Routine Genetic Testing for Thoracic Aortic Aneurysm and Dissection in a Clinical Setting

Bulat A. Ziganshin, MD, Allison E. Bailey, BS, Celinez Coons, Daniel Dykas, BS, Paris Charilaou, MD, Lokman H. Tanriverdi, Lucy Liu, BS, Maryann Tranquilli, RN, Allen E. Bale, MD, and John A. Elefteriades, MD

Aortic Institute at Yale-New Haven, and Department of Genetics, Yale University School of Medicine, New Haven, Connecticut

Background. **Hereditary factors play an important etiologic role in thoracic aortic aneurysm and dissection (TAAD), with a number of genes proven to predispose to this condition. We initiated a clinical program for routine genetic testing of individuals for TAAD by whole exome sequencing (WES). Here we present our initial results.**

Methods. **The WES was performed in 102 patients (mean age 56.8 years; range 13 to 83; 70 males [68.6%]) with TAAD. The following 21-gene panel was tested by WES: ACTA2, ADAMTS10, COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, ELN, FBLN4, FLNA, FBN1, FBN2, MYH11, MYLK, NOTCH1, PRKG1, SLC2A10, SMAD3, TGFB2, TGFBR1, TGFBR2.**

Results. **Seventy-four patients (72.5%) had no medically important genetic alterations. Four patients (3.9%) had a deleterious mutation identified in the FBN1, COL5A1, MYLK, and FLNA genes. Twenty-two (21.6%) previously unreported suspicious variants of unknown significance were identified in 1 or more of the following genes: FBN1 (n = 5); MYH11 (n = 4); ACTA2 (n = 2); COL1A1 (n = 2); TGFBR1 (n = 2); COL3A1 (n = 1); COL5A1 (n = 1); COL5A2 (n = 1); FLNA (n = 1); NOTCH1 (n = 1); PRKG1 (n = 1); and TGFBR3 (n = 1). Identified mutations had implications for clinical management.**

Conclusions. **Routine genetic screening of patients with TAAD provides information that enables genetically personalized care and permits identification of novel mutations responsible for aortic pathology. Analysis of large data sets of variants of unknown significance that include associated clinical features will help define the mutational spectrum of known genes underlying this phenotype and potential identify new candidate loci.**

(Ann Thorac Surg 2015;100:1604–12)
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Over the past decade it has become overwhelmingly evident that ascending thoracic aortic aneurysm and dissection (TAAD) has a strong genetic component [1–6]. Currently, TAAD can be subdivided into two main categories: (1) syndromic, associated with abnormalities of other organ systems; and (2) non-syndromic, with manifestations restricted to the aorta [5, 7]. Patients with syndromic thoracic aortic aneurysm suffer from Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome, arterial tortuosity syndrome aneurysm–osteoarthritis syndrome, cutis laxa syndrome, and transforming growth factor (TGF)β pathway related disease [5, 7, 8]. Non-syndromic thoracic aortic aneurysm includes 2 district subcategories; familial (more than one family member affected) and sporadic forms of TAAD [5, 8].

Aortic size currently remains the main criterion for prophylactic surgical intervention in patients with thoracic aortic aneurysm [9, 10]. However, there is evidence to suggest that patients with specific genetic mutations require earlier interventions at smaller aortic sizes. This is already reflected in the guidelines for management of thoracic aortic disease, with specific recommendations regarding treatment of patients with Marfan syndrome [11, 12]. In addition, recent studies on the genetics of TAAD, largely reflecting groundbreaking work by Dr Diana Milewicz, have shown that patients with certain specific genetic abnormalities have a different natural history course of thoracic aortic disease [5, 13]. For instance, there are certain genetic mutations that are exclusively involved with aortic dissection [14] (without aneurysm), so that aortic size loses its predictive ability. Other specific genetic defects cause aortic dissection at small aortic sizes [15] (ACTA2, Loeys-Dietz), so again traditional size criteria will not be predictive. Such modern information suggests that genetic testing of patients with TAAD may be important for determining the appropriate personalized treatment strategy for individual patients.

Three years ago we initiated a program of routine genetic testing of our patients with TAAD by comprehensive

Accepted for publication April 17, 2015.

Presented at the Poster Session of the Fifty-first Annual Meeting of The Society of Thoracic Surgeons, San Diego, CA, Jan 24–28, 2015.

Address correspondence to Dr Elefteriades, 789 Howard Ave, Clinic Bldg CB317, New Haven, CT 06519; e-mail: john.elefteriades@yale.edu.

The Appendices can be viewed in the online version of this article [http://dx.doi.org/10.1016/j.athoracsur.2015.04.106] on http://www.annalsthoracicsurgery.org.

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Published by Elsevier

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2015.04.106

whole exome sequencing (WES) (DNA sequencing the exons [coding regions] of all genes in the genome) [16]. WES has dramatic advantages. The WES is comprehensive (examining the whole exome in every patient, as opposed to performing multiple tests for different genetic syndromes). As WES becomes less costly, this approach may ultimately prove more cost effective than multiple syndrome-specific tests performed in different laboratories at distant geographic locations. We reasoned that a one-stop, comprehensive, reasonably economical genetic screening for all mutations currently known to cause thoracic aortic aneurysm might have advantages over the conventional piecemeal, multiple laboratory, expensive screenings commonly available. We also sought to initiate composition of a "dictionary" of specific genetic aberrations (both novel and previously reported) that are seen in patients with TAAD. This paper presents our initial findings from clinical application of whole exome sequencing at the Aortic Institute at Yale.

Material and Methods

Patient Profile

Genetic testing was offered to 192 new and returning patients with TAAD seen at the Aortic Institute from March 2012 until December 2014. Patients agreeing to testing, whose insurance covered clinical genetic tests, underwent whole exome sequencing (n = 102) (Table 1). Genetic testing was offered primarily to patients with ascending aortic disease, family history of aortic disease, early onset of aortic disease, suspected connective tissue disorders, insurance coverage of the test (or a combination of these factors).

In certain cases, if a variant was identified in a patient, family members were also screened by single site sequencing (Sanger) to confirm or rule out presence of a mutation previously identified in the proband. This study was approved by the Human Investigation Committee of Yale University. All patients consented to salivary-based whole exome sequencing.

Whole Exome Sequencing Methodology

See Appendix 1.

Table 1. Clinical Program of Whole Exome Sequencing (WES) Genetic Testing for Thoracic Aortic Aneurysm and Dissection, 2012 to 2014

Variable	Number	Percentage
Total number of patients:		
Enrolled into clinical genetic testing	192	100%
Insurance coverage denied	33	17.2%
WES completed	102	53.1%
Single site sequencing of family members[a] completed	13	6.8%
WES or single site sequencing of family members currently in progress	44	22.9%

[a] Of probands with significant findings.

Panel of Tested Genes

The entire exome was scanned for genetic variants that might underlie TAAD, but 21 specific genes known from previous studies to underlie this phenotype underwent more focused analysis. The full panel of tested genes is presented in Figure 1.

Clinical Interpretation of Sequence Variants

For clinical reporting, variants were classified according to the likelihood that they were causative of the patient's phenotype. We used the following definitions of variants:

POSITIVE FOR A DELETERIOUS MUTATION. In genes known to cause disease by loss of function, genetic alterations were considered deleterious if they were predicted to disturb the encoded protein; for example, premature termination codons, frameshifts, splice site mutations in invariant bases adjacent to exons, and whole-exon deletions or duplications. Missense alterations were considered definitely deleterious if they had a well-established association with disease based on multiple independent studies including segregation with disease in high-risk families, functional assays of the encoded protein, or demonstration of abnormal messenger (m)RNA transcript processing.

PROBABLE DISEASE-CAUSING MUTATION. This category included genetic variants for which the available evidence indicated greater than 90% certainty of pathogenicity. This designation was used for novel missense alterations occurring in the same codon as a well-established pathogenic variant. Variants predicted to alter RNA splicing (BDGP splice predictor program) but which were not located in the invariant splice sites flanking the exons were also included in this category.

VARIANT OF UNKNOWN SIGNIFICANCE. This designation was used for rare missense alterations and in-frame deletions affecting highly conserved amino acids, which did not meet the criteria listed above. Intronic variants whose effect on splicing was ambiguous, as well as nonsense and frameshift alterations located in the last exons or in the last 50 base pairs of the penultimate exon were also included in this category.

Results

Characteristics of Tested Patients

The study enrolled 192 patients. The WES was offered to 179 (93.2%) patients. To date, 102 of the original 192 patients (53.1%) have completed the testing (Table 1), and these patients form the study group. Another 44 WES are still in progress (time consuming test). Thirty-three patients were denied insurance coverage and did not undergo WES. Patients were seen by a cardiothoracic surgeon at an outpatient visit, when saliva samples for genetic testing were obtained. Patient characteristics are presented in Appendix 2 (Table A1). Indication for WES in the majority of patients was presence (or history of) of a thoracic aortic aneurysm (n = 83, 81.4%) or an aortic dissection (n = 15, 14.7%). Two patients had both an aneurysm and aortic dissection. Six patients (5.9%) had no clinically evident signs of thoracic aortic disease, but

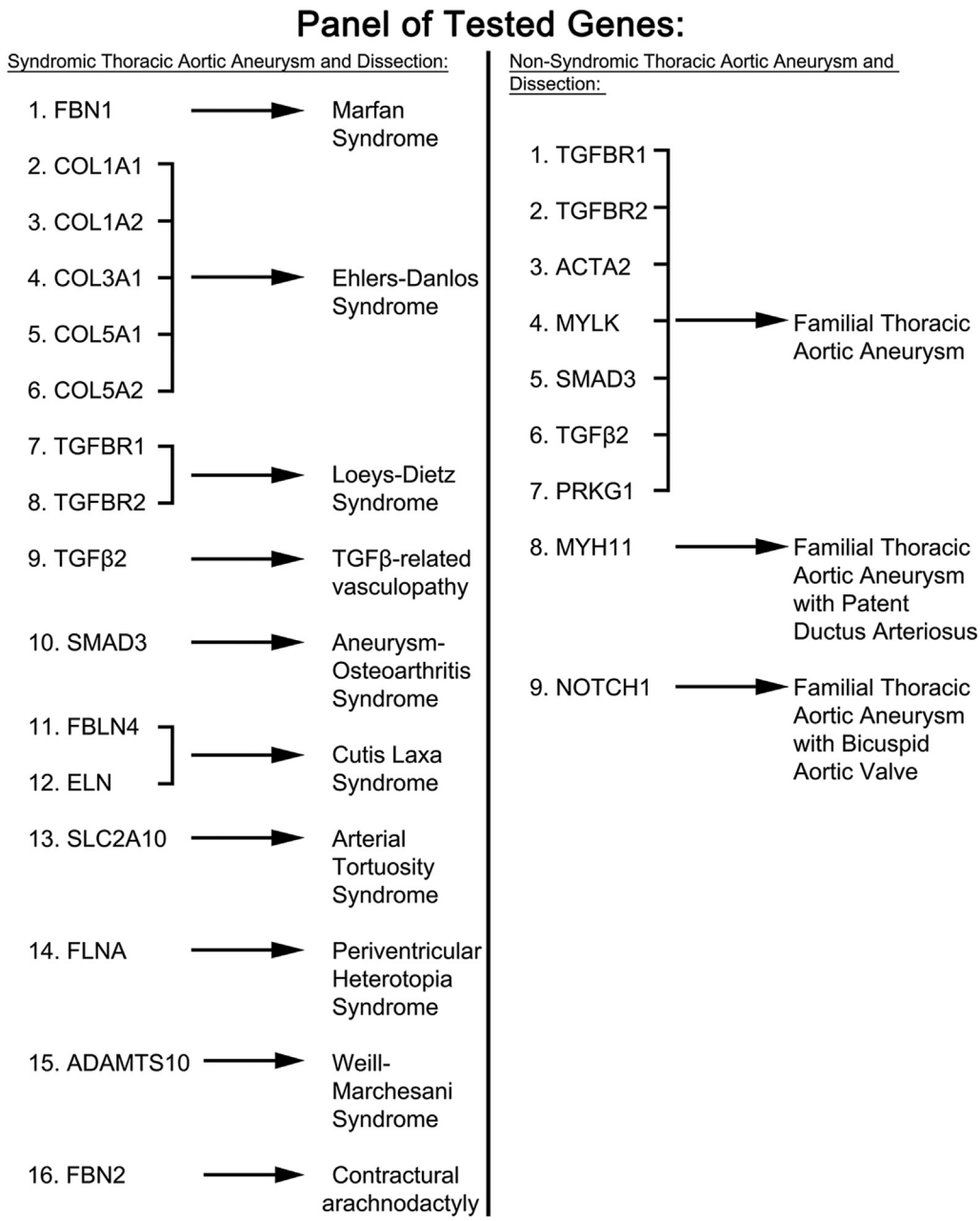


Fig 1. Panel of 21 tested genes. Note that TRFBR1, TGFBR2, SMAD2, and TGBβ2 genes appear in both lists (syndromic on the left, and non-syndromic on the right), so that the total number of genes tested is 21. (TAAD = thoracic aortic aneurysm and dissection.)

were tested either due to a strong family history of aortic disease (n = 4, 3.9%) or clinical suspicion of a connective tissue disorder (n = 2, 2.0%).

Forty-four patients (43.1%) had a positive family history of aortic or aneurysm related disease, defined as documented medical confirmation (by imaging study, surgical, or autopsy report) of aortic or cerebral aneurysm or dissection in at least 1 family member (alive or expired). Eighteen patients (17.6%) had a bicuspid valve, and 16 patients (15.7%) had concurrent coronary artery disease.

Results of Whole Exome Sequencing

Routine clinical application of whole exome sequencing was quite revealing, uncovering pertinent previously reported mutations, suspicious novel variants, and various incidental findings in 28 of the 102 patients studied (27.5%) (Fig 2; Table 2). Seventy-four patients (72.5%) had no mutations in the panel of TAAD genes and no reportable incidental findings. A detailed description of identified variants, as well as corresponding clinical information, is presented in Table 3.

Among the panel of genes responsible for TAAD, genetic alterations were identified in 23 patients (22.5%). In 3 patients more than 1 variant was found; thus, the total number of identified variants among this group of patients was 26. Four of these variants were found to be deleterious, in the COL5A1, FBN1, MYLK, and FLNA genes (patients, numbers 1 to 4 in Table 3). The remaining

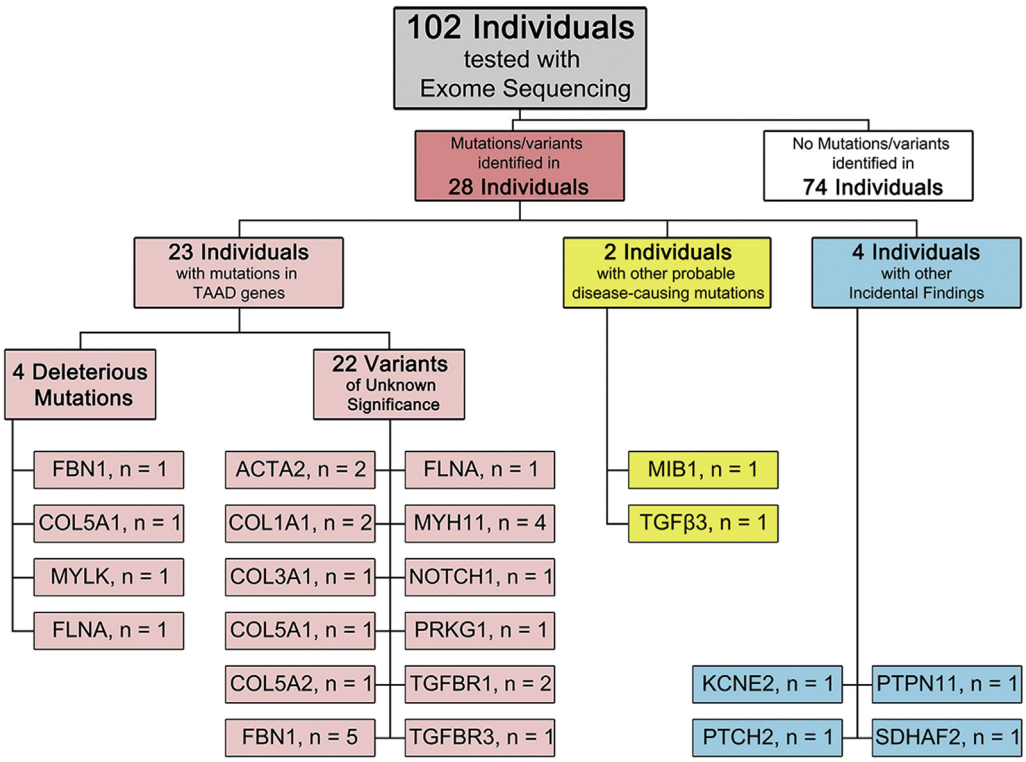


Fig 2. Summary of whole exome sequencing results. Note that 1 patient had both a variant of unknown significance among the thoracic aortic aneurysm and dissection (TAAD) genes and an incidental finding.

22 variants were considered to be of unknown significance: 5 variants in the FBN1 gene; 4 in the MYH11 gene; 2 each in the ACTA2, COL1A1, and TGFBR1 genes; and 1 in the COL3A1, COL5A1, COL5A2, FLNA, NOTCH1, PRKG1, and TGFBR3 genes (patients numbers 5 to 23).

There was no difference in likelihood of finding a medically important genetic alteration between younger patients (≤50 years) (29%, 9 of 31) and older patients (>50 years) (26.2%, 17 of 65) presenting with TAAD. The proportion of patients with a positive family history of aortic disease was identical in both groups—41.9% and 41.5% among the younger and older groups of patients, respectively.

In 2 patients probable disease causing mutations were identified in genes not belonging to the panel of TAAD genes. One patient had a stop mutation (nonsense) in the MIB1 gene (patient no. 24). The MIB1 (OMIM 608677) is a member of the Notch pathway, which plays an important role in development of the aortic valve and root. Another patient had a mutation in the TGFβ3 gene (patient no. 25). The TGFβ3 (OMIM 190230) has not been specifically associated with aortic aneurysm, but mutations in this gene cause a Loeys-Dietz-like syndrome.

Finally, 4 patients had medically actionable, incidental findings not related to aortic disease. These included mutations in the following genes: KCNE2 (previously reported to underlie drug-induced cardiac arrhythmias); PTPN11 (previously reported to cause LEOPARD syndrome [lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia; retardation of growth; deafness]).

Table 2. Results of Whole Exome Sequencing

Variable	Number of Patients	Percentage
Negative for mutations/variants	74	72.5%
Mutations/variants identified	28	27.5%
Number of mutations/variants identified in total:	32 variants	
Among a panel of 21 TAAD genes (no. of variants)	26 variants	
Positive for a deleterious mutation (no. of variants)	4 variants	
Variant of unknown significance (no. of variants)	22 variants	
Other probable disease-causing mutation (no. of variants)	2 variants	
Incidental findings (no. of variants)	4 variants	

no. = number; TAAD = thoracic aortic aneurysm and dissection.

Table 3. Detailed List of Identified Variants in Patients Tested by Whole Exome Sequencing

Nos.	Age, Sex	Affected Gene[a]	Chromosome Location (HG 19)	Variant (Protein Level)	Variant (DNA Sequence)	Variant Type	Variant Previously Reported	Variant Allele Frequency	Polyphen[b]	SIFT[c]	Conservation (PhyloP)[d]	Variant Related to Aortic Condition	Aortic Pathology	Aortic Valve Morphology	Proven Family History
1	67, M	COL5A1	9:137705828	IVS49-1	G>T	Splice Acceptor	No	<0.0008%	N/A	N/A	5.15	Deleterious	Ascending and descending aortic aneurysm	Trileaflet	No
2	30, M	FBN1	15:48780579	c.3193delG (p.E1065)	GAA>_AA	Frameshift Deletion	No	<0.0008%	N/A	N/A	N/A	Deleterious	Aneurysm of the aortic root and ascending aorta	Trileaflet	Yes
3	54, F	MYLK	3:123339147	S1759P	TCC>CCC	Missense	Yes [17]	<0.0008%	1.0	0	3.246	Deleterious	Type A aortic dissection	Trileaflet	Yes
4	44, F	FLNA	X:153588107	Y1324X	TAC>TAA	Nonsense	No	0.002%	N/A	N/A	N/A	Deleterious	Aortic root aneurysm	Trileaflet	Yes
5	60, M	ACTA2	10:90699264	G270R	GGG>AGG	Missense	No	<0.0008%	0.999	N/A	6.056	Unknown significance	Ascending aortic aneurysm	Trileaflet	Yes
6	39, M	ACTA2	10:90697957	I284N	ATC>AAC	Missense	No	<0.0008%	0.994	0	5.001	Unknown significance	Type B aortic dissection	Trileaflet	No
7	72, M	COL1A1	17:48273295	V349F	GTT>TTT	Missense	Yes [21][e]	0.011%	0.096	0	1.612	Unknown significance	Aneurysm of the aortic root and ascending aorta	Trileaflet	No
8	78, M	COL3A1	2:189863424	P668T	CCT>ACT	Missense	Yes [22][f]	0.17%	0.993	0.031	3.543	Unknown significance	Ascending aortic aneurysm	Trileaflet	No
9	60, M	COL5A1	9:137622272	A372D	GCT>GAT	Missense	No	<0.0008%	0.10	0.629	0.215	Unknown significance	Aortic root aneurysm	Trileaflet	No
10	68, F	COL5A2	2:189898828	G1490S	GGC>AGC	Missense	No	<0.001%	1.0	0.04	5.935	Unknown significance	Ascending aortic aneurysm	Trileaflet	Yes
11	63, M	FBN1	15:48818413	G301V	GGG>GTG	Missense	No	0.016%	0.043	0.212	2.682	Unknown significance	Ascending aortic aneurysm	Trileaflet	Yes
12	58, M	FBN1	15:48779550	P1141L	CCG>CTG	Missense	Yes [23][g]	0.072%	1.0	0.001	5.623	Unknown significance	Type A aortic dissection	Trileaflet	No
13	64, F	FBN1	15:48829874	C224R	TGT>CGT	Missense	No	<0.0008%	1	0.05	5.044	Unknown significance	Aneurysm of the aortic root and ascending aorta	Unknown	No
14	69, M	FBN1	15:48755380	G1708E	GGA>GAA	Missense	No	0.0008%	1	0.21	4.549	Unknown significance	Aneurysm of the aortic root and ascending aorta	Trileaflet	Yes
		PRKG1	10:53814320	T280M	ACG>ATG	Missense	No	0.006%	0.75	0.02	−0.083	Unknown significance			
		COL1A1	17:48263206	N1394S	AAC>AGC	Missense	No	0.089%	0.074	0.03	2.854	Unknown significance			
15	56, M	FBN1	15:48704843	E2717K	GAG>AAG	Missense	No	0.016%	0.893	0.27	5.986	Unknown significance	Ascending aortic aneurysm	Trileaflet	No
16	45, F	FLNA	X:153594808	A366T	GCC>ACC	Missense	No	0.001%	0.723	0.03	1.112	Unknown significance	Aortic root aneurysm	Trileaflet	Yes
17	64, F	MYH11	16:15808913	K1880M	AAG>ATG	Missense	No	<0.0008%	1.0	0	2.974	Unknown significance	Ascending aortic aneurysm	Trileaflet	No
			16:15814871	T1539N	ACC>AAC	Missense	No	<0.0008%	0.14	0.05	1.32	Unknown significance			
18	61, F	MYH11	16:15831403	D1066N	GAC>AAC	Missense	No	0.069%	1.0	0.003	5.387	Unknown significance	Ascending aortic aneurysm	Trileaflet	Yes
19	71, M	MYH11	16:15814883	R1542Q	CGG>CAG	Missense	No	0.23%	0.999	0.024	5.602	Unknown significance	Ascending aortic aneurysm	Trileaflet	No
20	52, M	NOTCH1	9:139405111	R912W	CGG>TGG	Missense	No	0.19%	0.997	0.02	1.041	Unknown significance	Aortic root aneurysm	Bicuspid	No

(*Continued*)

Table 3. Continued

Nos.	Age, Sex	Affected Gene[a]	Chromosome Location (HG 19)	Variant (Protein Level)	Variant (DNA Sequence)	Variant Type	Variant Previously Reported	Variant Allele Frequency	Polyphen[b]	SIFT[c]	Conservation (PhyloP)[d]	Variant Related to Aortic Condition	Aortic Pathology	Aortic Valve Morphology	Proven Family History
21	52, M[h]	TGFBR1	9:101895010	G188V	GGT>GTT	Missense	No	<0.0008%	1	0	6.076	Unknown significance[i]	Ascending aortic aneurysm and type B aortic dissection	Trileaflet	Yes
22	13, F[h]	TGFBR1	9:101895010	G188V	GGT>GTT	Missense	No	<0.0008%	1	0	6.08	Unknown significance[i]	None	Unknown	Yes
23	60, M	TGFBR3	1:92185703	Q386R	CAG>CGG	Missense	No	0.0018%	0.0	0.22	0.759	Unknown significance	Ascending aortic aneurysm	Trileaflet	Yes
24	30, M	MIB1	18:19437141	R906X	CGA>TGA	Nonsense	No	0.007%	N/A	N/A	N/A	Probable disease causing	Aortic root aneurysm	Trileaflet	No
25	58, M	TGFB3	14:76437987	R143X	AGA>TGA	Nonsense	No	<0.0008%	N/A	N/A	N/A	Probable disease causing	Aortic root aneurysm	Trileaflet	Yes

[a] Numbers (Nos.)1 to 23 are mutations in TAAD genes; numbers 24 and 25, other probable disease causing genes. [b] Polyphen 2 score prediction: ≥0.957, probably damaging; 0.956-0.453, possibly damaging; ≤0.452, benign. [c] SIFT score prediction: ≤ 0.05, deleterious; > 0.05, tolerated. [d] PhyloP conservation score prediction: ≤ 2.99, not conserved; 3.00–4.99, semi-conserved; ≥5.00, conserved. [e] This variant has been reported in a small osteogenesis imperfecta family, where there was little data about co-segregation with disease. [f] There is one report of this variant in a family with aortic and other aneurysms, but the variant did not completely co-segregate with disease in that family. [g] This variant has been previously reported in a patient with a Marfan-like phenotype, but there are no functional data or data on segregation in families. [h] Members of the same family. [i] This variant of unknown significance segregates with disease in the family.

F = female; HG = human genome; M = male; N/A = not applicable; SIFT = sorting intolerant from tolerant; TAAD = thoracic aortic aneurysm and dissection.

Testing of Family Members

In 4 families, after identification of the specific variant in a proband, a total of 13 other family members were tested by Sanger sequencing (single site), accomplishing comprehensive family screening (pedigrees of 2 families are presented in Figure 3). In one family (Fig 3A), single-site testing identified a deleterious MYLK mutation in 2 adolescents without clinical signs of thoracic aortic disease. In another family (2 members of which underwent WES, patients nos. 21 and 22; Fig 3B), in which a variant of unknown significance in the TGFBR1 gene was found to segregate with disease, single site testing confirmed the absence of this variant in a teenage son of patient number 21.

Comment

The current study reports our initial experience with routine genetic testing in patients with TAAD. To the best of our knowledge, this is among the first reported experiences of routine genetic testing of patients with thoracic aortic disease using whole exome sequencing in a clinical setting and for clinical purposes.

Having tested over 100 patients by whole exome sequencing, we found that rare variants in genes currently known to cause thoracic aortic aneurysm and aortic dissection were present in 22.5% of patients. Including other suspicious variants and genetic findings, the total "yield" rises to 25 of the 102 patients, or 24.5%. In 73% of the patients no mutations were identified.

This experience permitted personalized aneurysm management based on the genetic findings. Specifically, among patients found to harbor a mutation prone to dissect without severe aneurysmal dilatation (ACTA2 [14, 15], MYLK [17], Loeys-Dietz [18–20]) a policy of more frequent imaging and earlier prophylactic surgery was applied.

As more and more novel genes responsible for TAAD are being discovered, we anticipate that a "dictionary" of these genes and variants will grow rapidly, another benefit of routine WES in the clinical setting. Not only will new, significant variants be identified in genes already known to cause TAAD, but totally novel involved genes are likely to be identified. It will be especially important to "mine" WES data from patients in whom the initial testing found no genetic alterations that could explain their aortic condition. In our experience there were 74 such patients (72.5%). Furthermore, patients with negative genetic findings, yet with positive family history of aortic disease, would merit special attention and additional testing of their affected relatives by WES. Application of linkage analysis techniques in these patients and their family members could potentially identify novel genes responsible for thoracic aortic disease. Even without family studies, identifying the same extremely rare variant in 2 or more unrelated individuals with the same aortic phenotype would provide strong evidence for a role of the variant in their disease.

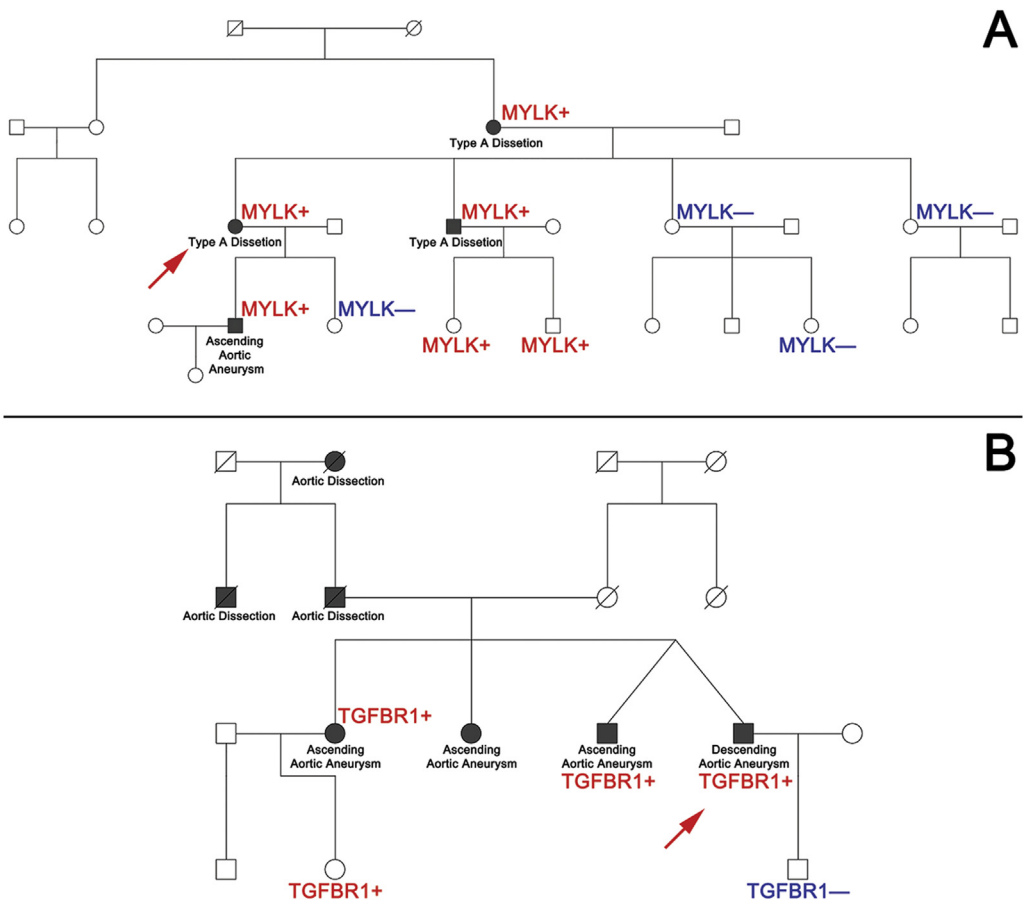


Fig 3. Pedigrees of 2 families who underwent comprehensive genetic testing. (A) A deleterious MYLK mutation was found in 6 out of 10 tested family members. (B) A variant of unknown significance was identified in the TGFBR1 gene, which segregated with disease.

At present, counseling patients with identified variants of unknown significance presents a challenge. Even though the identified variants are mutations within genes known to cause thoracic aortic disease, it is not yet known whether that particular mutation is disease causing. In these cases we pursue a frank discussion with the patients explaining that although the identified variants have not been previously linked with TAAD, they might very well be causative of the aortic condition in these patients. We hope that further studies on variant segregation with disease in families will help define these variants as either disease causing or benign.

One additional benefit of testing patients by WES is the ability to return to the data in the future to search the patients' exomes for novel genes found to be causative of TAAD. In our 3-year experience of performing WES we have already experienced this benefit. During the first 2 years our testing panel included only 12 genes. However, with recent advancements in the field and new genes being associated with TAAD, we have prospectively extended the panel to 21 genes. Retrospectively, we reviewed the exomes of all previously tested patients to make sure that the entire 21-gene panel was assessed for the entire cohort. This ability is a significant strength of our method.

Limitations

First, not all patients in whom whole exome sequencing was recommended were able to have the test done, due to denial of insurance coverage in 33 patients (17.2%). Second, the majority of the patients enrolled in clinical genetic testing had ascending aortic pathology. Moving forward, more patients with descending thoracic aortic disease should be tested. Finally, further detailed studies will be required to determine whether some of the reported variants of unknown significance indeed cause the disease and can be reclassified as either deleterious or benign. It should be noted that we adopted a very conservative policy regarding assigning responsibility to variants in known TAAD genes not previously reported. For such cases we used the conservative designation "variant of unknown significance." Extremely rare variants in genes known to cause the phenotype are often disease related, but we were reluctant to name them so until additional supporting evidence accrues.

Conclusion

In conclusion, our experience with routine WES in patients with TAAD reveals the following.

1. There is a high "yield" (~25%) in finding mutations likely relevant to the patient's thoracic aneurysm disease.
2. Genetic testing of patients with TAAD through WES permits identification of previously unreported variants on genes known to be responsible for aortic pathology. This will permit rapid population of a "dictionary" of specific TAAD mutations, likely to grow quickly to a large size.
3. Routine exome sequencing of DNA from patients with TAAD provides the opportunity for personalized management of patients tailored to the specifics of the genetic mutation. Known malignant behavior of specific mutations may warrant and permit prophylactic surgical interventions earlier and at smaller aortic size.
4. The WES of the proband permits straightforward, comprehensive screening of the family members by less complex and less costly single-site (Sanger) sequencing. This feature is likely to bear substantial clinical dividends in identifying TAAD and preventing related deaths. Once a causative mutation is identified in the proband, non-mutation carrying family members can be spared repeated imaging studies. Also, the instant comfort provided to non-affected family members is another important benefit of a WES program for TAAD.
5. Patients with no mutation on a known TAAD gene, especially those with affected family members, are likely to provide a clinical "gold mine" for mining WES data for totally novel TAAD genes.

Initiation of our whole exome sequencing program was sponsored by a research grant from Medtronic. Thanks to the generous initial support from Medtronic, the program is now self-supporting.

References

1. Biddinger A, Rocklin M, Coselli J, Milewicz DM. Familial thoracic aortic dilatations and dissections: a case control study. J Vasc Surg 1997;25:506–11.
2. Coady MA, Davies RR, Roberts M, et al. Familial patterns of thoracic aortic aneurysms. Arch Surg 1999;134:361–7.
3. Albornoz G, Coady MA, Roberts M, et al. Familial thoracic aortic aneurysms and dissections—-incidence, modes of inheritance, and phenotypic patterns. Ann Thorac Surg 2006;82:1400–5.
4. Milewicz DM, Guo DC, Tran-Fadulu V, et al. Genetic basis of thoracic aortic aneurysms and dissections: focus on smooth muscle cell contractile dysfunction. Annu Rev Genomics Hum Genet 2008;9:283–302.
5. Pomianowski P, Elefteriades JA. The genetics and genomics of thoracic aortic disease. Ann Cardiothorac Surg 2013;2:271–9.
6. Milewicz DM, Regalado ES, Shendure J, Nickerson DA, Guo DC. Successes and challenges of using whole exome sequencing to identify novel genes underlying an inherited predisposition for thoracic aortic aneurysms and acute aortic dissections. Trends Cardiovasc Med 2014;24:53–60.
7. El-Hamamsy I, Yacoub MH. Cellular and molecular mechanisms of thoracic aortic aneurysms. Nat Rev Cardiol 2009;6:771–86.
8. De Backer J, Campens L, De Paepe A. Genes in thoracic aortic aneurysms/dissections - do they matter? Ann Cardiothorac Surg 2013;2:73–82.
9. Davies RR, Goldstein LJ, Coady MA, et al. Yearly rupture or dissection rates for thoracic aortic aneurysms: simple prediction based on size. Ann Thorac Surg 2002;73:17–27.
10. Davies RR, Gallo A, Coady MA, et al. Novel measurement of relative aortic size predicts rupture of thoracic aortic aneurysms. Ann Thorac Surg 2006;81:169–77.
11. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. J Am Coll Cardiol 2010;55:e27–129.
12. Erbel R, Aboyans V, Boileau C, et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2873–926.
13. Elefteriades JA, Pomianowski P. Practical genetics of thoracic aortic aneurysm. Prog Cardiovasc Dis 2013;56:57–67.
14. Guo DC, Papke CL, Tran-Fadulu V, et al. Mutations in smooth muscle alpha-actin (ACTA2) cause coronary artery disease, stroke, and Moyamoya disease, along with thoracic aortic disease. Am J Hum Genet 2009;84:617–27.
15. Guo DC, Pannu H, Tran-Fadulu V, et al. Mutations in smooth muscle alpha-actin (ACTA2) lead to thoracic aortic aneurysms and dissections. Nat Genet 2007;39:1488–93.
16. Biesecker LG, Green RC. Diagnostic clinical genome and exome sequencing. N Engl J Med 2014;370:2418–25.
17. Wang L, Guo DC, Cao J, et al. Mutations in myosin light chain kinase cause familial aortic dissections. Am J Hum Genet 2010;87:701–7.
18. Pyeritz R, Jondeau G, Moran R, et al. Loeys-Dietz syndrome is a specific phenotype and not a concomitant of any mutation in a gene involved in TGF-beta signaling. Genet Med 2014;16:641–2.
19. Van Laer L, Dietz H, Loeys B. Loeys-Dietz syndrome. Adv Exp Med Biol 2014;802:95–105.
20. Loeys BL, Chen J, Neptune ER, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet 2005;37:275–81.
21. Witecka J, Augusciak-Duma AM, Kruczek A, et al. Two novel COL1A1 mutations in patients with osteogenesis imperfecta (OI) affect the stability of the collagen type I triple-helix. J Appl Genet 2008;49:283–95.
22. Tromp G, Wu Y, Prockop DJ, et al. Sequencing of cDNA from 50 unrelated patients reveals that mutations in the triple-helical domain of type III procollagen are an infrequent cause of aortic aneurysms. J Clin Invest 1993;91:2539–45.
23. Yuan B, Thomas JP, von Kodolitsch Y, Pyeritz RE. Comparison of heteroduplex analysis, direct sequencing, and enzyme mismatch cleavage for detecting mutations in a large gene, FBN1. Hum Mutat 1999;14:440–6.