



Thoracic aneurysm and dissection gene variants increase the risk of aortic-related adverse events in early-onset isolated Stanford type B aortic dissection after endovascular aortic repair

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Background: Researches on Marfan syndrome and Ehlers-Danlos syndrome leading to early-onset aortic dissection (AD) emphasize the importance of gene variants, but the genetic pathogenesis, clinical characteristics and outcomes of early-onset isolated Stanford type B aortic dissection (iTBAD) patients remain unclear and need to be further elucidated.

Methods: Isolated type B AD patients with an onset age of less than 50 years were enrolled in this study. Whole exome sequencing (WES) was performed to detect 11 known thoracic aortic aneurysm and dissection (TAAD) gene variants. Clinical characteristics and outcomes were compared between patients with and without gene variants. Multivariate Cox regression analysis was performed to identify independent risk factors for aortic-related adverse events (ARAEs) after endovascular aortic repair.

Results: A total of 37 patients were included. Ten patients carried 10 variants in five TAAD genes, four of whom carried pathogenic or likely pathogenic variants. Compared to patients without the variants, patients with variants had a lower incidence of hypertension (50.0% vs. 88.9%, $P=0.021$), a higher incidence of other vascular abnormalities (60.0% vs. 18.5%, $P=0.038$), all-cause mortality (40.0% vs. 3.7%, $P=0.014$) and aortic related mortality (30.0% vs. 3.7%, $P=0.052$). Multivariate analysis confirmed the presence of TAAD gene variants as the only independent risk factor for ARAEs [hazard ratio (HR) =4.00; 95% confidence interval (CI): 1.26–12.74; $P=0.019$].

Conclusions: Routine genetic testing is necessary for early-onset iTBAD patients. Individuals with a high risk of ARAEs can be identified by detecting TAAD gene variants, which is important for risk stratification and proper management.

Keywords: Aortic diseases; mutation; prognosis

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Introduction

Aortic dissection (AD) is one of the most life-threatening aortic disorders caused by intimal tear that separates layers within the aortic wall. It is characterized by acute onset, rapid progression, and a high mortality rate, especially in the event of aortic rupture (1). AD can be classified as Stanford type A or type B based on whether the ascending aorta is involved, with an average onset age of approximately 61 years old (2). To date, the following 11 genes are explicitly relevant to AD: *ACTA2*, *COL3A1*, *FBN1*, *MYH11*, *MYLK*, *SMAD3*, *TGFB2*, *TGFBR1*, *TGFBR2*, *PRKG1* and *LOX*, and are named as thoracic aortic aneurysm and dissection (TAAD) genes (3). With advances in bioinformatics technologies and high-throughput sequencing, the growing awareness of the key role played by genetic factors in pathogenesis of not only syndromic forms such as Marfan syndrome or Ehlers-Danlos syndrome, but also non-syndromic forms, often known as isolated AD, reinforces the importance of genetic testing (4). According to research on isolated Stanford type A AD, genetic variants contribute to an earlier age of onset (5), and thoracic AD patients with an age-of-onset of less than 50 years old demonstrated 5.5 times higher risk of carrying pathogenic variants (6). However, genetic variants and clinical characteristics of patients with early-onset isolated Stanford type B aortic dissection (iTBAD) have not been thoroughly elucidated.

Currently, thoracic endovascular aortic repair (TEVAR) is commonly used to treat TBAD with the advantages of less invasion and shorter operation time (7), as well as the superior effect on promoting aortic remodeling (8). However, the efficacy of TEVAR is challenged by different kind of postoperative adverse events such as endoleak,

enlargement of the distal aorta, stent-induced new entry (SINE), retrograde dissection, new dissection and aortic rupture. Numerous indicators, including aortic diameter (9), visceral vessels originating from a false lumen (10), and the number of stents (11), have been identified as risk factors for those adverse events. Additionally, a previous study revealed that Stanford type A AD patients with pathogenic variants required more reinterventions for the preserved native aortic root after open surgery (12). This finding indicates the influence of genetic factors on the prognosis of open surgery for type A AD; however, it is not clear whether they have an effect on the outcomes of TEVAR for TBAD.

Since younger patients are more likely to carry mutations and the effect of genetic status on the prognosis of TEVAR is unknown, it is worthwhile to detect TAAD gene variants in early-onset iTBAD and illustrate the underlying impact on TEVAR. Therefore, whole exome sequencing (WES) was performed for patients under 50 years of age, and the correlations between genotypes, phenotypes, and outcomes were explored to further identify high-risk patients after TEVAR. We present this article in accordance with the MDAR reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-1529/rc>).

Methods

Study population and design

Thirty-seven consecutive iTBAD patients attending Changhai Hospital from January 2019 to May 2021 with an onset age of less than 50 years old were enrolled in the study. Patients with any one of the following conditions were excluded: (I) Marfan syndrome, Ehlers-Danlos syndrome, or Turner syndrome according to the corresponding diagnostic criteria (13-15); (II) onset age of the initial symptom after the age of 50 years old; (III) iatrogenic or traumatic AD. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Committee on Ethics of Medicine of Navy Medical University (No. CHEC-Y2020-042). Written informed consent was collected from all the subjects participating in the study.

Definition

Computed tomographic angiography (CTA) was used to diagnose all cases. The factors observed included the maximum ascending and descending aortic diameter, number of arch vessels involved, visceral vessels (celiac

Highlight box

Key findings

- Gene variants in early-onset isolated TBAD patients significantly impaired the prognosis of TEVAR.

What is known and what is new?

- Aortic dissections with an age-of-onset less than <50 years old had a higher the risk of carrying variants.
- TAAD gene variants increased the risk of aortic-related adverse events after TEVAR.

What is the implication, and what should change now?

- Routine genetic testing is necessary for early-onset patients for additional risk stratification and refined management.

artery, superior mesenteric artery and renal arteries) arising from the false lumen, pleural effusion, hepatic cyst, renal cyst and other vascular abnormalities (branch arteries aneurysm and dissection).

Stanford type-B AD is intimal tearing with entry distal to the left subclavian artery and sparing of the ascending aorta. The timing of TEVAR from onset of symptoms was divided into hyperacute (<24 h), acute (1–14 days), subacute (15–90 days), and chronic (>90 days). Death from aortic rupture or death within 30 days of symptom onset, 30 days of the index procedure, or during the index hospitalization were deemed aortic-related death. Aortic-related adverse events (ARAEs) included early reintervention within 30 days of the index procedure or during the index hospitalization, complications after TEVAR such as endoleak, enlargement of the distal aorta, a SINE, retrograde dissection, new dissection, and aortic-related death. The primary endpoint was defined as all-cause death or ARAEs.

Follow up

All patients were advised to return to the hospital for follow-up on a regular basis. Follow-up was conducted by electronic medical records system or telephone at 1, 3, 6, 12 months and annually after TEVAR. The last follow-up was carried out in May 2022.

WES

Peripheral blood samples were collected from all the patients in EDTA tubes for DNA extraction. Genomic DNA was isolated with the HiBind® DNA Maxi-column according to the protocol. Total DNA concentration and quantity were assessed using a Qubit4 Fluorometer (Thermo Scientific™, Waltham, MA, USA). The Agilent SureSelect Human All Exon V6 kit (Agilent Technologies, Inc., Santa Clara, CA, USA) was used for DNA libraries construction and exome enrichment according to the manufacturer's instructions. WES was performed by the Origingene Corporation (Shanghai, China) using the Illumina HiSeq platform (Illumina, San Diego, CA, USA). Sequence reads were aligned to the human reference genome (GRCh37/hg19) by the Burrows Wheeler Aligner BWA v0.7.15 (16). Variants were called using the Genome Analysis Toolkit (GATK) and annotated by ANNOVAR (17,18). To detect copy number variations (CNVs), an analysis was carried out using the DECoN v1.0.2 program (19) with transProb of 0.0001, which is a tool for detecting variants in copy number from aligned

sequences based on the number of reads for each position. TAAD genes were carefully investigated and the reads count and normalized copy number of these genes were plotted.

Variants filtering

Intronic, synonymous, and benign variants in the ClinVar database and variants with a minor allele frequency (MAF) greater than 0.001 in the 1,000 genome and gnomAD databases were excluded. Rare Exome Variant Ensemble Learner (REVEL) score (20), Mendelian Clinically Applicable Pathogenicity (M-CAP) score (21), Sorting Intolerant From Tolerant (SIFT), MutationTaster, Combined Annotation Dependent Depletion (CADD) score, and Genomic Evolutionary Rate Profiling (GERP) were used to predict the functional impact of the variants. Variants in the exon region that conformed to the following criteria were retained: (I) CNVs, insert and deletion variants, nonsense variants, and splicing site changes; (II) missense variants with a REVEL score >0.3, M-CAP score >0.025, and meeting at least three of the following four rules (SIFT <0.1, MutationTaster = A or D, CADD score >10, GERP >2). Eleven genes explicitly associated with thoracic aortic aneurysm and dissection (TAAD) were identified as TAAD genes using the Clinical Genome Resource framework (3). Variants that met the above criteria and were involved in TAAD were considered candidate variants. The pathogenicity of candidate variants was assessed using American College of Medical Genetics and Genomics (ACMG) standards and guidelines (22).

Statistical analysis

Continuous variables were presented as mean ± standard deviation or median [interquartile range (IQR)], and categorical variables were presented as frequencies and percentages. Student's *t*-test was used to compare continuous variables with a normal distribution, while the Wilcoxon test was used to compare variables without a normal distribution. Categorical variables were compared using Fisher's exact test. The Cox proportional hazards regression model was used to screen for risk factors for ARAEs. Variables with a *P*<0.25 in the univariate analysis were included in the multivariate analysis using the backward likelihood ratio method. The event-free survival rate was analyzed using the Kaplan-Meier method, and the log-rank test was used to examine intragroup differences. A 2-tailed *P*<0.05 was considered statistically significant. All data were analyzed by SPSS 26.0 software.

Table 1 Clinical characteristics of patients with TAAD gene variants

Variable	Overall (n=37)	With variant (n=10)	Without variant (n=27)	P value
Age of onset, years	44.0 (38.0–46.0)	42.5 (39.0–46.0)	44.0 (37.5–46.5)	0.945
Male	34 (91.9)	8 (80.0)	26 (96.3)	0.172
Body mass index, kg/m ²	24.2 (23.0–25.4)	23.4 (23.0–24.6)	24.3 (23.4–25.4)	0.274
Family history	4 (10.8)	3 (30.0)	1 (3.7)	0.052
Other vascular abnormalities	11 (29.7)	6 (60.0)	5 (18.5)	0.038
Smoking history	10 (27.0)	4 (40.0)	6 (22.2)	0.407
Diabetes	1 (2.7)	0 (0.0)	1 (3.7)	1
Dyslipidemia	8 (21.6)	4 (40.0)	4 (14.8)	0.174
Hypertension	29 (78.4)	5 (50.0)	24 (88.9)	0.021
Hemorrhagic stroke	3 (8.1)	0 (0.0)	3 (11.1)	0.548
Chronic kidney disease	2 (5.4)	0 (0.0)	2 (7.4)	1
Hepatic cyst	13 (35.1)	4 (40.0)	9 (33.3)	0.716
Renal cyst	14 (37.8)	3 (30.0)	11 (40.7)	0.710
Pleural effusion	9 (24.3)	3 (30.0)	6 (22.2)	0.679
Ascending aortic diameter, mm	37.7 (35.8–39.2)	38.3 (37.4–39.2)	37.1 (35.7–39.4)	0.473
Descending aortic diameter, mm	40.1 (37.0–42.6)	42.5 (38.4–44.1)	39.3 (36.8–41.7)	0.137
Arch vessels involvement	12 (32.4)	3 (30.0)	9 (33.3)	1
Visceral vessels originating from false lumen	19 (51.4)	5 (50.0)	14 (51.9)	1
Timing of TEVAR ≤14 days	28 (75.7)	8 (80.0)	20 (74.1)	1
Number of stents ≥2	10 (27.0)	2 (20.0)	7 (25.9)	1
Endoleak	4 (10.8)	2 (20.0)	2 (7.4)	0.291
Distal enlargement	3 (8.1)	0 (0.0)	3 (11.1)	0.548
stent-induced new entry	2 (5.4)	0 (0.0)	2 (7.4)	1
New dissection	4 (10.8)	2 (20.0)	2 (7.4)	0.291
Reintervention	13 (35.1)	5 (50.0)	8 (29.6)	0.275
Mortality	5 (13.5)	4 (40.0)	1 (3.7)	0.014
In-hospital death	3 (8.1)	2 (20.0)	1 (3.7)	0.172
Aortic related death	4 (10.8)	3 (30.0)	1 (3.7)	0.052
Aortic related adverse events	15 (40.5)	6 (60.0)	9 (33.3)	0.258
Follow-up time, days	649.0 (508.0–836.0)	577.5 (487.0–880.8)	679.0 (515.5–827.0)	0.494

Values are median (25th to 75th percentile). Categorical variables were presented as n (%). TAAD, thoracic aortic aneurysm and dissection; TEVAR, thoracic endovascular aortic repair.

Results

Clinical information

A total of 37 patients younger than 50 years old, consisting of 34 men and 3 women, were enrolled in this study. The characteristics and radiological findings of all patients are

detailed in *Table 1*. After clinical examination, no additional syndrome features, such as ectopia lentis or skeletal abnormalities, were identified except for AD. The median age at onset was 44 years (IQR: 38–46). Hypertension was observed in 29 (78.4%) patients, and three patients experienced a hemorrhagic stroke before or concurrent

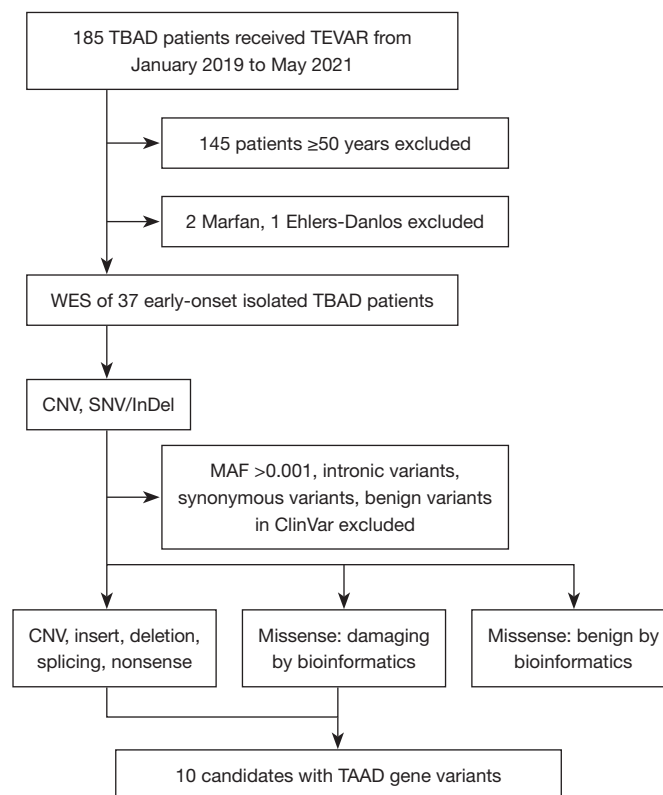


Figure 1 Flowchart of the study population and analysis flow of WES. TBAD, type B aortic dissection; TEVAR, thoracic endovascular aortic repair; WES, whole exome sequencing; CNV, copy number variation; SNV, single nucleotide variant; InDel, insert and deletion variant; MAF, minor allele frequency; TAAD, thoracic aortic aneurysm and dissection.

with the onset of AD. Thirteen (35.1%) patients had hepatic cysts, and 14 (37.8%) had renal cysts. The median maximum diameter of the ascending and descending aorta was 37.7 and 40.1 mm, respectively. More than half of the cases underwent TEVAR during the acute phase. A total of 55 grafts, including covered and bare stents, were implanted in all the patients.

Sequencing analysis

A pipeline was designed to identify candidate genes and variants, as presented in *Figure 1*. The average depth of WES data for these samples reached $\times 105.7$. The average coverage of the targeted exons (>10 reads) was 96.2%, and coverage (>20 reads) reached 94.7%. The minimum coverage depth threshold for variant calling was set to $\times 20$. Variants with a >250 quality score and $0.3 >$ allele fraction were considered for downstream analysis to improve the reliability of variation identification (23,24). Ten TAAD gene variants were filtered out from the ten patients (*Figure 2A*).

There were five single nucleotide variants (SNV), one stop-gain variant, one non-frameshift deletion, two CNV duplications, and one CNV deletion (*Figures 2B-2D*). Three variants were identified as pathogenic or likely pathogenic, of which FBN1 p.N1893S was previously reported in the ClinVar database, and others (COL3A1 p.G660V, TGFBR1 p.W458X) were novel. According to the ACMG standards and guidelines, COL3A1 p.G660V and TGFBR1 p.W458X variants should be classified as likely pathogenic and pathogenic based on the evidence of PM2 + PM5 + PM6 + PP3 and PVS1 + PM2 + PP3 + PP4, respectively. The details of the variants in all the patients are listed in *Table 2*.

Genotype and phenotype

A total of 37 patients were divided into two groups based on whether they carried the variants (*Table 1*). The median age of onset was comparable across cases with and without variants (42.5 *vs.* 44.0, $P=0.587$). Three patients with and one without TAAD gene variants had a family history. Variants

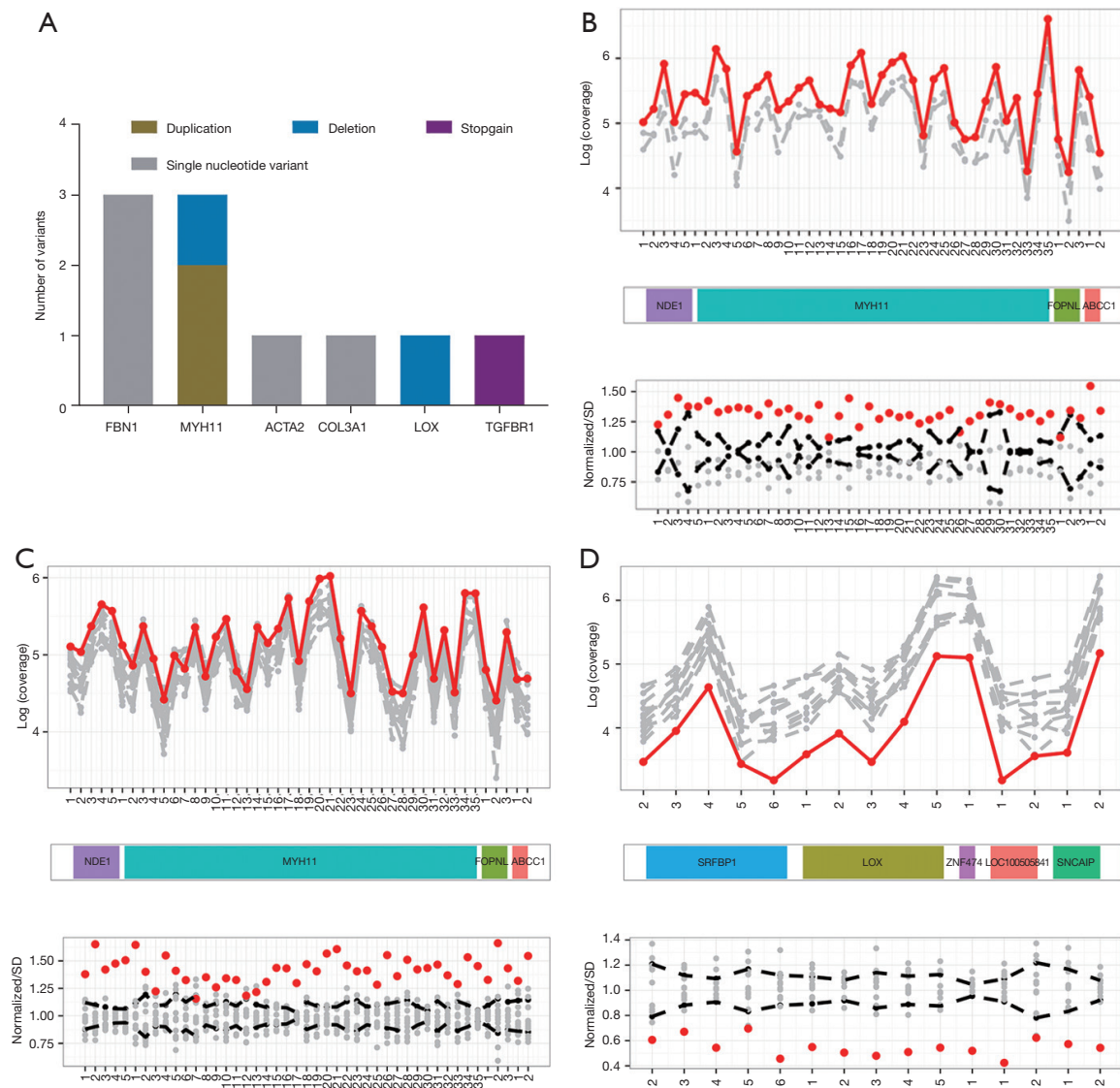


Figure 2 Distribution of candidate variants in TAAD genes and automated visualization of copy number variants from DECoN. (A) Different variant types are shown in different colors. (B,C) MYH11 gene; multi-exon duplication. (D) LOX gene; multi-exon deletion. The top plot shows the log-normalised coverage of the sample of interest (red) relative to reference samples (grey) and the bottom plot shows the ratio of observed to expected coverage with a 95% confidence interval in black. SD, standard deviation; TAAD, thoracic aortic aneurysm and dissection.

segregated by the phenotypes of families with TAAD gene variants. Hypertension was substantially less prevalent in mutant cases (50.0% *vs.* 88.9%, $P=0.021$). Conversely, other vascular abnormalities, such as branch artery aneurysms and dissection, were more common in mutant cases (60.0% *vs.* 18.5%, $P=0.038$). Additionally, patients with variants appeared to have a slightly larger median maximum diameter of the ascending and descending aorta (38.3 *vs.*

37.1 mm, $P=0.473$ and 42.5 *vs.* 39.3 mm, $P=0.137$), but not significantly.

TAAD genes variants and clinical outcomes

After a median follow-up of 649 days (508 to 836 days), 13 (35.1%) patients underwent reintervention. Five deaths occurred postoperatively, four from aortic rupture and one

Table 2 Summary of the genetic details of patients with TAAD gene variants

ID	Gender	Age	Gene	Variant	Type	gnomAD	ACMG	REVEL	M-CAP	SIFT	MutationTaster	CADD	GERP
1	F	40	<i>FBN1</i>	c.7636G>A;p.G2546R	SNV	0	VUS	0.949	0.968	D	D	35	6.02
2	M	37	<i>FBN1</i>	c.5678A>G;p.N1893S	SNV	0	LP	0.620	0.154	D	D	25.2	6.17
3	F	46	<i>FBN1</i>	c.5678A>G;p.N1893S	SNV	0	LP	0.620	0.154	D	D	25.2	6.17
4	M	21	<i>MYH11</i>	c.3766_3768del;p.K1256del	deletion	0.00004885	VUS	-	-	-	-	-	-
5	M	47	<i>MYH11</i>	chr16:15125593-16308306	CNV.dup	-	VUS	-	-	-	-	-	-
6	M	39	<i>MYH11</i>	chr16:14951075-16315688	CNV.dup	-	VUS	-	-	-	-	-	-
7	M	46	<i>ACTA2</i>	c.460G>A;p.V154M	SNV	0.000004068	VUS	0.912	0.711	D	D	20.6	5.98
8	M	45	<i>COL3A1</i>	c.1979G>T;p.G660V	SNV	0	LP	0.993	0.968	D	D	16.83	5.93
9	M	49	<i>LOX</i>	chr5:121187660-121788690	CNV.del	-	VUS	-	-	-	-	-	-
10	M	39	<i>TGFBR1</i>	c.1373G>A;p.W458X	stopgain	0	P	-	-	-	D	38	5.93

TAAD, thoracic aortic aneurysm and dissection; ACMG, American College of Medical Genetics and Genomics; REVEL, Rare Exome Variant Ensemble Learner; M-CAP, Mendelian Clinically Applicable Pathogenicity; SIFT, Sorting Intolerant From Tolerant; CADD, Combined Annotation Dependent Depletion; GERP, Genomic Evolutionary Rate Profiling; F, female; SNV, single nucleotide variant; VUS, variants of unknown significance; D, deleterious; M, male; LP, likely pathogenic; CNV.dup, copy number variation duplication; CNV.del, copy number variation deletion; P, pathogenic.

from a major stroke following the third intervention. All-cause and aortic-related mortality were higher in patients with variants than those without variants (40.0% *vs.* 3.7%, $P=0.014$ and 30.0% *vs.* 3.7%, $P=0.052$). A total of 15 patients suffered 19 ARAEs, including reintervention in hospital ($n=2$, 10.5%), endoleak ($n=4$, 21%), enlargement of distal aorta ($n=3$, 16%), SINE ($n=2$, 10.5%), new dissection ($n=4$, 21%), and aortic-related death ($n=4$, 21%).

Furthermore, clinical characteristics and genetic status were compared between groups with and without ARAEs. There were no significant differences between the two groups regarding the follow-up time, basic status, or surgical situation (*Table 3*). The proportion of patients with variants in the ARAEs group was likely to be higher but not significantly higher than that in the non-ARAE group (40.0% *vs.* 18.2%, $P=0.258$). The univariate and multivariate Cox hazard regression analyses of ARAEs are illustrated in *Table 4*. Variables that carry TAAD genes variants, structure variants, number of stents ≥ 2 , and onset age were revealed by univariate analysis with $P<0.25$. Multivariate analysis carrying TAAD gene variants [hazard ratio (HR) =4.00; 95% confidence interval (CI): 1.26–12.74; $P=0.019$] was confirmed as the only risk factor for ARAEs.

Kaplan-Meier curves of event-free survival rates based on genetic status were analyzed. As displayed in *Figure 3*, the event-free survival rate of patients with TAAD variants was significantly lower ($P=0.037$).

Discussion

In this study, 37 iTBAD patients with an onset age of less than 50 years were enrolled and treated with TEVAR. WES was performed to identify disease-causing variants. Ten (27.0%) patients were identified to have TAAD gene variants. Based on the ACMG guidelines, two novel pathogenic/likely pathogenic variants: *TGFBR1* p.W458X and *COL3A1* p.G660V were identified. Individuals with variants were more likely to have other vascular abnormalities and less likely to have hypertension. During the follow-up period, 15 patients developed 19 ARAEs. After multivariate Cox hazard regression analysis and Kaplan-Meier curve analysis, mutant patients were found to have four times the risk of ARAEs and a much lower event-free survival rate.

Previous studies have demonstrated that TAAD gene variants may decrease the age of onset, which is supported

Table 3 Clinical and genetic features of patients with ARAEs

Variable	ARAE (n=15)	Non-ARAE (n=22)	P value
Follow-up time, days	679.0 (517.5–846.5)	630.0 (508.0–812.2)	0.841
Age of onset, years	41.0 (38.0–45.0)	45.0 (39.2–47.0)	0.136
Male	14 (93.3)	20 (90.9)	1
Body mass index, kg/m ²	24.2 (23.4–25.0)	24.0 (23.0–25.2)	0.769
Family history	1 (6.7)	3 (13.6)	0.633
Other vascular abnormalities	5 (33.3)	6 (27.3)	0.728
Smoking history	3 (20.0)	7 (31.8)	0.481
Diabetes	0 (0.0)	1 (4.5)	1
Dyslipidemia	3 (20.0)	5 (22.7)	1
Hypertension	12 (80.0)	17 (77.3)	1
Hemorrhagic stroke	1 (6.7)	2 (9.1)	1
Chronic kidney disease	0 (0.0)	2 (9.1)	0.505
Hepatic cyst	5 (33.3)	8 (36.4)	1
Renal cyst	7 (46.7)	7 (31.8)	0.493
Pleural effusion	3 (20.0)	6 (27.3)	0.711
Ascending aortic diameter, mm	38.0 (36.0–39.6)	37.7 (35.9–38.8)	0.951
Descending aortic diameter, mm	41.3 (37.7–43.0)	39.1 (37.1–42.3)	0.448
Arch vessels involvement	6 (40.0)	6 (27.3)	0.488
Visceral vessels originating from false lumen	6 (40.0)	13 (59.1)	0.325
Timing of TEVAR ≤14 days	13 (86.7)	15 (68.2)	0.262
Number of stents ≥2	6 (40.0)	4 (18.2)	0.258
With variant	6 (40.0)	4 (18.2)	0.258
With LP/P variant	2 (13.3)	2 (9.1)	1
With structure variant	3 (20.0)	2 (9.1)	0.377

Values are median (25th to 75th percentile). Categorical variables were presented as n (%). ARAEs, aortic related adverse events; TEVAR, thoracic endovascular aortic repair; LP, likely pathogenic; P, pathogenic.

Table 4 Univariable and multivariable Cox regression analysis for ARAEs

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
With variant	2.88 (1.02–8.19)	0.047	4.00 (1.26–12.74)	0.019
Structure variant	2.17 (0.60–7.76)	0.235		
Number of stents ≥2	1.97 (0.62–5.79)	0.216	3.00 (0.91–9.86)	0.071
Age of onset	0.94 (0.88–1.01)	0.112		

ARAEs, aortic related adverse events; HR, hazard ratio; CI, confidence interval.

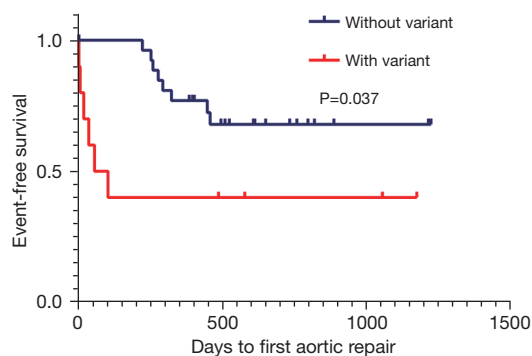


Figure 3 Kaplan-Meier survival analysis of ARAEs for patients with or without TAAD gene variants after TEVAR. The differences between two groups was assessed with log-rank test. The freedom from ARAEs in patients without variant was significantly higher than patients with variant. ARAEs, aortic-related adverse events; TAAD, thoracic aortic aneurysm and dissection; TEVAR, thoracic endovascular aortic repair.

by the fact that patients younger than 50 years have a significantly increased risk of carrying pathogenic variants (6,25). This study enrolled patients at this age threshold and found that the proportion of cases with variants was higher than that in other studies without age limitations, both for pathogenic variants and variants of unknown significance (VUS) (26). This demonstrates the impact of genetic mutations on the age of onset and emphasizes the importance of genetic testing in younger patients, which may be helpful for the early screening of family members and future precision gene therapy. In addition, routine variant-calling analysis by WES is suitable for detecting variants of short reads but not for variants of reads longer than 1 kb, such as CNVs. However, recurrent duplications of MYH11 have been reported in patients with AD and congenital heart malformation (27,28). Here, CNVs of MYH11 duplication and LOX deletion were identified from three patients' causal variants by DECoN v1.0.2 program, indicating that CNV cannot be ignored when detecting the disease-causing genes of AD.

Variants were classified into pathogenic/likely pathogenic, VUS, and benign/likely benign, according to ACMG guidelines. FBN1 p.N1893S variant was detected in 2 isolated AD patients without ectopia lentis or skeletal deformity from the same family, but it had been reported in patients with Marfan syndrome. This inconsistency suggests that factors other than FBN1 mutations affect disease phenotypes such as epigenetics. Two novel pathogenic/

likely pathogenic variants were identified, TGFBR1 p.W458X and COL3A1 p.G660V, which extended the spectrum of mutations. Although identifying pathogenic variants is meaningful for isolated aortic aneurysms or sporadic AD owing to the severity of the phenotypes (29,30), we believe that VUSs filtered by scientific methods are also of profound significance. This study detected 4 pathogenic/likely pathogenic variants and 6 VUSs. A combination of all variants influenced the TBAD phenotype, sustained by the fact that individuals with variants had more abnormalities in branch vessels and less history of hypertension. Furthermore, we found that TAAD variants increased the risk of ARAEs after TEVAR. Patients with the variants had significantly lower event-free survival rates during the follow-up period. This study not only revealed that TAAD genes play an important role in the pathogenesis, clinical features, and prognosis of early-onset iTBAD but also provided a new idea and method for early warning of ARAEs after TEVAR.

Limitations

One of the limitations of the study was that we did not consider all morphological features and process-related factors while analyzing the risk factors of ARAEs. Another limitation was the small sample size. Due to the low frequency and rarity of AD, mainly consisting of Stanford type A and elderly patients, only 37 samples were included when limiting the iTBAD patients of age younger than 50. Despite these limitations, our study included significant variables such as aortic diameter, visceral vessels originating from false lumen and the number of stents into the analysis, and met the principle of events per independent variable ≥ 10 in proportional hazards regression analysis (31), making the results of the study credible. Although our findings required further validation in a large sample size, we believe that genetic test in early-onset iTBAD is useful for identifying patients with high risk of adverse events.

Conclusions

This study found a high proportion of TAAD gene variants in patients with early-onset iTBAD, highlighting the need for genetic testing in these cases. Detecting TAAD gene variants can help identify patients at high risk of aortic related adverse events after TEVAR, contributing to additional risk stratification and refined management.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-1529/rc>

Data Sharing Statement: Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-1529/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-1529/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Committee on Ethics of Medicine of Navy Medical University (No. CHEC-Y2020-042). Written informed consent was collected from all the subjects participating in the study.

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