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Heritable Thoracic Aortic Disease Genes in Sporadic Aortic Dissection

Dong-chuan Guo, PhD, **Ellen M. Hostetler, BA**, **Yuxin Fan, PhD**, **Richard J. Kulmacz, PhD**, **Di Zhang, PhD**, **GenTAC Investigators**, **Deborah A. Nickerson, PhD**, **Suzanne M. Leal, PhD**, **Scott A. LeMaire, MD**, **Ellen S. Regalado, MSc**, and **Dianna M. Milewicz, MD, PhD**

Department of Internal Medicine, University of Texas Health Science Center at Houston, McGovern Medical School, 6431 Fannin Street, MSB 1.614, Houston, Texas 77030

An acute aortic dissection is a life-threatening cardiovascular condition that is preventable if individuals at risk are identified. Pathogenic variants in 11 genes confer a highly penetrant, dominantly inherited risk for aortic aneurysms and dissections with or without syndromic features (e.g., Marfan syndrome), termed heritable thoracic aortic disease (HTAD), and include *ACTA2*, *COL3A1*, *FBN1*, *LOX*, *MYH11*, *MYLK*, *PRKG1*, *SMAD3*, *TGFB2*, *TGFBR1*, and *TGFBR2* (1).

To explore genetic triggers for acute aortic dissections in individuals without a family history of thoracic aortic disease or syndromic features, we performed whole exome sequencing on a cohort of 355 such cases who were ≤56 years of age. Informed consent from the participants was obtained after approval from the institutional review boards. Whole exome sequencing data were filtered to include only heterozygous variants with a minor allele frequency <0.005 in the Exome Aggregation Consortium database and that alter amino acids in proteins (nonsynonymous, stop-loss, stop-gain, coding indel, frameshift, or splice site variants). The filtered variants were validated using Sanger sequencing. Rare variants were classified as pathogenic based on the American College of Medical Genetics guidelines and the following rules (2): 1) variants that cause nonsense-mediated decay or gene deletions occurring in genes for which haploinsufficiency is known to cause disease; 2) *FBN1* variants that disrupt amino acids in the epidermal growth factor–like calcium-binding domains and *COL3A1* variants that alter glycine residues in the helical domain; 3) variants previously reported to cause thoracic aortic disease and validated by genetic or functional data; and 4) rare missense variants recurrent in HTAD patients, not present in the Exome Aggregation Consortium database and located at protein domains where disease-causing mutations are reported. Pathogenic variants are located in the following protein domains: the cytoplasmic domains of transforming growth factor (TGF)-β type I and II receptors (*TGFBR1* and *TGFBR2*), MH2 domain of SMAD3, proteolytic cleavage site for the production of active TGF-β2 (*TGFB2*), 130-kDa isoform (short form) of *MYLK*, and procollagen C-proteinase cleaved active enzyme of lysyl oxidase (*LOX*).

Correspondence to: Dianna M. Milewicz.

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These analyses of the whole exome sequencing of the early age onset of sporadic thoracic aortic dissection (ESTAD) cohort found that 9.3% (n = 33) of the ESTAD cohort had a pathogenic variant in an HTAD gene. *FBN1* had the highest burden of pathogenic variants (4.2% of the cases), followed by *TGFBR1* (1.4%), *COL3A1* (1.1%), *SMAD3* (0.8%), *ACTA2* (0.8%), *TGFB2* (0.3%), and *TGFBR2* (0.3%). Cases with HTAD gene pathogenic variants were significantly younger at the time of aortic dissection (median age 39 years; interquartile range [IQR] 17 years) than cases with variants of unknown significance (VUSs) as to whether they cause disease (median age 47 years; IQR 11 years; p = 0.03) or no variants in HTAD genes (median age 47 years; IQR 11 years; p = 0.002) (3).

We then compared the burden of rare VUSs in HTAD genes in the subset of the ESTAD cases (cases with European ancestry and without a pathogenic HTAD variant; ESTAD-EA, n = 231) with that in the National Heart, Lung, and Blood Institute GO Exome Sequencing Project control database (ESP-EA; n = 4,300). The frequency of both total and missense VUSs in HTAD genes in the ESTAD-EA cohort (28% of the cases have ≥1 VUSs) was significantly higher than in the ESP-EA exomes (Table 1). At the same time, the burden of rare synonymous variants in these same HTAD genes was not increased in ESTAD-EA cases. Furthermore, the burden of VUSs in 10 genes predisposing to hypertrophic cardiomyopathy was also not increased in the ESTAD cases when compared with controls. These findings were replicated in affected probands in HTAD families when compared with controls; the burden of VUSs in HTAD genes was increased in 184 unrelated EA probands in whom no causative gene has been identified (Table 1).

In summary, exome sequencing of ESTAD cases revealed pathogenic variants in known HTAD genes, which supports genetic testing in individuals with dissections <56 years of age. The increased burden of VUSs found in known HTAD genes emphasizes how critical it is to classify these variants as disrupting protein function and predisposing to dissection, or as completely benign. Future studies are needed for more precise gene-specific curation of rare VUSs, which will provide critical information to prevent acute aortic dissections by identifying individuals with a risk for aortic dissection so that management to prevent dissections can be initiated.

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TABLE 1

Increased Burden of Rare VUSs and Rare Missense VUSs in the ESTAD Cases

	ESTAD-EA (n = 231)	ESP-EA (n = 4,300)	OR (95% CI)	p Value
VUSs in ESTAD-EA versus ESP-EA				
HTAD genes VUSs	74	712	2.42 (1.78–3.17)	2.0×10^{-8}
HTAD genes missense VUSs	70	708	2.21 (1.65–2.95)	3.9×10^{-7}
HTAD genes synonymous variants*	40	839	0.86 (0.61–1.23)	0.44
HCM genes VUSs†	23	350	0.80 (0.51–1.25)	0.33
VUSs in HTAD genes in ESTAD-EA versus ESP-EA				
ACTA2	2	2	18.77 (2.63–133.85)	0.01
TGFBR2	7	10	13.41 (5.06–35.55)	1.0×10^{-5}
TGFBR1	7	32	4.17 (1.82–9.55)	3.1×10^{-3}
LOX	3	19	2.97 (0.87–10.09)	0.10
MYLK	8	54	2.82 (1.33–6.00)	0.01
SMAD3	1	7	2.67 (0.33–21.76)	0.34
COL3A1	12	112	2.05 (1.11–3.77)	0.03
TGFB2	6	58	1.95 (0.83–4.57)	0.14
MYH11	18	233	1.48 (0.90–2.43)	0.14
FBN1	10	183	1.02 (0.53–1.95)	0.87

Values are the number of rare variants in genes grouped together (top section) or genes individually (lower section), unless otherwise indicated.

*Synonymous variants do not alter amino acid sequence.

†HCM genes.

CI = confidence interval; EA = European ancestry; ESP = Exome Sequencing Project; ESTAD = early onset of sporadic thoracic aortic dissection; HCM = hypertrophic cardiomyopathy; HTAD = heritable thoracic aortic disease; OR = odds ratio; VUSs = variants of unknown significance.