Patterns of genetic mutations explored by systematic screening of patients with aortopathy and their family members

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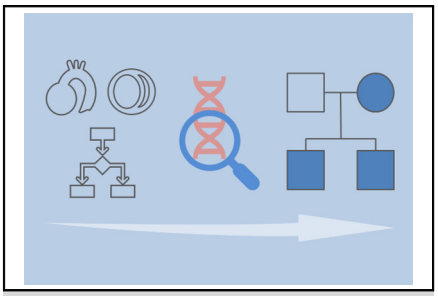
ABSTRACT

Objective: Genetic aortopathy, if left untreated, leads to aortic catastrophe in most affected individuals. We sought to determine the genetic mutation patterns and detection rates in patients with aortopathy and their families with a systematic screening protocol.

Methods: In 2016 to 2020, patients with aortic dissection or root aneurysm (Z score $\geq$2) and their first-degree relatives were enrolled in a prospective registry at a tertiary referral center. The individuals underwent systematic single- or multigene panel testing depending on clinical presentations.

Results: Among 575 enrolled individuals (mean age, 46.6 $\pm$ 14.5 years; 203 women), 346 (60.2%) underwent genetic testing. Rates of relevant gene mutations identified were 39.4% (91/231), 27.1% (54/199) and 72.4% (n = 105) in aneurysm, dissection, and family screening groups, respectively ($P < .001$). Mutated genes frequently identified were *FBN1* (n = 199; Marfan), *TGFBR1/2* or *SMAD3* (n = 14; Loeys-Dietz), *COL3A1/COL5A2* (n = 15; Ehlers-Danlos), and *ACTA2* (n = 10). After enrollment, 123 aortic surgeries were performed in 117 patients (20.3%) including 15 family members, with resultant operative mortality of 0.8% (n = 1). In logistic regression analysis, systemic score in Ghent nosology was the only significant factor associated with positive gene mutation (odds ratio, 14.81; 95% confidence interval, 6.87-31.96), and its 3.5 point cutoff showed the best predictive value with 78.2% sensitivity and 87.2% specificity.

Conclusions: Genetic aortopathy was identified in a considerable proportion of patients with aortopathy and their family members by systematic genetic testing. This strategy is recommended for timely diagnosis and proactive management of genetic aortopathy. (JTCVS Open 2023;15:27-37)



Stepwise screening of genetic aortopathy yielded a high mutation rate.

CENTRAL MESSAGE

Genetic aortopathy was identified in a substantial proportion of patients with aortopathy and their family members by systematic genetic testing.

PERSPECTIVE

Through systematic gene screening, genetic aortopathy was identified in a considerable proportion of patients presenting with aortic aneurysms or dissections and their first-degree relatives. Family screening would enable proactive management for patients with genetic aortopathy before the occurrence of aortic catastrophe.

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The registry and study protocol were approved by the Institutional Review Board of Asan Medical Center, Seoul, Korea (IRB No. 2017-0226; date of IRB approval, February 16, 2017).

Informed consent was obtained from all enrolled individuals in the Genetic Aortopathy Registry.

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Abbreviations and Acronyms
AUC = area under the curve
DES = diagnostic exome sequencing
EDS = Ehlers-Danlos syndrome
LDS = Loeys-Dietz syndrome
MFS = Marfan syndrome
OR = odds ratio
ROC = receiver-operating characteristic
TAAD = thoracic aortic aneurysm/dissection

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Aortopathy, which carries the risk of life-threatening aortic dissection or rupture, is caused by various medical conditions, including degenerative, inflammatory, and genetic causes. Among them, genetic aortopathy is a relatively rare condition, which includes Marfan syndrome (MFS), Ehlers-Danlos syndrome (EDS) type IV, Loeys–Dietz syndrome (LDS), and familial thoracic aortic aneurysm/dissection (TAAD). MFS is the most common genetic aortopathy, with a reported prevalence of 1.5 to 20 affected individuals per 100,000 people.[1-3] Most of these genetic aortic diseases are inherited in an autosomal dominant fashion, showing accelerated and more aggressive clinical courses than degenerative aortopathy, progressing at a relatively younger age.[4] However, many patients remain undiagnosed until the occurrence of a life-threatening aortic catastrophe, which often leads to death before accurate diagnosis.[2] The issue of underdiagnoses in genetic aortopathy may stem from several causes, such as the lack of sufficient awareness of rare medical conditions in general clinical practice, the additional cost associated with genetic testing, and patient-side refusal to get tested because of the concern of receiving potential social stigma attached to inheritable diseases. Additionally, the lack of simple and straightforward testing that can cover most known genetic aortic diseases may hinder the generalization of the effective diagnostic method for genetic aortopathy.

Various diagnostic tools for genetic aortopathy, such as panel assay and diagnostic exome sequencing (DES), have been recently developed and applied in clinical practice.[5,6] Through genetic testing, rare genetic aortopathy can be detected, especially in patients with nonsyndromic diseases that are difficult to diagnose early because of their lack of unique physical traits. Subsequent screening for the family members of the diagnosed patients would further facilitate early detection and lifesaving proactive measures among these individuals.

Therefore, we established an institutional genetic aortopathy registry adopting a systematic screening strategy and investigated the genetic mutation patterns and detection rates in patients with aortopathy and their family members.

MATERIALS AND METHODS

Study Population

In August of 2016, we established the Prospective Genetic Aortopathy Registry of the Aortic Center, Asan Medical Center Heart Institute, Seoul, Korea. We enrolled individuals who agreed to participate in the study among the adult patients (≥18 years of age) presenting with aortopathy—defined as aortic root aneurysm (Z score ≥2) or aortic dissection—and the first-degree relatives of patients with diagnosed genetic aortopathy. This study included individuals enrolled from August 2016 to September 2020.

Gene Testing

For the enrolled individuals, comprehensive medical and family histories were collected, and physical examination incorporating parameters relevant to the systemic score of the revised Ghent nosology criteria was undertaken by dedicated specialists. Computed tomography imaging on the entire aorta was also obtained. Patients with syndromic physical traits fulfilling the revised Ghent nosology criteria (ie, presence of ectopia lentis or systemic score ≥7) were subject to single-gene tests, such as fibrillin-1 (*FBN1*), transforming growth factor-beta receptor 1 (*TGFBR1*), *TGFBR2*, and collagen type III alpha 1 chain (*COL3A1*), based on their presumed clinical diagnoses. The DES test (Green Cross Laboratories), covering up to 62,000 exons of 4813 genes related to known human genetic disorders, was performed for individuals whose systemic score did not fulfill the revised Ghent criteria. Nonsyndromic patients, that is, those with no characteristic physical traits, underwent a single-gene test for smooth muscle aortic alpha-actin (*ACTA2*), the most common nonsyndromic genetic aortopathy. Patients positive for *ACTA2* were thus diagnosed with a form of nonsyndromic familial TAAD, whereas DES was subsequently performed for those with negative *ACTA2* results.

For individuals with a positive result for relevant gene mutations, the specific gene mutation screening was extended to their family members, beginning with their children and a parent who was most thought to have the gene mutation (based on medical histories and physical findings). If the particular parent tested negative, testing was extended to the other parent. However, if the parent tested positive, the screening extended to all siblings who could be contacted. Individuals whose parents tested negative for the mutations were considered carriers of de novo mutations, and the genetic screening was not extended to their siblings. The screening automatically extended to children and siblings for patients whose parents were not reachable (ie, deceased or refused to get tested). Family genetic screening was not conducted if the index patient tested negative for a mutation.

Since 2018, the single-gene test and DES were replaced with an institutional multi-gene panel test consisting of 16 well-established genes related to genetic aortopathy for cost and time efficiency. *ACTA2*, *COL3A1*, *FBN1*, methionine adenosyltransferase II alpha (*MAT2A*), myosin heavy chain 11 (*MYH11*), myosin light chain kinase (*MYLK*), notch receptor 1 (*NOTCH1*), protein kinase cyclic guanosine monophosphate-dependent 1 (*PRKG1*),

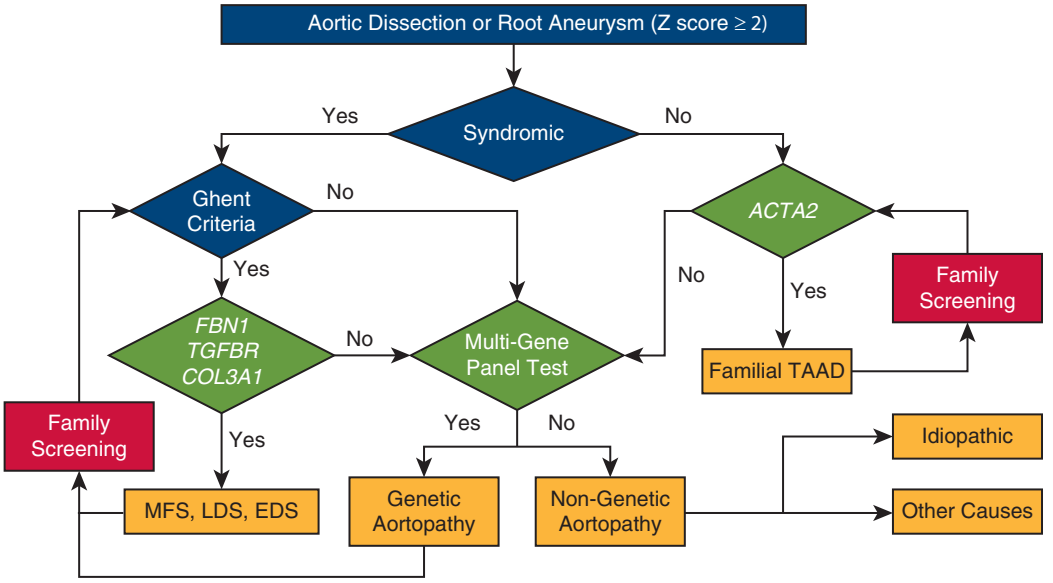

FIGURE 1. A comprehensive diagram presenting the stepwise protocol for genetic aortopathy diagnosis and screening. *TAAD*, Thoracic aortic aneurysm/dissection; *MFS*, Marfan syndrome; *LDS*, Loeys-Dietz syndrome; *EDS*, Ehlers-Danlos syndrome.

SKI proto-oncogene (*SKI*), solute carrier family 2 member 10 (*SLC2A10*), SMAD family member 3 (*SMAD3*), *SMAD4*, transforming growth factor-beta 2 (*TGFB2*), *TGFB3*, *TGFBR1*, and *TGFBR2*.[7] The systematic genetic testing process is summarized in Figure 1.

The genetic testing results were reported according to a 5-tier classification system as pathogenic, likely pathogenic, variant of uncertain significance, likely benign, and benign.[8] Among the variants, pathogenic, likely pathogenic, and variant of uncertain significance were interpreted as clinically significant mutations, and the rest were regarded as "no mutations." The test results were interpreted by expert geneticist-physicians in the Department of Medical Genetics.

Patient Care

According to the results, the treatment protocol was established for genetic counseling and integrated care in cardiology, cardiovascular surgery, obstetrics and gynecology, ophthalmology, and orthopedics, depending on the clinical presentations. After initial assessment and treatment, enrolled individuals were reevaluated through regular outpatient follow-up from the enrollment date. Any relevant imaging and blood tests were performed as required at 6 months, 12 months, and then annually. Individuals with confirmed genetic aortopathy were guided with relatively lower surgical thresholds for proactive aortic repair (maximal aortic diameter, 40-50 mm), offering detailed counseling regarding the benefits and risks of prophylactic aortic repair to patients.

Informed consent was obtained from all enrolled individuals in the Genetic Aortopathy Registry for publication of study data. The individuals were informed that they might withdraw consent and from the registry, at any time if desired. The registry and study protocol were approved by the Institutional Review Board of Asan Medical Center, Seoul, Korea (IRB No. 2017-0226; date of IRB approval, February 16, 2017).

Statistical Analysis

Data analyses were performed using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corporation). The normality of continuous data was determined by the Kolmogorov–Smirnov test. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as frequency and percentage. As appropriate, group differences in variables were compared by *t* test, 1-way analysis of variance, chi-square test, or Kruskal–Wallis test.

The odds ratios (ORs) of having a gene mutation were calculated using multivariable logistic regression with prespecified risk factors selected by univariable analyses as independent variables and having a gene mutation as the dependent variable. The cutoff value of the systemic score that predicts the presence of gene mutation was estimated with Youden's J statistic using the area under the curve (AUC) for the receiver-operating characteristic curve. All statistical tests were 2-sided.

RESULTS

Cohort Description

A total of 575 individuals were enrolled in the registry. Diagnoses of the index patients (ie, presenting with aortopathies, n = 430) included root aneurysm (n = 231) and aortic dissection (n = 199) (Table 1). The specific locations of aortic aneurysms and types of aortic dissections are detailed in Table E1. The family screening was extended to 145 individuals who were the first-degree relatives of patients diagnosed with genetic aortopathy. The family screening group was younger (37.7 ± 15.6 years), with more women (49.7%) and fewer patients with hypertension (49.7%) than the index patient groups (all $P < .001$).

Gene Testing Outcomes

Among the enrolled patients in the registry (n = 575), 346 (60.2%) individuals completed genetic testing, including 134 patients with root aneurysm (58.0%, 134/231), 94 with aortic dissection (47.2%, 94/199), and 118 screened family members (81.4%, 118/145) (Table 2).

Single *FBN1* mutation was the most frequent variant, constituting 77.2% (193/250) of the overall mutated genes, followed by *ACTA2* (n = 9, 3.6%), *COL3A1* (n = 9,

TABLE 1. Demographics and clinical features of enrolled individuals

Variable	Total (n = 575)	Root aneurysm (n = 231)	Aortic dissection (n = 199)	Family screening (n = 145)	*P* value
Age, y	46.6 ± 14.5	48.2 ± 13.7	51.3 ± 11.5	37.7 ± 15.6	<.001
Women	203 (35.3%)	69 (29.9%)	62 (31.2%)	72 (49.7%)	<.001
BSA, m^2	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.3	1.8 ± 0.3	.203
SBP, mm Hg	123.8 ± 16.1	124.8 ± 15.1	124.3 ± 18.0	121.6 ± 14.7	.173
DBP, mm Hg	71.5 ± 10.6	72.7 ± 10.1	70.1 ± 11.5	71.3 ± 9.9	.037
HR, beats/min	76.5 ± 13.7	76.8 ± 14.0	74.4 ± 14.3	79.0 ± 11.8	.01
DM	19 (3.3%)	8 (3.5%)	8 (4.0%)	3 (2.1%)	.598
Hypertension	413 (71.8%)	176 (76.2%)	165 (82.9%)	72 (49.7%)	<.001
Hyperlipidemia	34 (5.9%)	16 (6.9%)	15 (7.5%)	3 (2.1%)	.073
AF	20 (3.5%)	11 (4.8%)	7 (3.5%)	2 (1.4%)	.219
Stroke	13 (2.3%)	6 (2.6%)	5 (2.5%)	2 (1.4%)	.710
COPD	5 (0.9%)	3 (1.3%)	2 (1.0%)	0 (0.0%)	.405
CKD	3 (0.5%)	0 (0.0%)	3 (1.5%)	0 (0.0%)	.058

Values are mean ± SD or n (%). *BSA*, Body surface area; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *HR*, heart rate; *DM*, diabetes mellitus; *AF*, atrial fibrillation; *COPD*, chronic obstructive pulmonary disease; *CKD*, chronic kidney disease.

3.6%), and *TGFBR1/2* (n = 5, 2.0%) (Table 3). Multiple combined gene mutations were observed in 12 cases (4.8%). Each group showed high rates of gene mutations: 67.9% in the root aneurysm group (91/134), 57.4% in the aortic dissection group (54/94), and 89.0% in the family screening group (105/118).

The detection of *FBN1* mutation enabled additional MFS diagnoses in 11 patients, including 5 in the root aneurysm group and 6 in the aortic dissection group, who otherwise did not fulfill the revised Ghent criteria. Moreover, genetic testing was the only method enabling the diagnosis of other forms of genetic aortopathy than MFS, such as LDS (n = 8), EDS (n = 11), arterial tortuosity syndrome (n = 1), and nonsyndromic familial TAAD (n = 22) (Table 3).

Subgroup analysis revealed that patients who were syndromic had a significantly higher gene mutation rate than those who were nonsyndromic in the root aneurysm and aortic dissection groups (all $P < .001$, Table 2). In contrast, the family screening group showed comparable gene mutation rates between patients who were syndromic and nonsyndromic (92.3% vs 86.4%, respectively; $P = .467$).

Among index patients (root aneurysm or dissection) who underwent genetic testing (n = 228), clinical characteristics were compared between the mutation (+) and (−) groups (Table 4). Patients in the mutation (+) group were younger (43.2 ± 13.0 vs 49.8 ± 12.6 years; $P < .001$), had more syndromic patients (66.2% vs 11.6%; $P < .001$), and thus had higher systemic scores (7.4 ± 4.3 vs 1.5 ± 3.3 points; $P < .001$). The OR of carrying mutations was calculated using logistic regression with baseline factors as independent variables and carrying a mutation as the dependent variable. In the univariable logistic regression model, age less than 50 years (OR, 1.96; 95% confidence interval [CI], 1.13-3.39; $P = .016$) and syndromic feature (OR, 14.88; 95% CI, 7.06-31.36; $P < .001$) were identified as factors

TABLE 2. Gene mutation rates in enrolled individuals according to gene testing

	Root aneurysm (n* = 134)			Aortic dissection (n* = 94)			Family screening (n* = 118)		
Syndromic feature	Yes (n = 71)	No (n = 63)	*P* value	Yes (n = 33)	No (n = 61)	*P* value	Yes (n = 52)	No (n = 66)	*P* value
Mutation category			<.001			<.001			.003
Pathogenic	42 (59.2%)	10 (15.9%)		16 (48.5%)	6 (9.8%)		33 (63.5%)	19 (28.8%)	
Likely pathogenic	6 (8.5%)	2 (3.2%)		2 (6.1%)	5 (8.2%)		3 (5.8%)	7 (10.6%)	
VUS	10 (14.1%)	13 (20.6%)		7 (21.2%)	11 (18.0%)		6 (11.5%)	23 (34.8%)	
Missing value†	8 (11.3%)	0 (0.0%)		5 (15.2%)	2 (3.3%)		6 (11.5%)	8 (12.1%)	
No mutation	5 (7.0%)	38 (60.3%)		3 (9.1%)	37 (60.7%)		4 (7.7%)	9 (13.6%)	
Subtotal mutation	66 (93.0%)	25 (39.7%)	<.001	30 (90.9%)	24 (39.3%)	<.001	48 (92.3%)	57 (86.4%)	.467
Overall mutation‡	91 (67.9%)			54 (57.4%)			105 (89.0%)		

Values are n (%). *VUS*, Variant of uncertain significance. *Number of individuals who underwent genetic testing. †Mutation without mention of pathogenic strength. ‡$P < .001$.

TABLE 3. Mutated genes according to clinical presentation

Mutated gene	Entire cohort (n = 250)	Root aneurysm (n = 91)	Aortic dissection (n = 54)	Family screening (n = 105)
Single gene mutation (n = 238, 95.2%)				
Syndromic	213 (85.2%)	86 (94.5%)	40 (74.1%)	87 (82.9%)
FBN1 (MFS)	193 (77.2%)	82 (90.1%)	36 (66.7%)	75 (71.4%)
TGFBR1 (LDS type 1)	2 (0.4%)	0 (0.0%)	0 (0.0%)	2 (1.9%)
TGFBR2 (LDS type 2)	3 (1.2%)	1 (1.1%)	1 (1.9%)	1 (1.0%)
SMAD3 (LDS type 3)	3 (1.2%)	0 (0.0%)	2 (3.7%)	1 (1.0%)
COL3A1 (EDS)	9 (3.6%)	2 (2.2%)	0 (0.0%)	7 (6.7%)
COL5A2 (EDS)	2 (0.8%)	1 (1.1%)	0 (0.0%)	1 (1.0%)
SLC2A10 (arterial tortuosity syndrome)	1 (0.4%)	0 (0.0%)	1 (1.9%)	0 (0.0%)
Nonsyndromic (familial TAAD)	22 (8.8%)	3 (3.4%)	8 (14.8%)	11 (10.5%)
ACTA2 (SMC actin chain)	9 (3.6%)	0 (0.0%)	5 (9.3%)	4 (3.8%)
MYH11 (SMC myosin chain)	5 (2.0%)	0 (0.0%)	1 (1.9%)	4 (3.8%)
MYLK (SMC myosin chain)	5 (2.0%)	1 (1.1%)	1 (1.9%)	3 (2.9%)
PRKG1 (cGMP mediated SMC)	1 (0.4%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
NOTCH1	2 (0.8%)	1 (1.1%)	1 (1.9%)	0 (0.0%)
Other	3 (1.2%)	0 (0.0%)	2 (3.7%)	1 (1.0%)
Multi-gene mutations (n = 12, 4.8%)				
FBN1/COL3A1	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
FBN1/MYH11	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
FBN1/MYLK(HATD)	1 (0.4%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
FBN1/MYLK(HATD)/NOTCH1	1 (0.4%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
FBN1/SMAD3	1 (0.4%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
FBN1/TGFB3	1 (0.4%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
ACTA2/NOTCH1	1(0.4%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
TGFBR1/MYH11	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
TGFBR2/COL3A1	3 (1.2%)	0 (0.0%)	1 (1.9%)	2 (1.9%)
TGFBR2/MYLK(HATD)	1 (0.4%)	0 (0.0%)	1 (1.9%)	0 (0.0%)

Values are n (%). *MFS*, Marfan syndrome; *LDS*, Loeys-Dietz syndrome; *EDS*, Ehlers-Danlos syndrome; *TAAD*, thoracic aortic aneurysm/dissection; *SMC*, smooth muscle cell; *cGMP*, cyclic guanosine monophosphate.

significantly associated with positive gene mutation. In the multivariable model, the syndromic feature was the only significantly associated factor, with an age-adjusted OR of 14.81 (95% CI, 6.87-31.96; $P < .001$). Subsequent estimation of the cutoff value of the systemic score predicting gene mutation was performed using the AUC for the receiver-operating characteristic curve in the index patient group. The AUC was 0.839 (95% CI, 0.783-0.895; $P < .001$), and the optimal cutoff value of systemic score was 3.5 points (sensitivity, 78.2%; specificity, 87.2%) (Figure 2).

Surgical Therapy

Among all eligible individuals (n = 575), 500 aortic surgeries were performed in 375 patients; 123 and 377 surgeries were conducted after and before enrollment, respectively (Tables E2 and E3). Among the 123 new surgeries, 1 (0.8%) resulted in mortality after a redo Bentall procedure in a patient with root aneurysm on the first postoperative day. According to the categories, 198 operations were performed in the root aneurysm group (n = 231), including 145 and 53 operations before and after the registry enrollment, respectively. In the aortic dissection group (n = 199), 251 operations were performed, including 195 past and 56 new operations. In the family screening group (n = 145), 36 past and 15 new operations were conducted.

DISCUSSION

The present study showed a substantial proportion of genetic mutations among patients with aortopathy by the systematic genetic test strategy. The strategy comprises different initial gene tests depending on physical traits: *FBN1*, *TGBR*, and *COL3A1* for syndromic patients and *ACTA 2* for nonsyndromic ones. Then, DES or multi-gene panel tests were done if needed for cost-effectiveness (Figure 1). The subsequent family screening revealed multiple hidden genetic aortopathy in individuals who would have otherwise remained undiagnosed (Figure 3 and Video 1).

Genetic abnormality plays a crucial role in thoracic aortic diseases, and 20% of the first-degree relatives of patients with thoracic aortic disease are known to already have aortic aneurysm. Well-known genes associated with the thoracic aortic disease include *FBN1* of MFS, *TGFBR1/2*, *SMAD3*, *TGFB2* of LDS, and *COL3A1* of EDS.[9-11] Other genes associated with thoracic aortopathy, such as *MYTH11*,

TABLE 4. Clinical characteristics of the index patients according to gene mutation

Variable	Mutation (+) (n = 142)	Mutation (−) (n = 86)	*P* value
Age, y	43.2 ± 13.0	49.8 ± 12.6	<.001
Women	47 (33.1%)	22 (25.6%)	.294
Category			.093
Root aneurysm	90 (63.4%)	44 (51.2%)	
Aortic dissection	52 (36.6%)	42 (48.8%)	
BSA, m^2	1.8 ± 0.2	1.9 ± 0.2	.545
SBP, mm Hg	123.5 ± 16.2	126.3 ± 17.4	.209
DBP, mm Hg	71.0 ± 11.1	73.2 ± 11.6	.165
HR, beats/min	76.6 ± 13.7	77.8 ± 15.6	.552
DM	5 (3.5%)	4 (4.7%)	.941
Hypertension	116 (81.7%)	68 (79.1%)	.754
Hyperlipidemia	14 (9.9%)	3 (3.5%)	.130
AF	5 (3.5%)	7 (8.1%)	.227
Stroke	5 (3.5%)	1 (1.2%)	.515
COPD	1 (0.7%)	1 (1.2%)	1.000
CKD	1 (0.7%)	1 (1.2%)	1.000
Aortic root Z score ≥2	131 (92.3%)	74 (86.0%)	.200
Root aneurysm size, mm*	46.8 ± 16.9	45.1 ± 8.7	.071
Syndromic	94 (66.2%)	10 (11.6%)	<.001
Systemic score	7.4 ± 4.3	1.5 ± 3.3	<.001

Values are mean ± SD or n (%). *BSA*, Body surface area; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *HR*, heart rate; *DM*, diabetes mellitus; *AF*, atrial fibrillation; *COPD*, chronic obstructive pulmonary disease; *CKD*, chronic kidney disease. *Root aneurysm size was measured from the computed tomography; mutation (+) group (n = 44) versus mutation (−) group (n = 22).

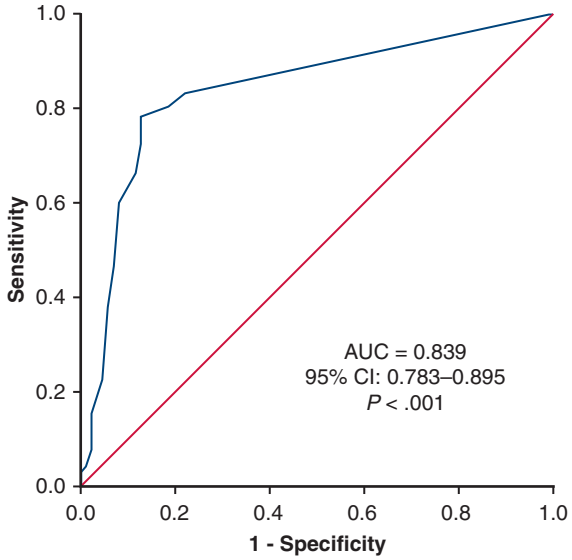

FIGURE 2. Receiver-operating characteristic curve for predicting gene mutation based on the systemic score of index patients. The optimal cutoff value was 3.5 points (sensitivity, 78.2%; specificity, 87.2%). *AUC*, Area under the curve; *CI*, confidence interval.

ACTA2, *NOTCH1*, *MYLK*, *PRKG1*, and *SKI*, have also been identified.[12] The proposed molecular mechanisms for developing aortopathies related to these genes are (1) extracellular matrix dysfunction (mutations in *FBN1*, *COL3A1*); (2) TGF-β signaling disruption (mutations in *TGFB2*, *TGFB3*, *TGFBR1*, *TGFBR2*, *SMAD3*); and (3) dysfunctional contractile apparatus of smooth muscle cells in the aortic wall (mutations in *ACTA2*, *MYH11*, *MYLK*).[13-15]

Genetic aortopathy progresses to aortic aneurysm and dissection with more rapid disease progression rates and complications than degenerative aortopathies and has characteristic physical traits in syndromic diseases such as MFS, EDS, and LDS. In MFS, the thoracic aorta progressively dilates over time, with a reported expansion rate of 1.0 to 1.9 mm/year. This condition led to death at a median age of 45 years before the 1980s, when the prophylactic surgical aorta repair was unavailable.[16,17] The survival has since improved because of the availability of proactive surgical therapy and beta-blocker medication, increasing the life expectancy of patients to more than 70 years, which is almost comparable to that of the reference population.[18] Moreover, an annual aortic enlargement of 10 mm or more is observed in patients with LDS, leading to death at an average age of 26 years.[17,19] Early diagnosis and proper treatment can significantly reduce mortality in patients with this rapidly progressing disease. The incidence of fatal complications during or immediately after vascular surgery is only 1.7% in LDS.[19] Therefore, emphasis has been provided on the need for early diagnosis through noninvasive imaging modalities or genetic testing. This subsequent monitoring and follow-up facilitate the appropriate use of antihypertensive medications that reduce the aortic dilatation rate and exert a prophylactic effect against fatal complications, such as aortic dissection and rupture.[20] Early diagnosis also facilitates subsequent imaging studies on the aorta at appropriate intervals pivotal for guiding preventive surgery at appropriate thresholds. In a study comparing surgical mortality rates between emergency and elective open aortic repairs in 675 patients with MFS, there was a huge difference in mortality rates (11.5% vs 1.5%), highlighting the importance of timely proactive elective surgery, which is only possible when the patients are under close surveillance.[21]

Most nonsyndromic TAAD is inherited in an autosomal dominant pattern, and causative genes have been investigated.[22,23] In nonsyndromic diseases, the annual aortic dilatation rates are approximately 0.5 to 0.7 mm, which is slightly slower than those of syndromic aortopathies, and the disease is limited to the cardiovascular system.[1,24] Nonetheless, nonsyndromic aortopathy continually progresses over time, potentially leading to fatal complications. Early detection, however, is challenging because of

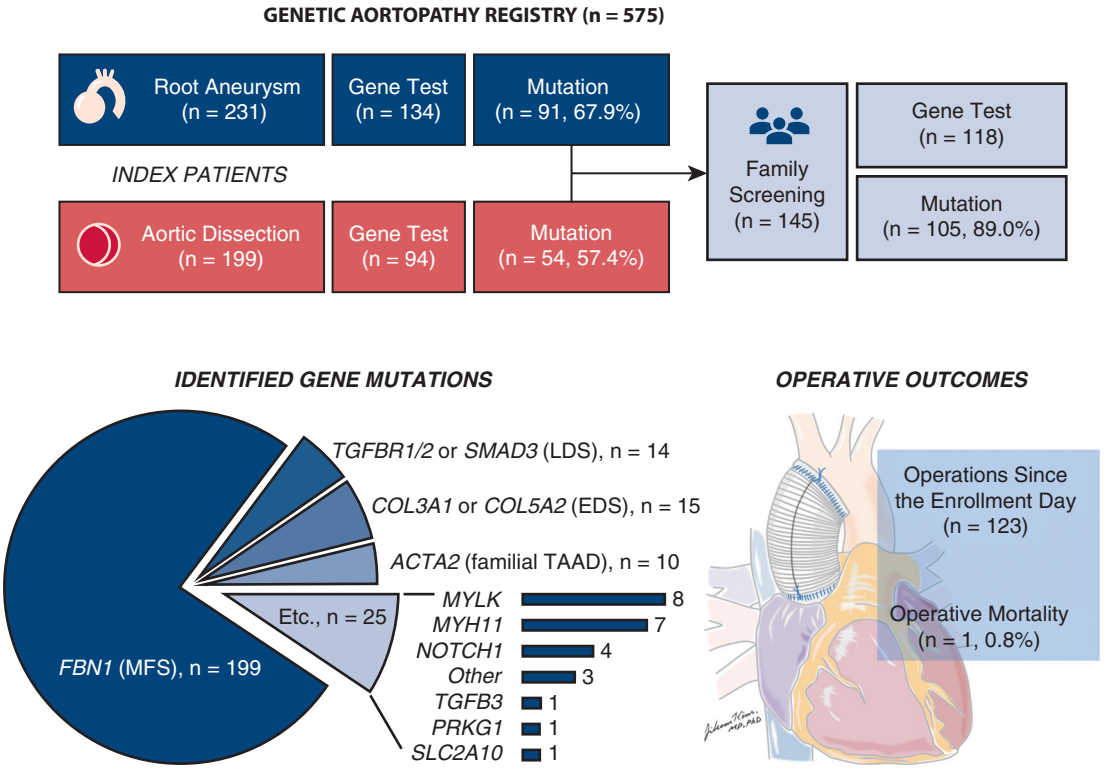

FIGURE 3. Outcomes of the systematic screening strategy for genetic aortopathy. *LDS*, Loeys-Dietz syndrome; *EDS*, Ehlers-Danlos syndrome; *TAAD*, thoracic aortic aneurysm/dissection; *MFS*, Marfan syndrome.

the absence of external manifestation in these individuals. Familial TAAD, in particular, is a typical nonsyndromic aortopathy. It presents at a younger age than sporadic aneurysms, has a higher growth rate, and does not correlate with traditional risk factors for aortic diseases, such as hypertension, dyslipidemia, or coronary artery disease.[15] In familial TAAD, mutations in *ACTA2* are most prevalent, ranging from 10% to 14%.[25] This disease could be detected incidentally on examinations for other reasons due to the absence of external features. In most cases, the first presentation is aortic dissection, rupture, or sudden death. For instance, in a study investigating the *ACTA2* mutation-associated aortic disease, the overall risk of mortality associated with the first aortic event in individuals with *ACTA2* mutations was 25% to 30% (33-43/132) at a median age of 36 years (interquartile range, 28-45). Those without an aortic event died of various reasons, including cardiac deaths, at a median age of 45 years (interquartile range, 28-63) (n = 11/145; mortality rate, 7.5%). However, there was no operative mortality related to elective aortic aneurysm repair in this study.[26] Accordingly, the importance of detecting this disease is stressed to prevent lethal outcomes in undiagnosed individuals. Familial TAAD may occur in people of all ages and always should be suspected in patients diagnosed with thoracic aortic disease at less than 60 years of age, and family screening is essential.[1] The genetic test is pivotal, especially in adolescents, because the normal aortic size on imaging tests does not preclude the diagnosis of this disease.[27]

VIDEO 1. Dr Jihoon Kim explains the main findings and implications of the study. Video available at: https://www.jtcvs.org/article/S2666-2736(23)00162-6/fulltext.

The clinical application of DES has been established and has recently been used actively to diagnose and manage patients with genetic aortopathy.[5,28] Additionally, panels for simultaneous multiple gene testing are also commercially available.[5,6] Along with clinical values, genetic testing has aided in identifying cellular and tissue events contributing to aortopathy, thereby offering novel therapeutic

strategies.[29] Precise diagnosis with genetic testing could also lead to the development of individualized treatment for patients with different genetic alterations.[27] However, the current international aortic disease guidelines do not specify the clinical use or requirement for these genetic tests. There is no guided policy to systematically detect and manage patients with genetic aortopathy. In addition, the current guidelines specify aortic aneurysm sizes for preventive surgery in MFS or LDS without additional mention of rare diseases, such as familial TAAD.[30,31] This may be due to insufficient data on the natural course of these rare diseases.[2] Therefore, additional clinical data with reasonably sized cohorts relevant to systematic genetic testing of genetic aortopathy are urgently required to enhance the body of evidence in this field.

In the present study, gene mutations were identified in 250 patients (43.5% of 575 total patients and 72.2% of 346 gene-tested patients), showing a relatively high frequency. By priority, awareness and clinical suspicion by attending physicians/surgeons are more important than genetic testing to appropriately identify patients with genetic aortopathy. However, the systematic screening algorithm per se is also believed to be an effective guiding tool to enhance awareness of these rare diseases. It has been further strengthened by the automatic referral to the Genetic Aortopathy Registry based on the enrollment criteria activating the diagnostic strategy in the host institution. We believe that this kind of systematic screening algorithm should be recommended strongly in future practice guidelines for further generalization. Within this algorithm, genetic testing also plays a crucial role. It has enhanced the diagnostic confirmation rates of MFS (by 11 more patients) and other syndromic diseases; for example, LDS, which was otherwise undistinctive from MFS in many cases, has been discriminated by genetic testing (n = 14). In particular, arterial tortuosity syndrome, an extremely rare autosomal recessive disease caused by a *SLC2A10* mutation, could be confirmed by genetic testing, without which accurate diagnosis would be impossible.[32] In addition to these syndromic disorders, we also detected 22 individuals with nonsyndromic familial TAAD, who may have remained undiagnosed without genetic testing. Thus, we believe that the present research is one of the most extensive series to detect as many individuals with familial TAAD.

Notably, the protocol confirmed genetic aortopathy in 105 family members through screening extension for 145 index patients (root aneurysm and dissection), of whom 15 individuals were offered proactive aortic surgery. Guided antihypertensive medications and timely aortic interventions offer significant clinical benefits for these individuals over the lifelong follow-up. Comprehensive care for endocrine, orthopedic, ophthalmologic, and pregnancy-related issues activated by the protocol is also expected to enhance the quality of life.

Study Limitations

This investigation is a single-center study on rare diseases, despite the prospective enrollment. Because the study setting is a tertiary referral center, most of the cases (index patients) referred are those in need of surgical therapy. Therefore, the results may not be generalizable to other settings. Selection bias is also prevalent because only patients with aortopathy who survived a past aortic event were enrolled in the registry.

Gene testing was completed in only 60.2% (346/575) of enrolled patients, despite earnest recommendations from the investigators to get genetic testing. This figure is believed to reflect real-world practice, in which the most frequent reason for not conducting genetic testing is patient refusal. Most of the patients were fearful of being diagnosed with the hereditary disease for several reasons, including guilty feelings toward their children and concerns about social stigmatization, future marriage, and childbirth. Another limiting issue against consenting to genetic testing was the cost of the tests. The psychosocial and financial burdens on families with genetic aortopathy are heavy. They tend to peak when the patient experiences aortic events (ie, aortic surgery, aortic complications, and death), constraining socioeconomic status at the most productive young ages.[33-35] Because this condition is predisposed to the heredity of poverty within families, the relatively high-cost genetic test is not affordable for this population, necessitating society-level financial and executive support for the adequate diagnosis and treatment of these patients and their families.

CONCLUSIONS

We identified genetic aortopathy in a considerable proportion of patients presenting with aortic aneurysms or dissections through systematic gene screening. Patients with hidden genetic aortopathy were also discovered by family screening. This strategy is encouraged for timely detection, accurate diagnosis, and subsequent proactive management of genetic aortopathy, including early surgery.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://www.aats.org/resources/1-systematic-screening-strategy-for-genetic-aortopathy-2.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or

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Key Words: aortic dissection, Ehlers-Danlos syndrome, genetic aortopathy, Loeys-Dietz syndrome, Marfan syndrome, thoracic aortic aneurysm

TABLE E1. Aortic pathologies according to the enrolled groups

Pathology	Root aneurysm (n = 231)	Aortic dissection (n = 199)	Family screening (n = 145)
Aortic aneurysm location			
Root	231 (100.0%)	7 (3.5%)	16 (11.0%)
Ascending	65 (28.1%)	4 (2.0%)	4 (2.8%)
Arch	5 (2.2%)	0 (0.0%)	1 (0.7%)
Descending thoracic	12 (5.2%)	0 (0.0%)	0 (0.0%)
Thoracoabdominal	5 (2.2%)	3 (1.5%)	1 (0.7%)
Abdominal	7 (3.0%)	1 (0.5%)	0 (0.0%)
Aortic dissection type			
DeBakey I	0 (0.0%)	112 (56.3%)	3 (2.1%)
DeBakey II	0 (0.0%)	16 (8.0%)	2 (1.4%)
DeBakey III	0 (0.0%)	71 (35.7%)	6 (4.1%)

Values are n (%).

TABLE E2. Numbers of aortic operations according to the enrolled groups

Operation	Root aneurysm (n* = 231)	Aortic dissection (n* = 199)	Family screening (n* = 145)	Total	*P* value
First	165 (71.4%)	170 (85.4%)	40 (27.6%)	375	<.001
Second	24 (10.4%)	59 (29.6%)	9 (6.2%)	92	<.001
Third	8 (3.5%)	19 (9.5%)	1 (0.7%)	28	<.001
Fourth	1 (0.4%)	3 (1.5%)	1 (0.7%)	5	.089
Total	198	251	51	500	

Values are n (%). *Number of individuals enrolled in respective groups.

TABLE E3. Number of aortic operations in the gene-tested groups

	Root aneurysm			Aortic dissection			Family screening		
Operation	Mutation (+) (n* = 91)	Mutation (−) (n* = 43)	*P* Value	Mutation (+) (n* = 54)	Mutation (−) (n* = 40)	*P* value	Mutation (+) (n* = 105)	Mutation (−) (n* = 13)	*P* value
First	60 (65.9%)	29 (67.4%)	.324	52 (96.3%)	35 (87.5%)	.227	23 (21.9%)	3 (23.1%)	.795
Second	13 (14.3%)	2 (4.7%)	.095	23 (42.6%)	10 (25.0%)	.123	5 (4.8%)	1 (7.7%)	.717
Third	3 (3.3%)	2 (4.7%)	.316	7 (13.0%)	3 (7.5%)	.365	1 (1.0%)	0 (0.0%)	.761
Fourth	0 (0.0%)	1 (2.3%)	.117	1 (1.9%)	1 (2.5%)	.492	1 (1.0%)	0 (0.0%)	.761

Values are n (%). *Number of individuals enrolled in respective groups.