (n = 23). They were further categorized by severity of associated aortic disease and risk of progression. Eleven genes in the definitive and strong groups were designated as "HTAAD genes" (category A). Eight genes were classified as unlikely to be progressive (category B) and 4 as low risk (category C). The remaining genes were recent genes with an uncertain classification or genes with no evidence of association with HTAAD.

CONCLUSIONS The ClinGen framework is useful to semiquantitatively assess the strength of gene-disease relationships for HTAAD. Gene categories resulting from the curation may inform clinical laboratories in the development, interpretation, and subsequent clinical implications of genetic testing for patients with aortic disease. (J Am Coll Cardiol 2018;72:605–15) © 2018 the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

Thoracic aortic aneurysms asymptomatically enlarge over time and can result in acute aortic dissections (collectively designated as TAAD), which are life-threatening events that can cause premature death in ≥50% of affected individuals. Over the last 25 years, pathogenic variants in numerous genes have been identified that predispose to heritable presentations of thoracic aortic aneurysms and dissections, collectively termed HTAAD. HTAAD includes a clinically and genetically heterogeneous group of disorders. Identification of the underlying gene triggering HTAAD is powerful information

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ABBREVIATIONS AND ACRONYMS

ClinGen = Clinical Genome Resource

HTAAD = heritable thoracic aortic aneurysms and dissections

TGF = transforming growth factor

VUS = variant(s) of uncertain significance

that can be used not only to identify family members at risk for the disease, but also to inform thoracic aortic disease surveillance and management, including timing of surgical repair, risk for additional vascular diseases, and systemic complications. Additionally, disease gene discovery for HTAAD continues to improve our understanding of the underlying pathophysiology of the disease and aid in the development of new treatment strategies (1–3).

SEE PAGE 616

Improved technology and decreased costs for DNA sequencing have increased the use of genetic testing for HTAAD. With the increasing number of putative disease-associated genes, DNA diagnostic laboratories have steadily expanded the number of genes that are either on disease-specific gene panels or analyzed and reported from exome or genome sequencing. This rapid expansion of sequencing, however, has risked the inclusion of genes that may have less meaningful evidence to support their association with HTAAD. This in turn leads to a high burden of uncertainty, as the vast majority of variants in these genes would be properly classified as variants of uncertain significance (VUS), and therefore cannot meaningfully inform the management of patients or their families. Although highly gene-dependent, the overall data on the relative proportion of VUS compared with pathogenic variants in disease genes is almost 3:1 (4). Understanding the importance of these variants in the pathogenesis of HTAAD is hampered by a lack of validated functional tools and the limited number of rigorously interpreted variants in disease-associated genes in publicly available databases.

When selecting genes for inclusion on diagnostic panels or reporting from exome/genome sequencing, the clinical validity (i.e., the strength of evidence that variation in that gene predisposes to the disease) needs to be carefully considered. For many of the genes offered on diagnostic panels, the association of rare variants in the gene with the disease is unequivocal. For example, *FBN1* is well established as the causal gene in individuals with Marfan syndrome, with occasional but well-established reports of thoracic aortic disease with subtle or absent manifestations of a systemic connective tissue disorder (5). In other cases, the strength of the data underlying the association between a given gene and thoracic aortic disease is limited, and further research is required to confirm or exclude a clinically relevant association.

There are also important questions about the clinical implications of pathogenic variants in certain genes. Some genes are associated with borderline enlargement of the aortic root or ascending aorta but without formal evidence that the enlargement progresses to dissection. An example is the *FBN2* gene, underlying congenital contractural arachnodactyly. Mild, nonprogressive aortic dilatation has been reported in children harboring *FBN2* pathogenic variants (6); a recent follow-up study did not reveal any evidence for progression to aortic dissection (B. Callewaert, personal communication, 2018). In contrast, other genes are associated with aortic dissection despite little to no preceding enlargement of the aorta; this is very well known for patients harboring *COL3A1* pathogenic variants, underlying vascular Ehlers-Danlos syndrome (7).

We assembled an international panel of experts for the Aortopathy Working Group to curate a list of genes with putative association to HTAAD using a semiquantitative framework provided by the Clinical Genome Resource (ClinGen) (8). In this framework, the genes are classified into pre-specified tiers based on the clinical, genetic, and experimental evidence, along with discussion and consensus of the experts.

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