Received: 2 November 2020 | Revised: 8 May 2021 | Accepted: 24 August 2021

DOI: 10.1002/mgg3.1800

Molecular Genetics & Genomic Medicine Open Access WILEY

ORIGINAL ARTICLE

Genetic testing and clinical relevance of patients with thoracic aortic aneurysm and dissection in northwestern China

Jinjie Li[1] | **Liu Yang**[1] | **Yanjun Diao**[1] | **Lei Zhou**[1] | **Yijuan Xin**[1] | **Liqing Jiang**[2] | **Rui Li**[1] | **Juan Wang**[1] | **Weixun Duan**[2] | **Jiayun Liu**[1]

[1]Department of Laboratory Medicine, Xijing Hospital, Fourth Military Medical University, Xi'an, China

[2]Department of Cardiovascular Surgery, Xijing Hospital, Fourth Military Medical University, Xi'an, China

Correspondence
Liu Jiayun, Department of Laboratory Medicine, Xijing Hospital, Fourth Military Medical University, Xi'an, China.
Email: jiayun@fmmu.edu.cn

Duan Weixun, Department of Cardiovascular Surgery, Xijing Hospital, Fourth Military Medical University, Xi'an, China.
Email: duanweixun@126.com

Abstract

Background: Thoracic aortic aneurysm and dissection (TAAD) is a life-threatening pathology that remains a challenge worldwide. Up to 40% of TAAD cases are hereditary with complex heterogeneous genetic backgrounds. The purposes of this study were to determine the diagnostic rate of patients with TAAD, investigate the molecular pathologic spectrum of TAAD by next-generation sequencing (NGS), and explore the future preclinical prospects of genetic diagnosis in patients at high -risk of study.

Methods: NGS was used to screen 15 genes associated with genetic TAAD in 212 patients from northwestern China. Clinical data of patients were gathered by electrocardiography, transthoracic echocardiography, and computed tomography.

Results: Of the 212 patients, 67 (31.60%) tested positive for a (likely) pathogenic variant, 42 (19.81%) had a variant of uncertain significance (VUS), and 103 (48.58%) had no variant (likely benign/benign/negative). A total of 135 reportable variants were detected in our test, among which 77 (57.04%) are first reported in this paper. A genotype–phenotype correlation of *FBN1* was assessed, and the data showed that the patients with truncating and splicing mutations are more prone to developing severe aortic dissection than those with missense mutations, especially frameshift mutations (82.76% vs. 42.86%). In this study, 43 (20.28%) patients had a family history of sudden death or TAAD, whereas 132 (62.26%) did not (the remaining 37 were not available), and the positive rate of genetic testing was higher in TAAD patients with family history than in those without (76.74% vs. 18.94%).

Conclusion: Our study concludes that genetic variation is an important consideration in the risk stratification of individualized prediction and disease diagnosis.

KEYWORDS

ACTA2, *FBN1*, genetic testing, Marfan syndrome, TAAD

Jinjie Li and Liu Yang contributed equally to this work.

1 | INTRODUCTION

Thoracic aortic aneurysm and dissection (TAAD) is one of the most common causes of sudden death today (Meszaros et al., 2000). According to data from the US Centers for Disease Control and Prevention, aortic rupture/dissection is the 19th leading cause of death among residents (43,000–47,000 deaths/year) (Hoyert et al., 2001). Patients with aortic aneurysms usually do not have any symptoms until they are diagnosed with aortic rupture/dissection, which makes the early diagnosis of aortic aneurysms difficult (Kuzmik et al., 2012; Nienaber & Clough, 2015). If high-risk patients are detected, and interventions are carried out in a timely manner, mortality can be greatly reduced (Huynh & Starr, 2013). Genetic variants can lead to the occurrence of aortic disease, thus providing feasibility for the early diagnosis and family screening of patients with aortic aneurysms (Jondeau et al., 2016; Regalado et al., 2015). If the individual is known to have a genetic predisposition to TAAD, treatment can be initiated as early as possible to prevent the risk of death from an aortic aneurysm or dissection. Studies have found that approximately 20%–40% of patients with TAAD syndrome have a family history, suggesting that a large portion of the disease is caused by genetic factors (Albornoz et al., 2006; Biddinger et al., 1997). A previous analysis of families with TAAD-affected individuals found that the disease mainly follows the autosomal dominant inheritance pattern, with incomplete penetrance, suggesting that single-gene variants are very likely to be the genetic causes of the disease. The clinical phenotype of TAAD is highly variable, not only in the age of onset and aortic lesions but also in other cardiovascular diseases, such as congenital heart disease (congenital aortic stenosis and patent ductus arteriosus), and other vascular diseases (intracranial aneurysms, coronary heart disease, and cerebrovascular obstructive diseases) (Erbel et al., 2014; Moll et al., 2011). The diversity of clinical manifestations of TAAD suggests that there may be multiple causative genes, and this view has been confirmed through the identification of various pathogenic gene variants in TAAD patients (Renard et al., 2018). Although some other genotype–phenotype studies have been performed in TAAD, the full spectrum of gene variants and the exact correlations to phenotype are still subject to debate (Gago-Diaz et al., 2017). A deeper understanding of the relation between genotype and phenotype can aid in clinical diagnosis. The objective of our study was, therefore, to summarize the different genetic variants and establish a genotype–phenotype correlation in a broad population of TAAD patients, with a particular focus on *FBN1* (OMIM 134797) and aortic events.

2 | METHODS

2.1 | Participants

The current study was approved by the ethics committee of Xijing Hospital and adhered to the Declaration of Helsinki. All experimental protocols were approved by the ethics committee of Xijing Hospital and were carried out in accordance with the approved guidelines. Each individual undergoing the genetic test was adequately informed regarding the benefits and risks of the test and signed the consent form.

Between August 2017 and September 2019, we tested a total of 212 patients with various aortic phenotypes, such as early onset aortopathy patients with no apparent secondary causes and patients suspected of having Marfan syndrome. Electrocardiography, transthoracic echocardiography, and computed tomography were the main methods used to examine the aorta and heart. The follow-up study was carried out in subsequent clinic visits to the outpatient department and by telephone interviews.

2.2 | Next-generation sequencing

The gene panel we used contains 15 genes known to be associated with Marfan syndrome and its related aortic diseases and has been described previously described (Yang et al., 2016). The 15 genes are *FBN1*, *TGFBR1* (OMIM 190181), *TGFBR 2* (OMIM 190182), *SMAD3* (OMIM 603109), *SMAD4* (OMIM 600993), *TGFB2* (OMIM 190220), *COL3A1* (OMIM 120180), *SLC2A10* (OMIM 606145), *MYH11* (OMIM 160745), *ACTA2* (OMIM 102620), *NOTCH1* (OMIM 190198), *MYLK* (OMIM 600922), *PRKG1* (OMIM 176894), *FBN2* (OMIM 612570), and *SKI* (OMIM 164780). Genomic DNA was extracted from ethylene diamine tetraacetic acid (EDTA)-anticoagulated whole blood and checked to ensure DNA quality and quantity before processing. Library preparation was performed according to the manufacturer's instructions (Ion AmpliSeq™ library kit 2.0, Life Technologies, Inc.). Pooled libraries (up to 12–15 samples per chip) were sequenced on an Ion 318TM Chip on a Life PGM™ Instrument. Suspected pathogenic variants and VUSs were confirmed using Sanger sequencing. Exons in *FBN1* with low (<20X) or no coverage were also subjected to Sanger sequencing to obtain 100% coverage.

2.3 | Familial screening

If findings showed a pathogenic genetic variant, first-degree relatives began a screening process consisting of

TABLE 1 Comparison of clinical characteristics in patients with (likely) pathogenic mutation and with no suspicious mutation

		(Likely) Pathogenic mutation (n = 67)	No suspicious mutation (n = 103)	*p*
Female sex, n (%)		19 (28.36%)	20 (19.41%)	0.175
Average age, n (%)		**31.60 ± 9.74 (y)**	**39.03 ± 10.35 (y)**	**<0.001**
Average height (Male/Female)		**180.42 ± 14.85/173.40 ± 8.72 (cm)**	**176.15 ± 6.68/164.87 ± 6.03 (cm)**	**<0.001/0.005**
Hypertension, n (%)		**9 (13.43%)**	**42 (40.78%)**	**<0.001**
Aortic dissection, n (%)		46 (68.66%)	72 (69.90%)	0.863
Aortic aneurysm	Aortic root, n (%)	**48 (71.64%)**	**48 (46.60%)**	**0.001**
	Ascending aortic, n (%)	34 (50.75%)	55 (53.40%)	0.735
Co-occurrence of aneurysms and dissections		**42 (62.69%)**	**47 (45.63%)**	**0.030**
Valvular disease, n (%)		33 (49.25%)	41 (39.80%)	0.225
Family history, n (%)		**33 (49.25%)**	**3 (2.91%)**	**<0.001**
Ectopia lentis, n (%)		**14 (20.90%)**	**4 (3.88%)**	**0.001**

an exhaustive physical examination, transthoracic echocardiography, and genetic testing to screen for the same variant that was found in the index case.

2.4 | Variant filter criteria

Nonsynonymous variants with a rare allele frequency <0.1% with the absence of variant alleles either in the 1000 Genomes Project database, the NCBI dbSNP database, the 5000 Exomes database, or in our reference samples (GRCh37/HG19) were taken for further analysis. Variants were categorized according to the American College of Medical Genetics (ACMG) (Richards et al., 2015). Specifically, the analysis was based on the following criteria: (a) whether they were previously reported in a functional study or in a family segregation study, (b) the nature of the variant (e.g., nonsense, frameshift indel, or splicing mutation [intron ±1 or ±2]), (c) variant frequency in the 1000 Genomes Project database or in the Exome Sequencing Project (ESP6500) and ExAC03, (d) conservation of the altered residue, (e) in silico-based computational prediction (SIFT, PolyPhen-2, or Mutation-Taster), (f) de novo occurrence, and (g) family segregation studies. Based on this information, a variant was classified into one of the five following categories: benign, likely benign, unknown significance, likely pathogenic, or pathogenic.

2.5 | Statistical analysis

Qualitative variables are expressed as percentages and relationship contrasts were analyzed using the χ^2 test or, failing that, the Fischer test. Quantitative variables expressed as mean ± standard deviation was analyzed using Student's *t*-test for variables that followed a normal distribution and the Mann–Whitney *U* test for those that did not. All statistical analyses were conducted using SPSS v21.

3 | RESULTS

3.1 | Clinical characteristics

A total of 212 patients with suspected genetic TAAD were enrolled in our cohort. The age of the patients ranged from 3.5 to 69 years, and their age at diagnosis was 38.14 ± 11.33 years. Among them, 166 patients were male (78.30%), and 46 patients were female (21.70%). The mean age of men and women was 38.11 ± 11.62 years and 38.22 ± 10.56 years. Forty-three (20.28%) patients had a family history of sudden death or TAAD. The mean age of them was 36.48 ± 9.32 years old. Furthermore, the mean age of 132 (62.26%) individuals with negative family history was 39.52 ± 12.44 years. The family history of the remaining 37 patients was not available. Of the 43 patients with a family history, 33 (76.74%) were identified with (likely) pathogenic variants. However, only 25 (18.93%) among 132 individuals had a negative family history.

Of the 212 patients, 67 (31.60%) tested positive for a (likely) pathogenic variant, 42 (19.81%) had a VUS, and 103 (48.58%) had no variant (likely benign/benign/negative) according to the 15-gene panel (mentioned in METHODS). Since a VUS should not be considered disease-causing, the clinical characteristics of patients with (likely) pathogenic variants were compared with

those of patients with no variant (summarized in Table 1). Patients carrying causative variant with an average age of 31.60 ± 9.74 years were younger than those carrying no significant variant, with an average age of 39.03 ± 10.35 years ($p < 0.001$). The average height of the patients with (likely) pathogenic variants was higher than that of the patients with no variant, both for males (180.42 ± 14.85/173.40 ± 8.72 cm, $p < 0.05$) and females (176.15 ± 6.65/164.87 ± 6.03 cm, $p < 0.05$). A family history was more frequent in patients with (likely) pathogenic variant (49.25% vs. 2.91%, $p < 0.05$). In our cohort, 19 individuals had ectopia lentis, and one had lost his sight. Of these 19 individuals, 14 carried likely pathogenic/pathogenic variants, 1 had a detected VUS, and 4 had no variant. Regarding cardiovascular issues, hypertension was more commonly found in patients with no variant (40.78% vs. 13.43%, $p < 0.05$), and the incidence of aortic root aneurysms was higher in patients with (likely) pathogenic variants than in patients with no variant (71.64% vs. 46.60%, $p < 0.05$). However, the differences in aortic dissection, ascending aortic aneurysm, and valvular disease were not significant between the two groups (68.66% vs. 69.90%, $p = 0.863$; 50.75% vs. 53.40%, $p = 0.735$; and 49.25% vs. 39.80%, $p = 0.225$, respectively). According to these data, there is a co-occurrence of an aortic aneurysm and dissection in both groups; these events occurred 42 times in patients with (likely) pathogenic variant and 47 times in patients with no variant, and the differences were significant (62.69% vs. 45.63%, $p < 0.05$).

3.2 | Genetic characteristics

The gene panel sequencing of 212 TAAD patients revealed 135 reportable variants in 109 patients. According to ACMG/AMP guidelines for variant classification, 67 (49.63%) were classified as (likely) pathogenic variants (Table 2), and 68 (50.37%) were classified as VUSs (Table S1). Several patients carried more than one pathogenic variant (PV), likely pathogenic variants (LPV), and/or VUS, which explains the difference between the number of variants and the number of patients with reportable variants. Twenty-three individuals with more than one PV, LPV, or VUS are listed in Table S2. (Likely) PV were identified in *FBN1*, *ACTA2*, *MYH11*, *TGFBR1*, *TGFB2*, and *COL3A1*, and VUSs were identified in 14 genes in the panel (all except for *SKI*) (Figure 1). Most (58/67) of the (Likely) PV occurred in the *FBN1* gene because the cysteine residues in this gene are evolutionarily conserved and have essential functions. Thus, disruption or production of a cysteine residue indicates that the variant is probably pathogenic.

Fifty-two of the 135 reportable variants (38.52%) have been reported in the ClinVar, HGMD, or UMD (http://www.umd.be/FBN1/) database, and 77 (57.04%) were first reported in our paper. At least 47 of the 109 patients' parents accepted genetic testing by Sanger sequencing for the variant identified in their child. Twenty-nine (61.70%) individuals inherited the variants from their parents, and the other 18 (38.30%) individuals had de novo variants, indicating that neither parent carried the same variant as the proband.

3.3 | Genotype–phenotype correlation of *FBN1*

Of all the 212 probands, 58 tested positive for a (likely) pathogenic *FBN1* variant. We investigated the correlation between the *FBN1* variant type and aortic events, and the results are shown in Table 3. Most patients showed more than one cardiovascular manifestation. Thirty-seven patients had a life-threatening aortic dissection, 46 had an aortic aneurysm, and 32 had severe valvular disease (including bicuspid aortic valve and mitral valve prolapse), and these patients underwent an appropriate vascular surgery. In addition, five patients had mild aortic dilation or only skeletal manifestations at a very young age (13.50 years); therefore, attention to aortic progression should be paid in future. The truncating and splicing mutations tended to result in more serious aortic dissection than missense mutations according to the data (82.76% [24/29] vs. 42.86% [12/28]). Moreover, patients with *FBN1* frameshift mutations experienced aortic dissection at an earlier age than those with missense mutations (32.0 years vs. 35.1 years). In addition, one unique deletion in *FBN1* (c.5796_5798delTCA, p. Ser1933del) was detected in a young male who had undergone surgery due to life-threatening aortic dissection when he was only 19 years old.

3.4 | Family analysis and variant reclassification

Family segregation studies can provide strong evidence for variation classification; hence, they should be performed when available. Eleven variants were reclassified through family segregation. The variants were downgraded to likely benign because their healthy family members also carried the variant, the variant details are shown in Table 4.

Notably, a novel variant *ACTA2* (c.583delC, p. Leu195Term) was found on our screen. The variant was first detected in the proband (II1) of a family affected by TAAD (Figure 2). The patient's two younger sisters and

TABLE 2 (Likely) Pathogenic mutations in our cohort

Sample ID	Gene	Transcript	Exon/Intron	Nucleotide change	Protein change	Mutation type	De novo	Pathogenicity	Report Ref (PMID)	ACMG Criteria
AD1	*FBN1*	NM_000138	exon12	c.1377_1378del	p. Leu459fs	Frameshift	NA	Pathogenic	19012347	PVS1+PM2+PS4_ Supporting
AD5	*FBN1*	NM_000138	intron52	c.6380-1G>A	splicing	Splicing	NA	Pathogenic	This paper	PVS1+PM2+PP4
AD6	*FBN1*	NM_000138	intron3	c.247+1G>A	splicing	Splicing	NA	Pathogenic	8406497	PVS1+PM2+PS4_ Supporting
AD13	*ACTA2*	NM_001141945	exon5	c.445C>T	p. Arg149Cys	Missense	NA	Likely Pathogenic	17994018	PS4+PM1+PM2+PP3
AD20	*FBN1*	NM_000138	intron47	c.5918-3G>T	splicing	Splicing	NA	Pathogenic	This paper	PVS1+PM2+ PP4
AD21	*FBN1*	NM_000138	exon58	c.7039_7040del	p. Met2347fs	Frameshift	NA	Pathogenic	11826022	PVS1+PM2+PM6
AD32	*FBN1*	NM_000138	exon24	c.2827_2828del	p. Leu943fs	Frameshift	NA	Pathogenic	This paper	PVS1+PM2+ PP4
AD38	*FBN1*	NM_000138	exon45	c.5435G>T	p. Cys1812Phe	Missense	Inherited from father	Likely Pathogenic	This paper	PS1+PM1+PM2+PP3
AD41	*FBN1*	NM_000138	exon40	c.4930C>T	p. Arg1644Ter	Stop gain	De novo	Pathogenic	12068374	PVS1+PS2+PM2
AD42	*FBN1*	NM_000138	exon14	c.1646_1647del	p. Thr549fs	Frameshift	NA	Pathogenic	25652356	PVS1+PM2+PS4_ Supporting
AD43	*FBN1*	NM_000138	exon10	c.1093T>C	p. Cys365Arg	Missense	NA	Likely Pathogenic	17657824	PS1+PM1+PM2+PP3
AD45	*FBN1*	NM_000138	exon61	c.7489delC	p. Gln2497fs	Frameshift	Inherited from mother	Pathogenic	This paper	PVS1+PM2+PP4
AD46	*FBN1*	NM_000138	exon10	c.1090C>T	p. Arg364Ter	Stop gain	NA	Pathogenic	12938084	PVS1+PM2+PS4_ Supporting
AD47	*FBN1*	NM_000138	exon65	c.8059_8060del	p. Val2687fs	Frameshift	NA	Pathogenic	This paper	PVS1+PM2+PS4_ Supporting
AD48	*FBN1*	NM_000138	exon48	c.5796_5798del	p.1932_1933del	Deletion	De novo	Likely Pathogenic	This paper	PS2+PM2+PM4
AD49	*FBN1*	NM_000138	exon25	c.3001dupA	p. Thr1001fs	Frameshift	NA	Likely Pathogenic	This paper	PVS1+PM2+
AD50	*FBN1*	NM_000138	exon41	c.4977delT	p. Gly1659fs	Frameshift	Inherited from mother	Pathogenic	This paper	PVS1+PM2+PP1
AD54	*FBN1*	NM_000138	exon56	c.6755_6756del	p. Glu2252fs	Frameshift	NA	Pathogenic	This paper	PVS1+PM2+PP4
AD63	*ACTA2*	NM_001141945	exon5	c.445C>T	p. Arg149Cys	Missense	NA	Pathogenic	17994018	PS3+PS4_ _Moderate +PM2+PP3+PP1
AD70	*ACTA2*	NM_001141945	exon2	c.115C>T	p. Arg39Cys	Missense	NA	Pathogenic	21248741	PS3+PS4_ _Moderate +PM2+PP3+PP1

(Continues)

TABLE 2 (Continued)

Sample ID	Gene	Transcript	Exon/Intron	Nucleotide change	Protein change	Mutation type	De novo	Pathogenicity	Report Ref (PMID)	ACMG Criteria
AD71	*FBN1*	NM_000138	exon35	c.4244G>A	p. Cys1415Tyr	Missense	De novo	Likely Pathogenic	Case record	PS2+PM1+PM2
AD72	*FBN1*	NM_000138	exon63	c.7754T>C	p. Ile2585Thr	Missense	De novo	Likely Pathogenic	10464652	PS2+PM1+PM2
AD76	*TGFB2*	NM_001135599	exon1	c.1A>G	p. Met1Val	Missense	NA	Pathogenic	27906200	PVS1+PS1+PM2
AD79	*FBN1*	NM_000138	intron47	c.5788+5G>A	Splicing	Splicing	NA	Pathogenic	7611299	PVS1+PS1+PM2
AD83	*FBN1*	NM_000138	exon45	c.5503T>G	p. Cys1835Gly	Missense	Inherited from father	Likely Pathogenic	28941062	PS1+PM1+PM2+PP3
AD84	*FBN1*	NM_000138	exon46	c.5627G>A	p. Cys1876Tyr	Missense	De novo	Pathogenic	16222657	PS2+PM1+PM2+PP3+PS4_ Supporting
AD86	*FBN1*	NM_000138	exon29	c.3555delC	p. Gly1185fs	Frameshift	NA	Pathogenic	This paper	PVS1+PM2+PM6
AD87	*FBN1*	NM_000138	exon22	c.2623T>C	p. Cys875Arg	Missense	Inherited from mother	Pathogenic	12938084	PS3+PM1+PM2+PP3+PP4
AD92	*FBN1*	NM_000138	exon4	c.284C>A	p. Ser95Ter	Stop gain	NA	Pathogenic	Case record	PVS1+PM2+PP1
AD102	*FBN1*	NM_000138	exon2	c.164G>A	p. Gly55Glu	Missense	De novo	Likely Pathogenic	22772377	PS2 +PM2+PP3
AD104	*FBN1*	NM_000138	exon59	c.7238G>A	p. Cys2413Tyr	Missense	De novo	Likely Pathogenic	31098894	PM1+PM2+PM6+PP3
AD112	*FBN1*	NM_000138	exon22	c.2638G>A	p. Gly880Ser	Missense	De novo	Likely Pathogenic	12402346	PM2+PM6+PS4_ Moderate+PP3_
AD113	*FBN1*	NM_000138	exon25	c.2953G>A	p. Gly985Arg	Missense	NA	Likely Pathogenic	11700157	PM2+PP1_Moderate+PS4_ Supporting+PP3
AD114	*FBN1*	NM_000138	exon45	c.5452T>A	p. Cys1818Ser	Missense	NA	Likely Pathogenic	This paper	PM1+PM2+PP3+PP1
AD116	*FBN1*	NM_000138	exon42	c.5162G>A	p. Cys1721Tyr	Missense	NA	Likely Pathogenic	9399842	PM1+PM2+PP3+PP1
AD120	*FBN1*	NM_000138	exon15	c.1735_1739del	p. Arg579fs	Frameshift	Inherited from mother	Pathogenic	This paper	PVS1+PM2+PP4
AD122	*FBN1*	NM_000138	exon7	c.557G>A	p. Cys186Tyr	Missense	Inherited from father	Likely Pathogenic	31098894	PM1+PM2+PP1+PP3
AD123	*FBN1*	NM_000138	exon7	c.557G>A	p. Cys186Tyr	Missense	Inherited from father	Likely Pathogenic	31098894	PM1+PM2+PP1+PP3

(Continues)

TABLE 2 (Continued)

Sample ID	Gene	Transcript	Exon/Intron	Nucleotide change	Protein change	Mutation type	De novo	Pathogenicity	Report Ref (PMID)	ACMG Criteria
AD124	*FBN1*	NM_000138	exon62	c.7606G>A	p. Gly2536Arg	Missense	Inherited from mother	Likely Pathogenic	11748851	PM2+PS4_Moderate+PP3+PP4
AD126	*FBN1*	NM_000138	exon20	c.2305T>G	p. Cys769Gly	Missense	NA	Likely Pathogenic	This paper	PM1+PM2+PM5+PP3
AD129	*FBN1*	NM_000138	exon32	c.3838+2T>C	Splicing	Splicing	Inherited from mother	Likely Pathogenic	This paper	PVS1+PM2
AD130	*COL3A1*	NM_000090	exon15	c.998G>T	p. Gly333Val	Missense	Inherited from mother	Likely Pathogenic	This paper	PM2+PM5+PP1+PP3
AD131	*FBN1*	NM_000138	exon63	c.7712G>A	p. Cys2571Tyr	Missense	Inherited from mother	Likely Pathogenic	Case record	PM1+PM2+PP3+PS4_Supporting
AD133	*FBN1*	NM_000138	exon35	c.4336G>A	p. Asp1446Asn	Missense	Inherited from father	Likely Pathogenic	Case record	PS3+PM2+PP1
AD136	*FBN1*	NM_000138	exon39	c.4813G>T	p. Glu1605Ter	Stop gain	De novo	Pathogenic	This paper	PVS1+PM2+PM6
AD138	*FBN1*	NM_000138	exon37	c.4505G>A	p. Cys1502Tyr	Missense	Inherited from mother	Likely Pathogenic	16476890	PM1+PM2+PP3+PS4_Supporting
AD139	*FBN1*	NM_000138	exon22	c.2607delC	p. Ala869fs	Frameshift	Inherited from father	Pathogenic	This paper	PVS1+PM2+PP1
AD141	*TGFBR1*	NM_001130916	exon3	c.527T>A	p. Met176Lys	Missense	De novo	Likely Pathogenic	This paper	PM2+PM5+PM6+PP3
AD142	*FBN1*	NM_000138	intron12	c.1468+5G>A	Splicing	Splicing	Inherited from father	Pathogenic	10464652	PVS1+PM2+PS4_Supporting
AD143	*ACTA2*	NM_001613	exon7	c.772C>T	p. Arg258Cys	Missense	NA	Likely Pathogenic	26153420	PS3+PM2+PP3
AD148	*FBN1*	NM_000138	exon55	c.6628T>C	p. Cys2210Arg	Missense	De novo	Likely Pathogenic	24793577	PM1+PM2+PM6
AD149	*FBN1*	NM_000138	exon7	c.640G>A	p. Gly214Ser	Missense	NA	Likely Pathogenic	22262941	PS1+PM2+PP3

(Continues)

TABLE 2 (Continued)

Sample ID	Gene	Transcript	Exon/Intron	Nucleotide change	Protein change	Mutation type	De novo	Pathogenicity	Report Ref (PMID)	ACMG Criteria
AD151	*FBN1*	NM_000138	exon14	c.1693C>T	p. Arg565Ter	Stop gain	De novo	Pathogenic	19618372	PVS1+PM2+PM6
AD154	*FBN1*	NM_000138	exon64	c.7869dupC	p. Asn2624fs	Frameshift	De novo	Pathogenic	This paper	PVS1+PM2+PM6
AD161	*FBN1*	NM_000138	exon58	c.7082C>A	p. Ser2361Ter	Stop gain	Inherited from father	Pathogenic	Case record	PVS1+PM2+PP1
AD165	*FBN1*	NM_000138	exon59	c.7325G>A	p. Cys2442Tyr	Missense	NA	Likely Pathogenic	Case record	PM1+PM2+PM5+PP3
AD167	*FBN1*	NM_000138	exon38	c.4589G>A	p. Arg1530His	Missense	Inherited from father	Likely Pathogenic	23794388	PM1+PM2+PM5
AD168	*FBN1*	NM_000138	exon36	c.4387A>C	p. Asn1463His	Missense	Inherited from mother	Likely Pathogenic	This paper	PM1+PM2+PM5+PP1+PP3
AD171	*MYH11*	NM_002474	exon28	c.3728T>C	p. Leu1243Pro	Missense	De novo	Likely Pathogenic	Case record	PS2+PM2+PP3
AD179	*FBN1*	NM_000138	exon27	c.3250G>C	p. Gly1084Arg	Missense	NA	Likely Pathogenic	Case record	PM1+PM2+PP1+PP3
AD181	*FBN1*	NM_000138	exon13	c.1546C>T	p. Arg516Ter	Stop gain	NA	Pathogenic	12938084	PVS1+PM2+PS4_ Supporting
AD183	*FBN1*	NM_000138	exon13	c.1585C>T	p. Arg529Ter	Stop gain	De novo	Pathogenic	27175573	PVS1+PM2+PM6+PS4_ Supporting
AD197	*TGFBR1*	NM_001130916	exon3	c.478A>G	p. Arg160Gly	Missense	De novo	Likely Pathogenic	Case record	PS2+PM2+PP3
AD199	*FBN1*	NM_000138	exon62	c.7694G>T	p. Cys2565Phe	Missense	NA	Pathogenic	25652356	PS1+PM1+PM2+PP3+PP4
AD207	*FBN1*	NM_000138	exon15	c.1793G>T	p. Cys598Phe	Missense	NA	Likely Pathogenic	Case record	PM1+PM2+PM5+PP3
AD211	*FBN1*	NM_000138	exon37	c.4567C>T	p. Arg1523Ter	Stop gain	NA	Pathogenic	10874320	PVS1+PS2PS4_Supporting
AD213	*FBN1*	NM_000138	intron12	c.1468+5G>A	Splicing	Splicing	De novo	Pathogenic	10464652	PVS1+PM2+PM6+PS4_ Supporting

Note: Mutation names are given according to HGVS nomenclature guidelines and numbered with respect to each gene cDNA sequence (+1 = A of ATG) obtained from the National Center for Biotechnology Information (NCBI) database (accession numbers are transcript numbers that have been list in the table).

Abbreviation: NA, not available.

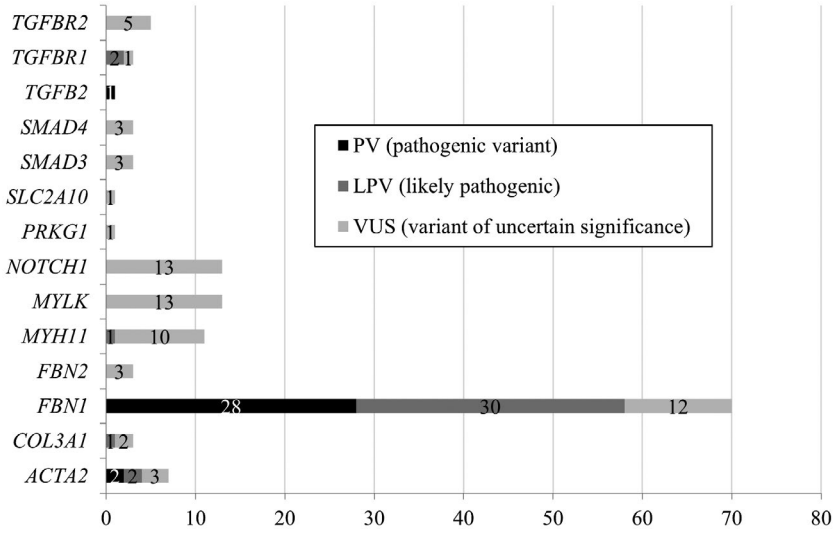

FIGURE 1 Summary of reportable variants identified per gene. The distribution of reportable variants, including pathogenic variants (PVs), likely pathogenic variants (LPVs), and variants of uncertain significance (VUSs), identified in a 15 gene panel across the cohort of 212 individuals is shown. Numbers of PVs, LPVs, and VUSs per gene are given. Among the 135 reportable variants, 31 were pathogenic, 36 were likely pathogenic, and 68 were VUSs

TABLE 3 *FBN1* mutation type and average age in patients with various aortic events

		Aortic dissection	Aortic aneurysm	Valvular disease	Marfan with mild aortic dilation
Truncating	Frameshift (n = 13)	11 (32.0y)	11 (33.3y)	4 (33.8y)	0
	Nonsense (n = 9)	7 (36.8y)	7 (32.8y)	5 (29.5y)	0
Splicing (n = 7)		6 (32.8y)	5 (35.5y)	4 (26y)	1 (3.5y)
Deletion (n = 1)		1 (19.0y)	1 (19.0y)	1 (19.0y)	0
Missense (n = 28)		12 (35.1y)	22 (33.8y)	18 (34.6y)	4 (16y)
Total (n = 58)		37	46	32	5

Abbreviation: y, years old.

one younger brother died suddenly around the age of 35 years, and his younger brother (II5) was diagnosed with aortic dissection when he was 39 years old. The variant mentioned above was identified by Sanger sequencing in the DNA of II5. However, we still classified the variant as a VUS due to the loss of function of the *ACTA2* gene via an unknown molecular mechanism. Further functional studies are necessary to confirm its pathogenicity.

4 | DISCUSSION

Genetic testing for rare disease-causing variants in TAAD genes is used worldwide now. It is crucial to identify individuals with an increased risk for TAAD because dissections and the associated premature deaths are preventable. NGS has become a practical screening method to identify disease-related gene variants (Chong et al., 2015). In our study, NGS was performed to determine variants in 15 candidate genes associated with TAAD in 212 patients from northwestern China. We found 135 variants in 109 patients, 77 of which were first detected by us, enriching the gene mutation spectrum of TAAD. The high rate of novel variants (62.22%, 84/135) is due to the high degree of clinical and genetic heterogeneity of hereditary TAAD, much of which is unique to the patient's family. These 135 variants were classified according to the ACMG guidelines (Richards et al., 2015); 67 were classified as (likely) PV and 68 were classified as VUSs. Because of the strict enrollment conditions, the positive rate in our study (31.60%, 67/212) was higher than that in others (Proost et al., 2015; Zheng et al., 2018; Ziganshin et al., 2015).

In our study, the mean age of patients was 38.14 ± 11.33 years, which is significantly younger than that of patients with AAD in the Sino-Registry of Aortic Dissection (RAD) in China (51.8 ± 11.4 years) and the International Registry of Acute Aortic Dissection (IRAD, 63.1 ± 14.0 years) (Wang et al., 2014). Previous studies have reported more men than women with AAD (Fang et al., 2017; Zheng et al., 2018). The proportion of male patients in this study was 78.30%, consistent with that of patients in the Sino-RAD (77.8%), and higher than that of patients in the IRAD (65.3%). Our results show that patients with causative variants have obvious clinical distinctions from patients without variants. First, patients with causative variants were significantly younger than those without variants, and the average height of patients in the causative variant

TABLE 4 Reclassified variants in our tests

Sample ID	Gene	Transcript	Exon/Intron	Nucleotide change	Protein change	Variant called	Variant reclassification	Reclassification based on	Pop Freq MAX	Report Ref (PMID)
AD32	*MYH11*	NM_002474	exon28	c.3766A>C	p. Lys1256Gln	VUS	likely benign	Family segregation	0.001	This paper
AD44	*NOTCH1*	NM_017617	exon21	c.3334G>A	p. Val1112Ile	VUS	likely benign	Family segregation	0.0003	This paper
AD47	*MYH11*	NM_002474	exon28	c.3766A>C	p. Lys1256Gln	VUS	likely benign	Family segregation	0.001	This paper
AD51	*COL3A1*	NM_000090	exon5	c.469T>G	p. Ser157Ala	VUS	likely benign	Family segregation	.	This paper
AD58	*MYH11*	NM_022844	exon41	c.5798C>G	p. Pro1933Arg	VUS	likely benign	Family segregation	.	This paper
AD58	*COL3A1*	NM_000090	exon51	c.4351G>T	p. Gly1451Cys	VUS	likely benign	Family segregation	.	This paper
AD59	*FBN2*	NM_001999	exon17	c.2260G>A	p. Gly754Ser	VUS	likely benign	Family segregation	.	19006240
AD79	*FBN1*	NM_000138	exon61	c.7559C>T	p. Thr2520Met	VUS	likely benign	Family segregation	0.0001	17657824
AD171	*MYH11*	NM_002474	exon28	c.3728T>C	p. Leu1243Pro	VUS	Likely pathogenic	Family segregation	.	Case record
AD197	*TGFBR1*	NM_001130916	exon3	c.478A>G	p. Arg160Gly	VUS	Likely pathogenic	Family segregation	.	2724990
AD213	*NOTCH1*	NM_017617	exon34	c.7229C>T	p. Pro2410Leu	VUS	likely benign	Family segregation	0.00007	Case record

Note: Mutation names are given according to HGVS nomenclature guidelines and numbered with respect to each gene cDNA sequence (+1 = A of ATG) obtained from the National Center for Biotechnology Information (NCBI) database (accession numbers are as the same as transcript numbers which have been list in the table).

Abbreviation: VUS, variants of unknown significance.

group was distinctly higher than that of patients in the no variant group. Second, although there was no significant difference in the incidence of aortic dissections, ascending aortic aneurysms, or valvular diseases between the two groups, aortic root aneurysms were more severe in the causative variants group. This suggests that patients with causative variants suffer from the earlier onset and more severe phenotypes. Third, as we expected, hypertension was more commonly found in the no variant group, since hypertension is the main predisposing factor of nonhereditary TAAD. Overall, the phenotype of patients with detected causative variants is distinguishable from those without variants. The differences in clinical characteristics may reflect different pathophysiologic processes between the two groups. In addition, although the ratio of males to females in all patients studied was almost 3:1, this is consistent with previous reports (Pape et al., 2015; Zheng et al., 2018). However, in the (likely) PV group, the male/female ratio decreased to 2.53:1, which may be related to poor lifestyle choices made by men (e.g., smoking and alcohol abuse).

Many studies have shown that patients with pathogenic *FBN1* variants are at risk for developing Marfan syndrome, and a detailed genotype–phenotype correlation between the *FBN1* variant type and aortic events was investigated (Tan et al., 2017). In this study, most of the variants were detected in the *FBN1* gene, including 58 (likely) PVs and 12 VUSs. Among the 58 (likely) PVs, missense mutations (28/58) and frameshift mutations (13/58) had the highest incidence. However, most of the VUSs were missense mutations (9/12). In summary, the incidence of missense mutations was the highest, followed by frameshift mutations, which is mostly consistent with the literature, but the ratios were slightly different (Becerra-Munoz et al., 2018; Franken et al., 2016). Furthermore, patients with truncating and splicing mutations were more prone to developing severe aortic dissections than those with missense mutations, especially frameshift mutations, in which patients showed an earlier age of aortic dissection occurrence than those with missense mutations. Similarly, Baudhuin et al. and Yang et al. once reported that a higher frequency of truncating or splicing *FBN1* variants in patients with Marfan syndrome who experienced an aortic event than in those who did not (Baudhuin et al., 2015; Yang et al., 2016). However, the mechanism is still not clear.

In this study, 43 (20.28%) patients had a family history of sudden death or TAAD, which falls within the previously reported 20–40% range of patients with a family history (Dietz et al., 1991; Fang et al., 2017). When considering family history, the variant detection rate was 76.74% (33/43), whereas that in patients

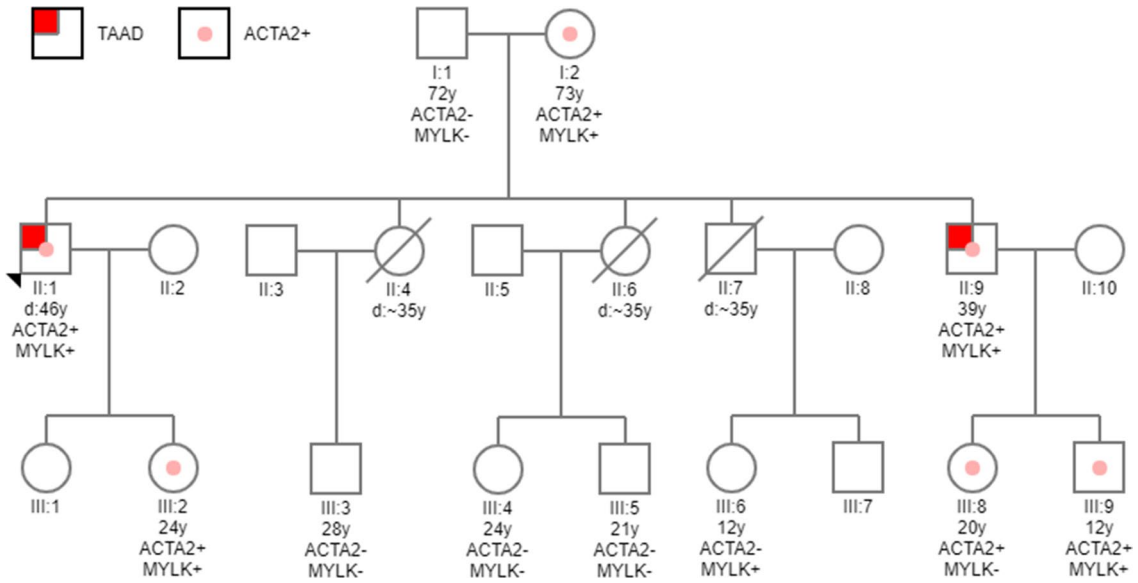

FIGURE 2 Pedigree of the family with the *ACTA2* (p. Leu195Term) variant. Circles represent females, squares represent males, and the arrowhead indicates the proband. A diagonal line through a symbol indicates that the individual is deceased, with their age of death shown below the symbol. Age at detection is shown below each individual. Symbols used to represent disease and variant status are indicated in the figure key. TAAD, Thoracic aortic aneurysm and dissection

without a family history was 18.93% (25/132). This result indicates that genetic testing is more efficient in TAAD patients with family history than in those without. According to the ACMG guidelines, we readjusted the pathogenic grades of 10 variants by family member verification, and the variants were downgraded to likely benign because the healthy family members also carried the same variants. An *ACTA2* nonsense mutation was detected in our test in a distinctive TAAD family. The molecular mechanism of TAAD induced by missense mutations in *ACTA2* due to dominant-negative effects has been defined (Guo et al., 2007). However, the mechanism of the loss of function of *ACTA2* is not yet clear, although Marjolijn Renard et al. once reported nonsense mutations in two TAAD patients (Renard et al., 2013). As a result, we classified this variant as a VUS. Further functional studies are needed to confirm its pathogenicity in future work.

Although the results of our study are important, the number of patients in our study is still insufficient. Larger sample size is critical for determining the correlation between genotype and phenotype. For patients with a VUS, we performed relative verification only in a family with a family history, which may have resulted in the omission of some potentially positive information. Our panel contains only 15 genes, and genes that are not yet included may also have PVs. These variants are difficult to detect due to limitations in gene panel detection methods. Our team is currently experimenting with whole-exome sequencing to overcome these shortcomings.

ACKNOWLEDGMENTS

We are grateful to the patients and their families for their participation. We would like to thank the medical teams, technicians, and sonographers whose work supports the clinic.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Jinjie Li performed the majority of the data analysis and wrote the manuscript. Liu Yang was in charge of patient recruitment, sample, and clinical information collection. Yanjun Diao was in charge of communication with the clinicians. Lei Zhou analyzed the sequencing data. Yijuan Xin performed the NGS sequencing and Sanger validation. Liqing Jiang and Juan Wang collected samples and communicated with patients. Rui Li was in charge of the clinical evaluation and sample management. Weixun Duan gave a direction on the experiment, data analysis, and interpretation. Jiayun Liu was in charge of the project design and revised the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Jinjie Li https://orcid.org/0000-0002-4439-6276
Liu Yang https://orcid.org/0000-0003-0045-8380

REFERENCES

Albornoz, G., Coady, M. A., Roberts, M., Davies, R. R., Tranquilli, M., Rizzo, J. A., & Elefteriades, J. A. (2006). Familial thoracic aortic aneurysms and dissections–incidence, modes of inheritance, and phenotypic patterns. *Annals of Thoracic Surgery*, *82*(4), 1400–1405. https://doi.org/10.1016/j.athoracsur.2006.04.098.

Baudhuin, L. M., Kotzer, K. E., & Lagerstedt, S. A. (2015). Increased frequency of FBN1 truncating and splicing variants in Marfan syndrome patients with aortic events. *Genetics in Medicine*, *17*(3), 177–187. https://doi.org/10.1038/gim.2014.91.

Becerra-Muñoz, V. M., Gómez-Doblas, J. J., Porras-Martín, C., Such-Martínez, M., Crespo-Leiro, M. G., Barriales-Villa, R., de Teresa-Galván, E., Jiménez-Navarro, M., & Cabrera-Bueno, F. (2018). The importance of genotype-phenotype correlation in the clinical management of Marfan syndrome. *Orphanet Journal of Rare Diseases*, *13*(1), 16. https://doi.org/10.1186/s13023-017-0754-6.

Biddinger, A., Rocklin, M., Coselli, J., & Milewicz, D. M. (1997). Familial thoracic aortic dilatations and dissections: A case control study. *Journal of Vascular Surgery*, *25*(3), 506–511. https://doi.org/10.1016/s0741-5214(97)70261-1.

Chong, J. X., Buckingham, K. J., Jhangiani, S. N., Boehm, C., Sobreira, N., Smith, J. D., Harrell, T. M., McMillin, M. J., Wiszniewski, W., Gambin, T., Coban Akdemir, Z. H., Doheny, K., Scott, A. F., Avramopoulos, D., Chakravarti, A., Hoover-Fong, J., Mathews, D., Witmer, P. D., Ling, H., ... Bamshad, M. J. (2015). The genetic basis of mendelian phenotypes: discoveries, challenges, and opportunities. *American Journal of Human Genetics*, *97*(2), 199–215. https://doi.org/10.1016/j.ajhg.2015.06.009.

Dietz, H. C., Cutting, C. R., Pyeritz, R. E., Maslen, C. L., Sakai, L. Y., Corson, G. M., Puffenberger, E. G., Hamosh, A., Nanthakumar, E. J., Curristin, S. M., Stetten, G., Meyers, D. A., & Francomano, C. A., ... 1991). Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. *Nature*, *352*(6333), 337–339. https://doi.org/10.1038/352337a0.

Erbel, R., Aboyans, V., Boileau, C., Bossone, E., Bartolomeo, R. D., Eggebrecht, H. ... Guidelines, E. S. C. C. f. P. (2014). 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). *European Heart Journal*, *35*(41), 2873-2926. https://doi.org/10.1093/eurheartj/ehu281

Fang, M., Yu, C., Chen, S., Xiong, W., Li, X., Zeng, R., Zhuang, J., & Fan, R. (2017). Identification of novel clinically relevant variants in 70 southern chinese patients with thoracic aortic aneurysm and dissection by next-generation sequencing. *Scientific Reports*, *7*(1), 10035. https://doi.org/10.1038/s41598-017-09785-y.

Franken, R., Groenink, M., de Waard, V., Feenstra, H. M. A., Scholte, A. J., van den Berg, M. P., Pals, G., Zwinderman, A. H., Timmermans, J., & Mulder, B. J. M. (2016). Genotype impacts survival in Marfan syndrome. *European Heart Journal*, *37*(43), 3285–3290. https://doi.org/10.1093/eurheartj/ehv739.

Gago-Díaz, M., Ramos-Luis, E., Zoppis, S., Zorio, E., Molina, P., Braza-Boïls, A., Giner, J., Sobrino, B., Amigo, J., Blanco-Verea, A., Carracedo, Á., & Brion, M. (2017). Postmortem genetic testing should be recommended in sudden cardiac death cases due to thoracic aortic dissection. *International Journal of Legal Medicine*, *131*(5), 1211–1219. https://doi.org/10.1007/s00414-017-1583-9.

Guo, D., Pannu, H., Tran-Fadulu, V., Papke, C., Yu, R., Avidan, N., & Sparks, E. (2007). Mutations in smooth muscle alpha-actin (ACTA2) lead to thoracic aortic aneurysms and dissections. *Nature Genetics*, *39*(12), 1488–1493.

Hoyert, D. L., Arias, E., Smith, B. L., Murphy, S. L., & Kochanek, K. D. (2001). Deaths: final data for 1999. *National Vital Statistics Reports*, *49*(8), 1–113.

Huynh, T. T., & Starr, J. E. (2013). Diseases of the thoracic aorta in women. *Journal of Vascular Surgery*, *57*(4 Suppl), 11S–17S. https://doi.org/10.1016/j.jvs.2012.08.126.

Jondeau, G., Ropers, J., Regalado, E., Braverman, A., Evangelista, A., Teixedo, G., & Montalcino Aortic, C. (2016). International registry of patients carrying TGFBR1 or TGFBR2 mutations: Results of the MAC (Montalcino Aortic Consortium). *Circulation: Cardiovascular Genetics*, *9*(6), 548–558. https://doi.org/10.1161/CIRCGENETICS.116.001485.

Kuzmik, G. A., Sang, A. X., & Elefteriades, J. A. (2012). Natural history of thoracic aortic aneurysms. *Journal of Vascular Surgery*, *56*(2), 565–571. https://doi.org/10.1016/j.jvs.2012.04.053.

Meszaros, I., Morocz, J., Szlavi, J., Schmidt, J., Tornoci, L., Nagy, L., & Szep, L. (2000). Epidemiology and clinicopathology of aortic dissection. *Chest*, *117*(5), 1271–1278. https://doi.org/10.1378/chest.117.5.1271.

Moll, F. L., Powell, J. T., Fraedrich, G., Verzini, F., Haulon, S., & Waltham, M. ... European Society for Vascular, S (2011). Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. *European Journal of Vascular and Endovascular Surgery*, *41*(Suppl 1), S1–S58. https://doi.org/10.1016/j.ejvs.2010.09.011.

Nienaber, C. A., & Clough, R. E. (2015). Management of acute aortic dissection. *Lancet*, *385*(9970), 800–811. https://doi.org/10.1016/S0140-6736(14)61005-9.

Pape, L. A., Awais, M., Woznicki, E. M., Suzuki, T., Trimarchi, S., Evangelista, A., & O'Gara, P. (2015). Presentation, diagnosis, and outcomes of acute aortic dissection: 17-year trends from the international registry of acute aortic dissection. *Journal of the American College of Cardiology*, *66*(4), 350–358. https://doi.org/10.1016/j.jacc.2015.05.029.

Proost, D., Vandeweyer, G., Meester, J. A. N., Salemink, S., Kempers, M., Ingram, C., Peeters, N., Saenen, J., Vrints, C., Lacro, R. V., Roden, D., Wuyts, W., Dietz, H. C., Mortier, G., Loeys, B. L., & Van Laer, L. (2015). Performant mutation identification using targeted next-generation sequencing of 14 thoracic aortic aneurysm genes. *Human Mutation*, *36*(8), 808–814. https://doi.org/10.1002/humu.22802.

Regalado, E. S., Guo, D. C., Prakash, S., Bensend, T. A., Flynn, K., Estrera, A., & Milewicz, D. M. (2015). Aortic disease presentation and outcome associated with ACTA2 mutations. *Circulation: Cardiovascular Genetics*, *8*(3), 457–464. https://doi.org/10.1161/CIRCGENETICS.114.000943.

Renard, M., Callewaert, B., Baetens, M., Campens, L., MacDermot, K., Fryns, J. P., & De Backer, J. (2013). Novel MYH11 and ACTA2 mutations reveal a role for enhanced TGFbeta signaling in FTAAD. *International Journal of Cardiology*, *165*(2), 314–321. https://doi.org/10.1016/j.ijcard.2011.08.079.

Renard, M., Francis, C., Ghosh, R., Scott, A. F., Witmer, P. D., Adès, L. C., Andelfinger, G. U., Arnaud, P., Boileau, C., Callewaert, B. L., Guo, D., Hanna, N., Lindsay, M. E., Morisaki, H., Morisaki,

T., Pachter, N., Robert, L., Van Laer, L., Dietz, H. C., ... De Backer, J. (2018). Clinical validity of genes for heritable thoracic aortic aneurysm and dissection. *Journal of the American College of Cardiology*, *72*(6), 605–615. https://doi.org/10.1016/j.jacc.2018.04.089.

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W. W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., & Rehm, H. L. (2015). Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in Medicine*, *17*(5), 405–424. https://doi.org/10.1038/gim.2015.30.

Tan, L., Li, Z., Zhou, C., Cao, Y., Zhang, L., Li, X., Cianflone, K., Wang, Y., & Wang, D. W. (2017). FBN1 mutations largely contribute to sporadic non-syndromic aortic dissection. *Human Molecular Genetics*, *26*(24), 4814–4822. https://doi.org/10.1093/hmg/ddx360.

Wang, W., Duan, W., Xue, Y., Wang, L., Liu, J., Yu, S., & Registry of Aortic Dissection in China Sino, R. A. D. I. (2014). Clinical features of acute aortic dissection from the Registry of Aortic Dissection in China. *Journal of Thoracic and Cardiovascular Surgery*, *148*(6), 2995–3000. https://doi.org/10.1016/j.jtcvs.2014.07.068.

Yang, H., Luo, M., Fu, Y., Cao, Y., Yin, K., Li, W., Meng, C., Ma, Y., Zhang, J., Fan, Y., Shu, C., Chang, Q., & Zhou, Z. (2016). Genetic testing of 248 Chinese aortopathy patients using a panel assay. *Scientific Reports*, *6*, 33002–33009. https://doi.org/10.1038/srep33002.

Zheng, J., Guo, J., Huang, L., Wu, Q., Yin, K., Wang, L., Zhang, T., Quan, L. I., Zhao, Q., & Cheng, J. (2018). Genetic diagnosis of acute aortic dissection in South China Han population using next-generation sequencing. *International Journal of Legal Medicine*, *132*(5), 1273–1280. https://doi.org/10.1007/s00414-018-1890-9.

Ziganshin, B. A., Bailey, A. E., Coons, C., Dykas, D., Charilaou, P., Tanriverdi, L. H., Liu, L., Tranquilli, M., Bale, A. E., & Elefteriades, J. A. (2015). Routine genetic testing for thoracic aortic aneurysm and dissection in a clinical setting. *Annals of Thoracic Surgery*, *100*(5), 1604–1611. https://doi.org/10.1016/j.athoracsur.2015.04.106.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

How to cite this article: Li, J., Yang, L., Diao, Y., Zhou, L., Xin, Y., Jiang, L., Li, R., Wang, J., Duan, W., & Liu, J. (2021). Genetic testing and clinical relevance of patients with thoracic aortic aneurysm and dissection in northwestern China. *Molecular Genetics & Genomic Medicine*, 9, e1800. https://doi.org/10.1002/mgg3.1800