



Genetic variants in Chinese patients with sporadic Stanford type A aortic dissection

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Background: Genetic disorders are strongly associated with aortic disease. However, the identities of genetic mutations in sporadic Stanford type A aortic dissection (STAAD) are not clear. The present study analysed the possible genetic mutations of the known pathogenic genes of aortic disease and the clinical characteristics in patients with sporadic STAAD.

Methods: We analysed genetic mutations in 26 genes that underlie aortic aneurysms and dissections in 100 sporadic STAAD patients and 568 healthy controls after whole-genome sequencing (WGS). Clinical features and in-hospital death were determined in all STAAD patients.

Results: In total, 60 suspicious pathogenic mutations (56 novel and 4 previously reported) in 19 genes were identified in 50% (50/100) of patients, and 14 patients had more than 1 mutation. The ascending aortic diameter was extended in patients with mutations (49.1±12.3 *vs.* 43.7±11.2 mm, *P*=0.023), and the DeBakey type I phenotype was more common in patients with mutations in genes that coded extracellular matrix (ECM) components than in patients with mutations in other genes (96.6% *vs.* 66.7%, *P*=0.007). Patients with fibrillin-1 (*FBNI*) mutations were younger than patients without *FBNI* mutations (44.7±11.0 *vs.* 53.5±12.1, *P*=0.030). Subgroup analyses revealed an increased risk of in-hospital mortality in mutation carriers (44.4% *vs.* 10.5%, *P*=0.029) but only in patients who received conservative treatment.

Conclusions: Half of Chinese patients with a sporadic form of STAAD may carry mutations in known pathogenic genes of aortic disease, and these patients may exhibit distinct clinical features and poor clinical outcomes with the use of conservative treatment.

Keywords: Aortic dissection (AD); gene mutation; Stanford type A; mortality; clinical features

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Introduction

Aortic dissection (AD) is a catastrophic cardiovascular condition that involves separation of the layers of the aortic wall. Stanford type A AD (STAAD) involves the ascending aorta, and it is further divided into DeBakey type I or type II based on the extent of the dissection (1,2). Patients with STAAD have a stronger genetic component than patients with Stanford type B AD or abdominal aortic aneurysms, which are more associated with lifestyle-linked risk factors, such as hypertension, atherosclerosis, age and sex (3,4).

Genetic disorders are strongly associated with aortic disease, and genetic disorder-induced aortic wall weakness may cause aortic aneurysms and dissection. Approximately 11–19% of patients with AD have first-degree relatives who are diagnosed with aortic aneurysm or dissection, and 80% of patients show a sporadic form of AD (5,6). Patients with aortic aneurysms and dissections are further classified as nonsyndromic or syndromic according to whether the abnormalities are limited to the cardiovascular system. Hereditary diseases of connective tissues are often associated with syndromic AD, and most of these patients develop an autosomal dominant disorder caused by mutations in certain genes, such as fibrillin-1 [(*FBNI*); Marfan syndrome (MFS)], fibrillin-2 [(*FBN2*); Beals syndrome], collagen type III alpha 1 chain [(*COL3A1*); Ehlers-Danlos syndrome (EDS), vascular type] and transforming growth factor beta receptor [(*TGFBR*); Loeys-Dietz syndrome (LDS)], whereas mutations located in acetyl coA acetyltransferase 2 (*ACAT2*), myosin heavy chain 11 (*MYH11*) and *SMAD2* seem to affect patients with a family history and exhibit a nonsyndromic form (7). However, the genetic risk factors for patients with sporadic STAAD are not clear.

Next-generation sequencing (NGS) technology is widely used for clinical testing in the search for a genetic cause of disease. Panel testing of multiple genes has emerged as the preferred approach. However, the method of panel testing presupposes that the abnormalities that are of clinical relevance are confined to the panel of tested genes. Therefore, NGS-based whole-genome sequencing (WGS) and targeted gene panel analysis in combination with complementary methods provide a comprehensive and feasible approach for genetic diagnostics.

We analysed 26 specific genes that are known to underlie aortic aneurysm and dissection in 100 Chinese patients with sporadic STAAD and used WGS to clarify whether genetic variants in suspicious pathogenic genes were associated with sporadic STAAD.

We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/jtd-20-2758>).

Methods

Study population and data collection

Patients with suspected STAAD who were admitted to the emergency centre of Fuwai Hospital from 2012 to 2014 were primarily enrolled when blood samples for genetic testing were obtained within 24 hours of admission. Another 568 healthy control samples were obtained from individuals undergoing physical examination. The diagnosis of STAAD was confirmed using multidetector computed tomography scanning. All of the included patients reported the absence of a first-degree relative with aortic aneurysm or dissection in a detailed medical history inquiry. Patients with AD secondary to surgery, trauma and pregnancy were excluded. Baseline characteristic data were recorded, including sex, age, and previous medical histories, such as hypertension, diabetes mellitus, coronary artery disease, smoking status and drinking status. Other recorded clinical characteristics included baseline vital signs at admission (systolic/diastolic blood pressure and heart rate), imaging examinations and hospital management (medical therapy or surgical intervention). An experienced surgeon-in-charge determined the rationale and strategy of the surgical techniques according to the guidelines for the diagnosis and treatment of aortic disease (8,9). The primary end point was in-hospital all-cause mortality, and the evaluation of mortality was obtained from our hospital's medical database. The study was performed in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Fuwai Hospital (No. 2012-396). Informed consent was obtained from all patients.

WGS and variant calling method

Genomic DNA was isolated from blood samples. Novogene performed WGS. DNA libraries were sequenced on an Illumina HiSeq X according to the manufacturer's instructions to generate paired-end 150 bp reads, and the researchers were blinded to phenotypic labels during the WGS process. Primer sequences were trimmed from FASTQ files using cutadapt (v 1.9.1) 20 prior to read mapping to the reference genome (UCSC hg19) using

BWA-MEM. SAMtools (version 1.0) was used for variant calling and the identification of single-nucleotide variants (SNVs) and indels. Only variants with QualByDepth (QUAL) >20, Depth (DP) >4, and RMS MappingQuality (MQ) >40 passed the filter.

Mutation analysis

WGS was performed to scan for genetic variants that may underlie STAAD. This study also analysed 26 specific previously known genes (with exact OMIM numbers) that underlie aortic aneurysm and dissection. The detailed panel of tested genes is presented in *Table 1*. Polymorphic variants were excluded if their allelic frequency was >0.01 in the 1000 Genomes Project (in all populations, <http://www.internationalgenome.org/1000-genomes-browsers>) or in the 568 healthy controls. Variants were considered pathological if they met one of the following criteria: (I) previously reported as pathological in the NCBI ClinVar database; (II) nonsense and indel (frameshift or nonframeshift) mutations; (III) novel missense mutations that indicated a damaging effect in SIFT20 (<http://sift.jcvi.org/>) or PolyPhen-219 (<http://genetics.bwh.harvard.edu/pph2/>); and (IV) variations in the splice site within 3 bp of the exon.

Statistical analysis

All statistical analyses were performed using SPSS version 19.0 (SPSS, Inc., Chicago, Illinois, USA). Continuous variables are presented as the means \pm SD or the medians and interquartile range-based Gaussian distribution. Baseline characteristics were compared between groups using unpaired Student's *t* tests or chi-square tests. The in-hospital mortality was compared between the different groups using chi-square tests. A *P* value of <0.05 was considered statistically significant.

Results

Patient clinical characteristics

In total, 104 sporadic subjects who were diagnosed with STAAD were primarily enrolled, and WGS was performed in 96.1% (100/104) of patients with higher-quality blood DNA samples. The summarized clinical characteristics are shown in *Table 2*. The average age of these patients was 52.7 \pm 12.3 years, and 62.0% (62/100) of the enrolled patients were male. Eighty-four cases showed the DeBakey

I AD phenotype, 16 cases were DeBakey type II, and 65 patients (65.0%) had a history of hypertension.

Technical performance: coverage and variant calling

After the entire run was completed, on average, 89.79 GB of Illumina sequencing data per subject were generated. The average sequencing depth of WGS was 32.58 \pm 2.59 \times , with an average coverage of 99.39% of the genome. The average depth of the analysed target genes of all samples was over 20 \times , and the coverage of the analysed genes in a specific sample was over 99.38% (*Table S1*). The percentage of each gene sequence covered using this assay is presented in *Table S2*. A summary of the quality control for WGS is presented in *Table S3*.

Genetic variants of panel genes for WGS

Site-based data

In total, 130 mutations were screened in the tested genes from the panel, including 5 indel mutations and 125 SNV mutations. Seventy mutations were excluded as common polymorphisms or neutral rare variants according to the exclusion criteria. After exclusion, 60 mutations, including 5 indels and 55 SNVs in 19 panel genes, were identified as disease-associated mutations (*Figure 1*), and the allelic frequency of the identified variants in healthy controls is detailed in *Table S4*. Fifty-six mutations were novel, and 4 mutations were previously reported. Mutations located in the extracellular matrix (ECM)-coding genes, especially in *FBN1* (10 mutations, 16.7%) and *COL5A1* (6 mutations, 10.0%), constituted 61.7% (37/60) of these variants. Seventeen mutations (28.3%) were found in cytoskeletal or smooth muscle contraction apparatus protein-coding genes, and 5 mutations were found in coding genes in the transforming growth factor- β (TGF- β) pathway (2 in *TGFBR1*, 2 in *TGFBR2* and 1 in *TGFBR3*). Only 1 mutation was identified in the *NOTCH1* gene, which was related to neural crest migration. Detailed site-based information is shown in *Table 3*.

Case-based data

We identified genetic mutations in half of the patients (50/100) using the gene panel for aortic aneurysm and dissection. The other half of the patients showed no deleterious mutations. From the data, more than 1 variant was found in 14 patients (1 patient had 4 mutations, 2

Table 1 Panel of the 26 tested genes

No.	Type	Gene	OMIM No.	Clinical manifestation
1	ECM proteins	<i>FBN1</i>	154700	Marfan's syndrome
2	ECM proteins	<i>FBN2</i>	612570	Beals syndrome; Contractural arachnodactyly
3	ECM proteins	<i>MFAP5</i>	616166	Aortic aneurysm, familial thoracic 9
4	ECM proteins	<i>COL1A1</i>	130000	Ehlers-Danlos syndrome, classic type
5	ECM proteins	<i>COL1A2</i>	130060	Ehlers-Danlos syndrome, procollagen proteinase deficient
6	ECM proteins	<i>COL3A1</i>	130050	Ehlers-Danlos syndrome, vascular type
7	ECM proteins	<i>COL5A1</i>	130000	Ehlers-Danlos syndrome, classic type
8	ECM proteins	<i>COL5A2</i>	130000	Ehlers-Danlos syndrome, classic type
9	ECM proteins	<i>ADAMTS2</i>	225041	Ehlers-Danlos syndrome type 7
10	ECM proteins	<i>ADAMTS10</i>	277600	Weill-Marchesani syndrome 1
11	ECM proteins	<i>PLOD1</i>	225400	Ehlers-Danlos syndrome, hydroxylysine-deficient
12	ECM proteins	<i>PLOD3</i>	612394	Bone fragility with contractures, arterial rupture, and deafness
13	ECM proteins	<i>ELN</i>	123700	Williams syndrome, Supravalvar aortic stenosis
14	ECM proteins	<i>EFEMP2</i>	614437	Cutis laxa autosomal recessive IIA
15	TGF- β pathway	<i>TGFBR1</i>	609192	Loeys-Dietz syndrome 1
16	TGF- β pathway	<i>TGFBR2</i>	190182	Loeys-Dietz syndrome 2
17	TGF- β pathway	<i>SMAD3</i>	613795	Loeys-Dietz syndrome 3
18	TGF- β pathway	<i>TGFB2</i>	190220	Loeys-Dietz syndrome 4
19	TGF- β pathway	<i>TGFB3</i>	615582	Loeys-Dietz syndrome 5
20	Cytoskeletal/smooth muscle contraction apparatus proteins	<i>MYH11</i>	132900	Aortic aneurysm, familial thoracic 4
21	Cytoskeletal/smooth muscle contraction apparatus proteins	<i>ACTA2</i>	611788	Aortic aneurysm, familial thoracic 6
22	Cytoskeletal/smooth muscle contraction apparatus proteins	<i>MYLK</i>	613780	Aortic aneurysm, familial thoracic 7
23	Cytoskeletal/smooth muscle contraction apparatus proteins	<i>PRKG1</i>	615436	Aortic aneurysm, familial thoracic 8
24	Cytoskeletal/smooth muscle contraction apparatus proteins	<i>FLNA</i>	300375	Heterotopia, periventricular, Ehlers-Danlos variant
25	Neural crest migration	<i>NOTCH1</i>	109730	Familial thoracic aortic aneurysm with bicuspid aortic valve
26	Facilitative glucose transporter	<i>SLC2A10</i>	208050	Arterial tortuosity syndrome

ECM, extracellular matrix; TGF, transforming growth factor.

Table 2 Clinical characteristics of tested patients with Stanford type A AAD

Clinical characteristics	Total (n=100)
Age at onset, years	52.7±12.3
Male, n (%)	62 (62.0)
Family history, n (%)	0 (0.0)
Phenotype	
DeBakey type I, n (%)	84 (84.0)
Comorbidities and risk factors	
Hypertension, n (%)	65 (65.0)
Diabetes mellitus, n (%)	4 (4.0)
Coronary artery disease, n (%)	4 (4.0)
Smoke, n (%)	34 (34.0)
Alcohol history, n (%)	13 (13.0)
Clinical features	
BMI, kg/m ²	25.2±3.7
Ascending aorta diameter, mm	46.4±12.1
Facial features	0 (0.0)
Skeletal abnormalities	0 (0.0)

BMI, body mass index.

patients had 3 mutations, and 11 patients had 2 mutations), and the other 36 patients carried only 1 mutation (*Figure 2*).

Genetic mutations and clinical features and in-hospital death

Baseline clinical feature

Patients were grouped according to the presence of pathogenic variants [with (n=50) or without mutations of the panel genes (n=50)]. Patients with mutations were subdivided into a single-mutation group (n=36) or multiple-mutation group (n=14) according to the number of variants. Patients with mutations were further subdivided into groups based on whether they had mutations in the ECM coding gene (n=29) or only carried mutations in other genes (n=21). Comparisons of clinical characteristics in patients with respect to the presence and type of pathogenic mutations are detailed in *Table 4*.

An extended ascending aortic diameter was found in patients with mutations in the panel genes (49.1±12.3 *vs.* 43.7±11.2 mm, P=0.023) compared to patients without

mutations. The DeBakey type I phenotype was more common in patients with mutations in ECM coding genes than in patients with mutations in other genes (96.6% *vs.* 66.7%, P=0.007). Other clinical features were comparable between the groups (all Ps >0.05). *Table S5* shows the clinical characteristics of patients with the top 3 most frequent gene mutations (*FBN1*, *MYH11*, *MYLK*) in this cohort. *FBN1* was the most frequently mutated gene (n=10), and the onset age differed significantly between the three genes (P=0.021). The onset age of patients with mutations in *FBN1* was younger than that of patients without *FBN1* mutations (44.7±11.0 *vs.* 53.5±12.1, P=0.030).

In-hospital outcome

The overall in-hospital mortality was 12.0% (12/100) in all enrolled patients with STAAD. Of these patients, 66.6% (8/12) died of aortic rupture, and 33.3% (4/12) died of cardiac issues (*Table S6*). Clinical outcomes in these patients were summarized according to the presence, number and type of mutations (*Figure 3*). In-hospital mortality was 3-fold higher in patients with mutations than in patients without mutations, but the difference was not statistically significant (18.0% *vs.* 6.0%, P=0.065). The in-hospital death rate was comparable regardless of the number or type of mutation the patients carried (all Ps >0.05, *Figure 3A*).

Because of the significant impact of surgical treatment on in-hospital death from STAAD, patients were subdivided into a conservative treatment group and a surgical intervention group. The in-hospital mortality was 27.0% (10/37) and 3.2% (2/63) in patients with conservative and surgical treatments, respectively. Subgroup analysis of in-hospital mortality was also performed in different treatment groups according to the presence, number and type of mutations. *Figure 3B* shows that in-hospital mortality was comparable between patients with and without mutations who received surgical treatment (3.1% *vs.* 3.2%, P=1.000). However, increased in-hospital mortality in mutation carriers was observed only in patients who received conservative treatment (44.4% *vs.* 10.5%, P=0.029). When the in-hospital mortality was compared between the mutation number and mutations in different gene groups, no statistically significant differences were observed (all Ps >0.05, in *Figure 3C,D*).

Discussion

The current study analysed genetic variants of 26 panel genes that cause thoracic aortic aneurysm and aortic

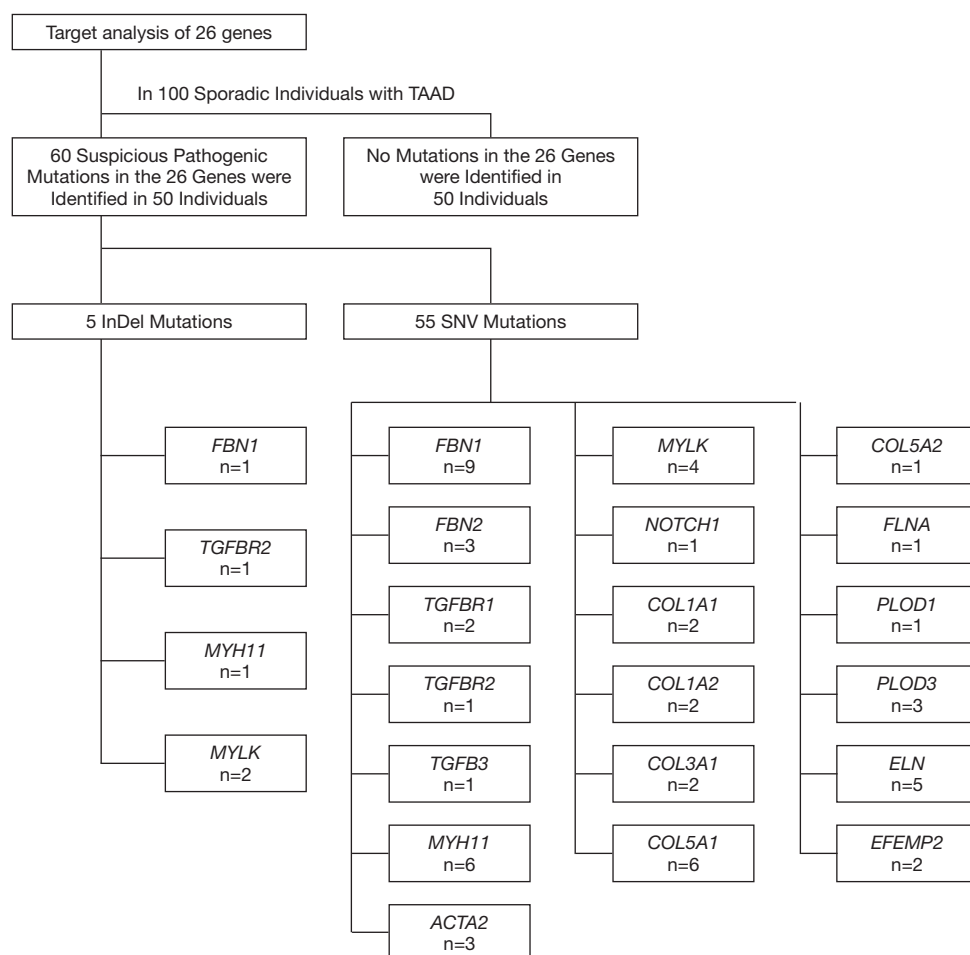


Figure 1 Summary of the genetic variants of the panel genes based on the results of whole-genome sequencing. STAAD, Stanford type A aortic dissection; SNV, single-nucleotide variants.

dissection (TAAD) in 100 patients with sporadic STAAD using WGS. Sixty probable disease-causing mutations were identified in half of the enrolled patients for 19 of the 26 panel genes. Fifty-six of these mutations were newly discovered, and 4 mutations were previously reported. Patients with mutations in the panel genes had an ascending aorta with a larger diameter and a poorer in-hospital outcome than patients without mutations. Patients with mutations in ECM coding genes seemed more likely to develop a severe AD phenotype (DeBakey type I) than patients with mutations in other genes.

Previous studies have shown that genetic disorders are associated with aortic aneurysm and dissection. NGS-based gene panel testing is widely used to detect genetic susceptibility to aortic disorders. Three studies investigated the genetic variants in TAAD in European populations.

Poninska *et al.* used whole-exome sequencing (WES) and a gene panel to study 51 patients with TAAD and reported a 35.3% diagnostic yield (10). Campens *et al.* found variants in 13% of TAAD patients using a panel of 7 genes (11). Proost *et al.* screened 14 genes from 55 patients and identified 15 pathogenic mutations and six variants of uncertain significance (12). An American study with a larger sample size (n=102) showed that 4.9% of patients carried a pathogenic/likely pathogenic variant, and 22% had a variant of uncertain significance based on a 21-gene panel (13). Wooderchak *et al.* found pathogenic variants in 10% of patients and variants of uncertain significance in 18% of patients (14). Zheng *et al.* found genotype-positive variants in 28.8% of TAAD patients in a South Chinese Han cohort using a 69-gene panel (15), and Fang *et al.* identified 40 variants (3 pathogenic, 10 likely pathogenic

Table 3 Detailed list of identified variants in patients with mutations of panel genes

No.	Affected genes	Chromosome location (HG 19)	Transcription	Exon	Variant (DNA level)	Variant (protein level)	Variant type	Variant previously reported	Sift [†]	Polyphen [†]	Patient ID	Age, sex
1	FBN1	Chr15:48703206	NM_000138	exon66	c.T8597A	p.I2866N	Missense	Novel	D	P	A486	59, F
	FBN1	Chr15:48717611	NM_000138	exon60	c.T7408G	p.C2470G	Missense	Novel	D	D	A403	43, F
	FBN1	Chr15:48720626	NM_000138	exon57	c.G6914C	p.G2305A	Missense	Novel	T	D	A65	55, M
	FBN1	Chr15:48737635	NM_000138	exon48	c.G5855A	p.G1952E	Missense	Novel	D	D	A483	51, M
	FBN1	Chr15:48766500	NM_000138	exon34	c.C4162T	p.R1388C	Missense	Novel	D	P	A73	45, M
	FBN1	Chr15:48787358	NM_000138	exon22	c.G2639A	p.G880D	Missense	Novel	D	D	A342	48, M
	FBN1	Chr15:48787384	NM_000138	exon22	c.A2613C	p.L871F	Missense	Novel	D	D	A291	20, F
	FBN1	Chr15:48812996	NM_000138	exon10	c.G1007C	p.C336S	Missense	Novel	T	D	A458	42, M
	FBN1	Chr15:48738912	NM_000138	exon47	c.5778delT	p.N1926fs	Frameshift deletion	Novel	D	D	A203	49, M
	FBN1	Chr15:48802262	NM_000138	exon14	c.C1693T	p.R665X	Nonsense	Known	D	D	A434	35, M
2	MYH11	Chr16:15814118	NM_002474	exon34	c.G4843A	p.A1615T	Missense	Novel	D	P	A437	60, M
	MYH11	Chr16:15820797	NM_002474	exon28	c.A3766C	p.K1256Q	Missense	Novel	D	D	A445; A485	51, F; 81, F
	MYH11	Chr16:15814752	NM_002474	exon33	c.G4735A	p.D1579N	Missense	Novel	D	D	A295	76, M
	MYH11	Chr16:15814883	NM_002474	exon33	c.G4604A	p.R1535Q	Missense	Novel	D	D	A486; A263	59, F; 46, M
	MYH11	Chr16:15815415	NM_002474	exon32	c.A4442T	p.K1481M	Missense	Novel	T	D	A313	72, F
	MYH11	Chr16:15931842	NM_001040113	exon2	c.A268G	p.M90V	Missense	Novel	D	D	A483	51, M
3	MYH11	Chr16:15820794	NM_002474	exon28	c.3757_3759del	p.1253_1253del	Nonframeshift deletion	Novel	D	D	A315	67, M
	MYLK	Chr3:123356997	NM_053026	exon28	c.G4675A	p.V1559M	Missense	Novel	D	D	A242	55, M
	MYLK	Chr3:123419455	NM_053026	exon17	c.C2653T	p.R885C	Missense	Novel	T	D	A137	70, M
	MYLK	Chr3:123427731	NM_053026	exon14	c.C1747G	p.P583A	Missense	Novel	T	D	A199	30, F
	MYLK	Chr3:123427662	NM_053026	exon14	c.G1816A	p.G606R	Missense	Novel	D	D	A197; A260	38, M; 77, F
	MYLK	Chr3:123337586	NM_053031	exon2	c.113_114insTG	p.A38fs	Frameshift insertion	Novel	D	D	A480	52, F

Table 3 (continued)

Table 3 (continued)

No.	Affected genes	Chromosome location (HG 19)	Transcription	Exon	Variant (DNA level)	Variant (protein level)	Variant type	Variant previously reported	Sift [†]	Polyphen [†]	Patient ID	Age, sex
	MYLK	Chr3:123452658	NM_053025	exon10	c.1179_1181del	p.393_394del	Nonframeshift deletion	Novel	D	D	A209	49, F
4	COL5A1	Chr9:137582848	NM_000093	exon2	c.C200T	p.S67F	Missense	Novel	D	P	A459	44, M
	COL5A1	Chr9:137591878	NM_000093	exon3	c.G401A	p.R134H	Missense	Novel	D	D	A185	46, F
	COL5A1	Chr9:137623972	NM_000093	exon9	c.C1388T	p.P463L	Missense	Novel	D	D	A436	66, M
	COL5A1	Chr9:137698140	NM_000093	exon42	c.C3364A	p.P1122T	Missense	Novel	D	B	A458	42, M
	COL5A1	Chr9:137701090	NM_000093	exon43	c.C3428T	p.P1143L	Missense	Novel	T	D	A309	38, M
	COL5A1	Chr9:137727015	NM_000093	exon65	c.A5335G	p.N1779D	Missense	Novel	D	B	A282	54, F
5	ELN	Chr7:73474880	NM_001278939	exon26	c.G1883C	p.G628A	Missense	Novel	D	-	A199	30, F
	ELN	Chr7:73470666	NM_001278913	exon17	c.G1108A	p.G370S	Missense	Novel	T	D	A295	76, M
	ELN	Chr7:73466278	NM_001278913	exon14	c.C806T	p.A269V	Missense	Novel	D	D	A95	43, M
	ELN	Chr7:73461035	NM_001278918	exon9	c.C449T	p.P150L	Missense	Novel	T	D	A201	75, F
	ELN	Chr7:73449715	NM_000501	exon2	c.G104C	p.G35A	Missense	Novel	T	D	A239	66, F
6	ACTA2	Chr10:90701550	NM_001141945	exon5	c.G446A	p.R149H	Missense	Known	D	D	A130; A406	42, M; 64, F
	ACTA2	Chr10:90699437	NM_001141945	exon7	c.G635A	p.R212Q	Missense	Known	D	D	A199; A476	30, F; 43, F
	ACTA2	Chr10:90707140	NM_001141945	exon3	c.G133T	p.V45L	Missense	Novel	D	D	A451	76, F
7	COL1A2	Chr7:94055131	NM_000089	exon44	c.G2905A	p.V969M	Missense	Novel	D	B	A349	57, M
	COL1A2	Chr7:94052321	NM_000089	exon40	c.G2456A	p.R819H	Missense	Novel	D	D	A199; A291	30, F; 20, F
8	FBN2	Chr5:127714544	NM_001999	exon12	c.A1643C	p.D548A	Missense	Novel	T	D	A282	54, F
	FBN2	Chr5:127800434	NM_001999	exon6	c.G809T	p.R270L	Missense	Novel	D	D	A246	60, M
	FBN2	Chr5:127670946	NM_001999	exon30	c.G3889A	p.G1297S	Missense	Novel	D	D	A457	43, M
9	PLOD3	Chr7:100854915	NM_001084	exon12	c.G1315A	p.A439T	Missense	Novel	D	P	A320	40, M
	PLOD3	Chr7:100850890	NM_001084	exon17	c.C1904T	p.T635I	Missense	Novel	T	D	A58	68, F
	PLOD3	Chr7:100858379	NM_001084	exon6	c.G670A	p.G224R	Missense	Novel	D	D	A180	63, F

Table 3 (continued)

Table 3 (continued)

No.	Affected genes	Chromosome location (HG 19)	Transcription	Exon	Variant (DNA level)	Variant (protein level)	Variant type	Variant previously reported	Sift [†]	Polyphen [†]	Patient ID	Age, sex
10	COL1A1	Chr17:48267260	NM_000088	exon37	c.C2573G	p.A858G	Missense	Novel	D	B	A349	57, M
	COL1A1	Chr17:48269364	NM_000088	exon30	c.G2005A	p.A669T	Missense	Novel	T	D	A65	55, M
11	COL3A1	Chr2:189870953	NM_000090	exon42	c.C3061A	p.L1021I	Missense	Novel	T	D	A180	63, F
	COL3A1	Chr2:189859447	NM_000090	exon20	c.1348-3C>T	-	Splicing site	Novel	-	-	A480	52, F
12	EFEMP2	Chr11:65635400	NM_016938	exon10	c.G1102A	p.V368I	Missense	Novel	T	D	A131	58, F
	EFEMP2	Chr11:65638012	NM_016938	exon5	c.G485A	p.C162Y	Missense	Novel	D	D	A342	48, M
13	TGFBR1	Chr9:101904938	NM_001130916	exon4	c.C695T	p.T232M	Missense	Novel	D	D	A217	38, M
	TGFBR1	Chr9:101911496	NM_001130916	exon8	c.G1190A	p.C397Y	Missense	Novel	D	D	A64	55, F
14	TGFBR2	Chr3:30732951	NM_003242	exon7	c.G1564A	p.D522N	Missense	Known	D	D	A290	31, F
	TGFBR2	Chr3:30713543	NM_003243	exon4	c.871_873del	p.291_291del	Nonframeshift deletion	Novel	D	D	A291	20, F
15	COL5A2	Chr2:189918632	NM_000393	exon37	c.C2488T	p.R830W	Missense	Novel	-	D	A163	49, M
16	FLNA	ChrX:153590106	NM_001110556	exon20	c.G2876A	p.S959N	Missense	Novel	D	D	A448	53, F
17	NOTCH1	Chr9:139993702	NM_017617	exon32	c.C5944T	p.R1982W	Missense	Novel	D	D	A457	43, M
18	PLOD1	Chr1:12017040	NM_000302	exon7	c.C710T	p.P237L	Missense	Novel	D	D	A349	57, M
19	TGFB3	Chr14:76427339	NM_003239	exon6	c.C1007T	p.P336L	Missense	Novel	D	D	A246	60, M

[†], SIFT prediction: D, not tolerated; T, tolerated; [†], PolyPhen prediction: D, probably damaging; P, possibly damaging; B, benign; -, not applicable.

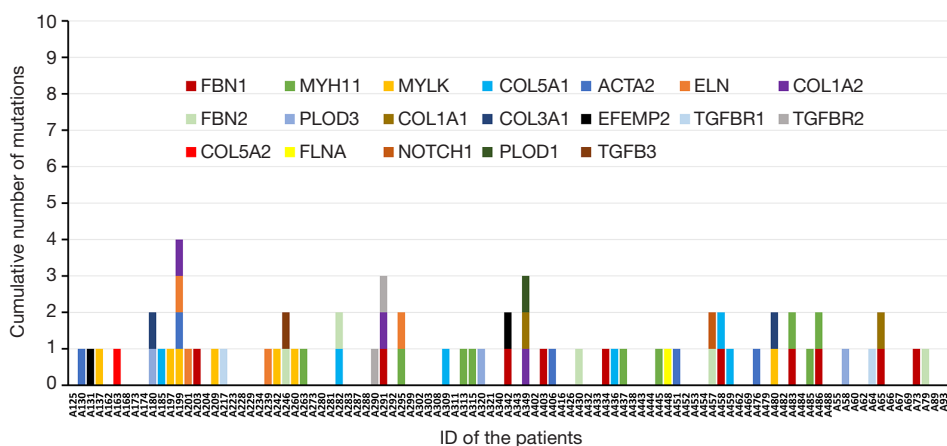


Figure 2 Gene mutations identified by whole-genome sequencing in 100 subjects with sporadic Stanford type A aortic dissection. Fourteen percent of patients (14/100) carried more than one mutation.

and 27 variants of uncertain significance) in 36 of 70 TAAAD patients (16). Similar to the two Chinese investigations, the genotype-positive rate in our study was clearly higher than that in Western cohorts. The higher mutation rate may be due to the following reasons. First, we only included patients without a family history, and the genetic changes in sporadic patients may differ from those in patients with a family history. These patients may have a greater likelihood of carrying a single mutation with a relatively lower penetrance and show a sporadic form. Second, we only included patients with STAAD who had a stronger genetic component than patients with Stanford type B AD or patients with aortic aneurysms who showed associations with lifestyle-linked risk factors. Third, the patients included in this study were primarily northern Han Chinese people, whose genetic backgrounds are completely different and who have a younger onset age of AD compared to Western populations.

MFS is the most common aortic aneurysm syndrome caused by heterozygous mutations in *FBN1*. A genome-wide association study (GWAS) analysed 765 sporadic cases of TAAAD, including STAAD, and found that common single-nucleotide polymorphisms (SNPs) in the *FBN1* gene were significantly associated with an increased risk of developing aortic aneurysms and dissections (17). Rare mutations of *FBN1* were also found in 15.75% of STAAD cases in a Chinese population (18). Mutations in *FBN1* were also the most frequent (10 mutations, 1 known and 9 novel) in sporadic STAAD in our study. However, except for a previously reported stop-gain mutation (exon 14, pR565X) (19), none of these mutations were located in the

central coding sequences (exons 24–32) of the *FBN1* gene, the disturbance of which may cause a severe phenotype of MFS (20,21). The location of these variants may partially explain the milder penetrance and variable expressivity in the sporadic form. Consistent with studies that reported on Marfan and non-Marfan patients with aortic disorders (22,23), patients carrying mutations in *FBN1* were younger than other patients in our study.

Collagens are the most important components of the ECM, and certain coding genes in collagens are related to EDS. The syndrome, which causes a disorder in the connective tissue, is divided into different phenotypes based on changes in different genes (24,25). AD is one of the most severe complications of this syndrome, especially in EDS type IV (also known as vascular type, with mutations in *COL3A1*) (26). Patients with EDS show poor prognosis due to the fragility of aortic tissues and poor wound healing. According to data from a previous study (27) and our study, a considerable proportion of sporadic cases of AD showed likely pathogenic variants in EDS-related genes, which may partially explain the poor outcome in some of the AD patients. Other genetic variants were also found in genes responsible for LDS (mutations related to the TGF- β signalling pathway) at a relatively lower ratio (5% cases). De novo mutations were found in 75% of patients with LDS (28), and LDS can occur in sporadic form (29). Five probable pathogenic variants were also found in LDS-related genes in our cohort, including *TGFBR1*, *TGFBR2* and *TGFB3*.

The ECM is the key structural component of the aorta, as ECM elements provide elasticity and tensile

Table 4 Baseline characteristics of sporadic subjects diagnosed with Stanford type A AAD related to the presence, number and type of pathogenic mutations

Clinical characteristics	Total (n=100)		Mutations of the panel genes		Number of mutations of the panel genes		Type of mutations		
	With (n=50)	Without (n=50)	P value	Single (n=36)	Multiple (n=14)	P value	ECM coding (n=29)	Other (n=21)	P value
Age at onset, years	52.7±12.3	52.7±13.8	0.948	53.5±13.8	50.7±13.9	0.522	50.7±12.5	55.5±15.3	0.228
Male, n (%)	62 (62.0)	29 (58.0)	0.410	20 (55.6)	9 (64.3)	0.547	20 (69.0)	9 (42.9)	0.086
Height, cm	169.1±7.7	168.5±7.8	0.455	167.9±7.9	170.1±7.8	0.382	170.1±7	166.2±8.6	0.083
Weight, kg	71.9±12.3	71.5±12.5	0.737	71.8±11.8	70.9±14.4	0.836	74±13.1	68.1±10.8	0.102
BMI, kg/m ²	25.2±3.7	25.1±3.8	0.915	25.4±3.6	24.4±4.5	0.426	25.5±4	24.7±3.7	0.449
DeBakey type I, n (%)	84 (84.0)	42 (84.0)	1.000	10 (88.9)	10 (71.4)	0.197	28 (96.6)	14 (66.7)	0.007
Hypertension, n (%)	65 (65.0)	33 (66.0)	0.834	24 (66.7)	9 (64.3)	1.000	18 (62.1)	15 (71.4)	0.490
Diabetes mellitus, n (%)	4 (4.0)	0 (0.0)	0.126	0 (0.0)	0 (0.0)	1.000	0 (0.0)	0 (0.0)	1.000
Coronary artery disease, n (%)	4 (4.0)	2 (4.0)	1.000	0 (0.0)	2 (14.3)	0.131	2 (6.9)	0 (0.0)	0.503
Smoke, n (%)	34 (34.0)	17 (34.0)	1.000	12 (33.3)	5 (35.7)	1.000	14 (48.3)	6 (28.6)	0.160
Alcohol history, n (%)	13 (13.0)	6 (12.0)	1.000	4 (11.1)	2 (14.3)	1.000	4 (13.8)	4 (19.0)	0.706
SBP, mmHg	119.7±18.9	119.6±18.2	0.962	118±18.9	123.6±16.6	0.310	118.9±20.4	120.6±15.2	0.741
DBP, mmHg	62.9±12.2	63.2±13.2	0.794	61.4±13.3	67.9±12.1	0.110	62.2±12.3	64.6±14.5	0.537
Heart rate, bpm	84.8±11.9	84.1±12.2	0.525	83.3±13.2	86.1±9.2	0.458	86.1±14	81.3±8.7	0.175
Ascending aorta diameter, mm	46.4±12.1	49.1±12.3	0.023	49.9±12.7	47.1±11.5	0.465	49.3±11.9	48.9±13.2	0.904
Surgical intervention, n (%)	63 (63.0)	32 (64.0)	0.836	22 (61.6)	10 (71.4)	0.495	21 (72.4)	11 (52.4)	0.145

ECM, extracellular matrix; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

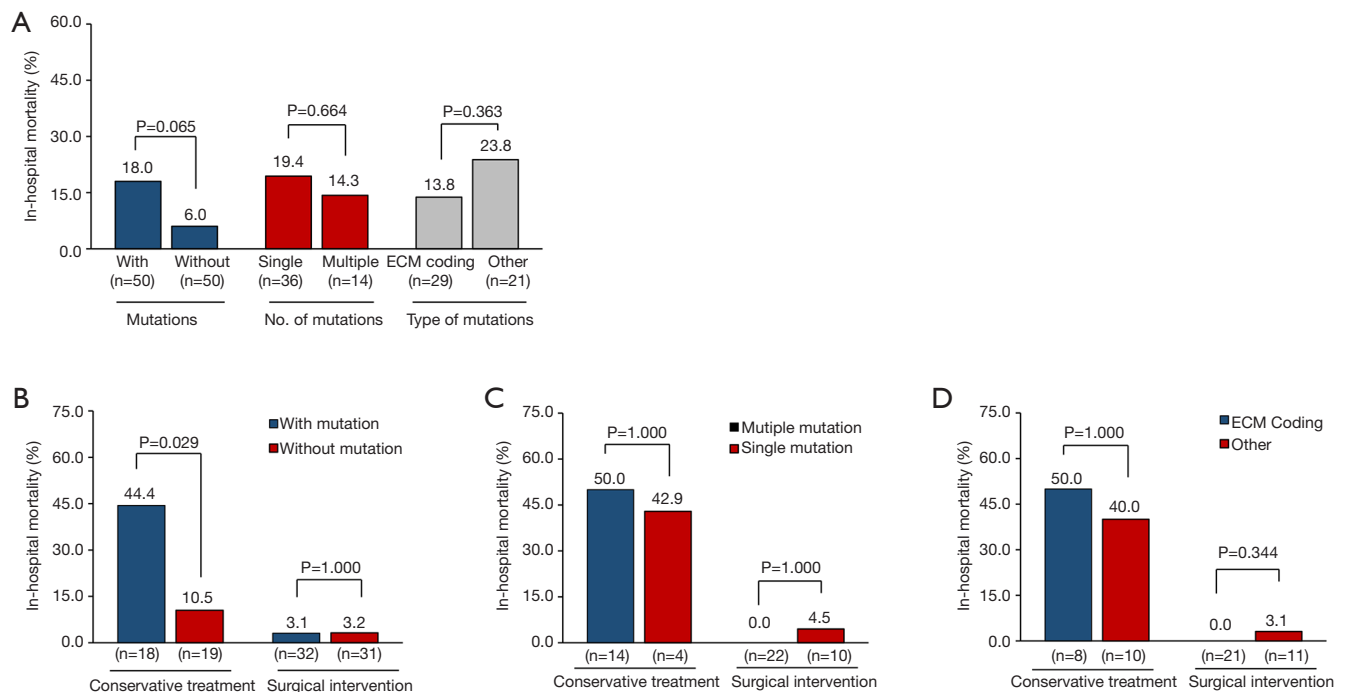


Figure 3 In-hospital outcome in subjects with Stanford type A aortic dissection. (A) Comparison of in-hospital mortality according to the presence, number and type of mutations. Subgrouped comparisons of all-cause mortality stratified by the presence (B), number (C) and type (D) of mutations in patients who received conservative treatment or surgical intervention.

strength to blood vessel walls. The ECM also provides important growth factors, such as TGF- β (6). In our study, the DeBakey type I phenotype was more common in patients with mutations in ECM coding genes (96.6%), which indicates a larger extent of damage. The findings indicated that defects in the ECM components likely had a destructive impact on the structure of the aorta and showed a distinct relationship with the clinical phenotype.

Genetic variants related to vascular smooth muscle cell (SMC) contractility often show associations with nonsyndromic aortic aneurysms and dissections, such as actin alpha 2 (*ACTA2*), *MYH11* and myosin light-chain kinase (*MYLK*). The *ACTA2* gene encodes an SMC-specific isoform of the contractile protein α -actin (30-32). Mutations in *ACTA2* are the most common reason for nonsyndromic aortic aneurysms and dissection and account for approximately 2–4% of sporadic cases of aortic disorder (7,32). Similar to previously reported results, we found that 5% (5/100) of patients carried 3 mutations in *ACTA2*. Two of these mutations were previously reported (33) but corresponded to different changes (p. R149H and p.R212Q). The number of mutations in *MYLK* and

MYH11 was 13, affecting 16 patients, and all of these mutations were novel. Mutations in *MYH11* are associated with familial TAAD (5), but the average age of onset was difficult to judge in different familial forms. Nine sporadic patients who carried mutations in *MYH11* in our study were older than the other patients. However, this observation may be due to the limited sample size, and further confirmation in a larger cohort is needed in future studies.

The clinical data of this study revealed that genetic differences showed an association with the phenotype of the individual and clinical outcomes. Variants that increase susceptibility to AD may also increase the risk of in-hospital death. This phenomenon stresses the importance of genetically personalized care and subsequent precision treatment in STAAD, especially patients with mild-to-moderate dilation of the ascending aorta, even without a family history. Although additional novel genes were associated with aortic diseases, routine genetic testing using classic gene panels showed strength in the identification of pathogenic variants in STAAD patients (13). A considerable proportion of STAAD patients were associated with

mutations in known pathogenic genes. We also recommend that routine genetic testing be performed first in clinical practice, and other patients with AD may undergo WGS or WES to identify previously unreported changes.

The present study has two important strengths. First, the present study used an enlarged panel of classic pathogenic genes to investigate AD-related genetic changes in a Chinese population with a rare mutation analysis strategy and did not analyse only common polymorphisms. The rate of mutation carriers in our cohort was almost twice the rate of TAAD in a study performed in a Western population (10-14). This difference may partially explain the younger onset age of AD in Chinese patients (34). Second, the present study revealed the potential impact of certain genetic changes on the clinical features and outcomes of AD, which may be of great transitional significance in clinical management.

Several limitations of the present study must be mentioned. First, confounding factors may exist due to the single-centre setting, and the findings obtained in this cohort may not extend to other populations. The small sample size also did not allow for extended analyses of subgroups and corrections. Second, whether the probable pathogenic variants are disease-causing or benign must be determined. Finally, we only primarily reviewed part of the data from WGS, and further analyses and confirmations have not been completed. Despite the relatively small sample size, the clinical features and outcomes showed a relationship with the pathogenic genotype. However, the insufficient sample size restricted further analyses of clinical data, and confirmations from a large multicentre cohort may be needed in the future.

Conclusions

Our study indicated that half of Chinese patients with sporadic STAAD may carry mutations in known pathogenic genes of aortic disease and may exhibit severe clinical features and poor clinical outcomes with conservative treatment.

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Footnote

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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 performed in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Fuwai Hospital (No. 2012-396). Informed consent was obtained from all patients.

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Table S1 Coverage and depth of WGS in the 100 type A AAD patient

Sample:	Average depth:	Coverage	Coverage_at_least_4X	Coverage_at_least_10X	Coverage_at_least_20X
A125	30.84	99.70%	99.31%	96.89%	81.47%
A130	33.41	98.96%	98.44%	95.78%	81.59%
A131	38.59	99.02%	98.70%	97.68%	92.04%
A137	31.76	99.71%	99.28%	96.99%	84.51%
A162	31.72	98.99%	98.55%	96.51%	83.94%
A163	31.5	99.67%	98.89%	94.49%	75.82%
A168	41.26	99.04%	98.75%	97.99%	94.24%
A173	36.44	99.77%	99.52%	98.49%	91.04%
A174	31.96	99.73%	99.46%	98.13%	88.04%
A180	30.59	98.91%	98.36%	95.32%	78.69%
A185	32.39	98.98%	98.63%	97.28%	87.88%
A197	29.8	99.64%	98.59%	92.81%	71.44%
A199	29.89	99.58%	98.42%	91.70%	68.95%
A201	33.04	98.99%	98.58%	97.01%	86.55%
A203	32.02	99.70%	99.41%	97.96%	87.40%
A204	37.47	99.76%	99.51%	98.44%	90.95%
A209	31.69	99.74%	99.34%	97.02%	84.03%
A217	31.79	99.68%	99.25%	96.70%	82.11%
A223	31.11	99.70%	99.07%	95.21%	77.12%
A228	32.29	98.93%	98.22%	94.86%	80.85%
A229	31.38	99.74%	99.39%	97.50%	85.64%
A234	37.17	99.68%	99.28%	97.58%	88.68%
A239	35.41	98.93%	98.55%	96.98%	87.15%
A242	32.3	99.70%	99.20%	96.26%	81.10%
A246	29.92	99.71%	99.19%	96.24%	79.93%
A260	31.23	98.99%	98.67%	97.61%	89.11%
A263	35.04	99.66%	99.04%	95.90%	82.99%
A273	41.94	98.98%	98.64%	97.62%	92.50%
A280	30.85	99.00%	98.55%	96.38%	82.61%
A281	30.58	99.64%	99.20%	96.58%	81.76%
A282	31.58	98.99%	98.59%	96.85%	85.80%
A283	34.06	99.71%	99.32%	97.32%	85.90%
A287	31.69	99.68%	99.16%	96.16%	81.21%
A288	30.37	99.60%	98.66%	93.44%	73.34%
A290	33.24	99.02%	98.77%	98.10%	92.47%
A291	31.86	98.99%	98.38%	95.22%	80.51%
A292	39.85	99.70%	99.30%	97.32%	87.30%
A295	30.64	99.67%	99.07%	95.32%	77.40%
A299	35.41	99.69%	99.18%	96.41%	82.99%
A302	29.99	98.30%	95.20%	85.66%	63.78%
A303	31.67	99.72%	99.44%	98.03%	87.56%
A308	30.48	99.63%	98.69%	93.32%	72.25%
A309	30.36	99.71%	99.12%	95.38%	76.20%
A311	30.39	99.49%	98.09%	91.22%	69.16%
A313	30.48	98.97%	98.62%	97.04%	83.59%
A315	38.62	99.74%	99.49%	98.48%	91.64%
A320	30.91	99.67%	99.30%	97.18%	83.82%
A321	31.62	98.96%	98.51%	96.22%	81.75%
A340	31.26	99.63%	99.08%	95.88%	79.57%
A342	30.41	99.65%	99.24%	96.83%	82.17%
A343	37.2	98.92%	98.46%	96.37%	86.05%
A349	36.04	99.61%	98.95%	95.44%	80.66%
A402	32.34	99.50%	98.03%	91.08%	70.34%
A403	33.12	98.96%	98.05%	93.79%	78.68%
A406	30.48	98.90%	98.20%	94.48%	76.68%
A416	32.15	99.65%	99.02%	95.35%	78.72%
A426	30.38	99.75%	99.47%	98.00%	86.79%
A430	35.92	99.62%	98.93%	95.15%	79.73%
A432	33.22	98.99%	98.48%	95.88%	80.85%
A433	31.31	98.99%	98.50%	96.26%	83.16%
A434	40.59	99.74%	99.52%	98.77%	93.68%
A436	32.16	99.69%	99.26%	96.71%	82.02%
A437	31.68	99.69%	99.25%	96.83%	84.14%
A438	34.19	98.93%	98.51%	96.57%	85.02%
A443	33.28	99.68%	99.02%	95.32%	78.88%
A444	33.52	99.75%	99.47%	98.12%	88.47%
A445	30.53	98.94%	98.59%	97.16%	86.40%
A448	31.65	98.96%	98.29%	95.00%	78.01%
A451	30.57	99.00%	98.58%	96.54%	82.84%
A452	30.98	98.97%	98.60%	96.93%	84.74%
A453	32.52	99.69%	99.16%	96.20%	81.13%
A454	30.36	99.76%	99.48%	97.86%	85.88%
A457	31.52	99.66%	98.84%	94.19%	75.82%
A458	31.01	99.69%	99.20%	96.23%	80.14%
A459	31.45	99.68%	99.02%	95.41%	79.15%
A462	33.17	99.54%	98.45%	93.20%	75.16%
A469	30.9	99.72%	99.28%	96.68%	81.69%
A476	35.02	98.94%	98.25%	95.50%	83.33%
A479	32.61	99.52%	98.22%	91.96%	71.85%
A480	30.85	99.00%	98.57%	96.58%	83.47%
A482	30.95	98.89%	98.19%	94.50%	76.60%
A483	31.06	99.65%	99.13%	95.91%	79.24%
A484	33.41	99.62%	98.96%	95.33%	79.77%
A485	33.47	99.02%	98.68%	97.38%	89.49%
A486	32.14	98.95%	98.29%	94.90%	77.42%
A488	29.7	99.64%	98.56%	92.40%	69.91%
A55	30.69	99.68%	99.38%	97.74%	85.72%
A58	31.79	99.00%	98.66%	97.11%	88.11%
A60	33.03	98.98%	98.53%	96.45%	86.06%
A62	30.17	99.54%	98.47%	93.09%	73.17%
A64	30.94	98.96%	98.48%	96.28%	83.66%
A65	31.91	99.74%	99.45%	97.69%	86.14%
A66	34.75	99.76%	99.56%	98.63%	90.96%
A67	31.57	99.62%	98.71%	94.16%	75.64%
A69	32.47	99.01%	98.66%	97.38%	86.72%
A73	32.96	99.74%	99.44%	98.05%	88.55%
A79	30.9	99.31%	96.33%	86.32%	66.24%
A89	32.85	99.54%	98.09%	91.82%	72.21%
A93	30.62	98.74%	93.85%	82.06%	63.44%
A95	31.74	99.34%	97.44%	89.83%	68.87%

Table S2 Coverage and depth for mutated genes in the specific sample

Sample Name	Gene Name	Coverage	Average_depth
A130	<i>ACTA2</i>	99.87%	30.2246
A131	<i>EFEMP2</i>	100.00%	43.645
A137	<i>MYLK</i>	99.93%	29.7771
A163	<i>COL5A2</i>	99.88%	20.84
A180	<i>COL3A1</i>	99.73%	20.5221
A180	<i>PLOD3</i>	100.00%	38.8249
A185	<i>COL5A1</i>	99.94%	33.8456
A197	<i>MYLK</i>	99.93%	31.5416
A199	<i>ACTA2</i>	99.91%	28.695
A199	<i>COL1A2</i>	100.00%	24.2759
A199	<i>ELN</i>	100.00%	43.9571
A199	<i>MYLK</i>	99.93%	36.5527
A201	<i>ELN</i>	100.00%	36.8722
A203	<i>FBN1</i>	99.85%	30.1679
A209	<i>MYLK</i>	99.96%	33.3259
A217	<i>TGFBR1</i>	99.91%	28.6477
A239	<i>ELN</i>	100.00%	39.8526
A242	<i>MYLK</i>	99.96%	33.8056
A246	<i>FBN2</i>	99.92%	25.7389
A246	<i>TGFB3</i>	100.00%	33.7657
A260	<i>MYLK</i>	99.94%	28.324
A263	<i>MYH11</i>	99.97%	37.2004
A282	<i>COL5A1</i>	99.96%	31.8914
A282	<i>FBN2</i>	99.95%	28.0741
A290	<i>TGFBR2</i>	99.92%	30.0931
A291	<i>COL1A2</i>	100.00%	26.6247
A291	<i>FBN1</i>	99.91%	28.0966
A291	<i>TGFBR2</i>	99.92%	30.6375
A295	<i>ELN</i>	100.00%	34.95
A295	<i>MYH11</i>	99.97%	32.0569
A309	<i>COL5A1</i>	99.99%	41.9906
A313	<i>MYH11</i>	99.97%	30.3203
A315	<i>MYH11</i>	100.00%	36.8508
A320	<i>PLOD3</i>	100.00%	29.5451
A342	<i>EFEMP2</i>	100.00%	31.1949
A342	<i>FBN1</i>	99.85%	28.9298
A349	<i>COL1A1</i>	100.00%	49.4951
A349	<i>COL1A2</i>	99.87%	26.4775
A349	<i>PLOD1</i>	99.55%	40.2722
A403	<i>FBN1</i>	99.82%	27.453
A406	<i>ACTA2</i>	99.90%	29.3615
A430	<i>FBN2</i>	99.79%	27.226
A434	<i>FBN1</i>	99.95%	36.0172
A436	<i>COL5A1</i>	99.95%	38.768
A437	<i>MYH11</i>	100.00%	26.2422
A445	<i>MYH11</i>	99.97%	26.4547
A448	<i>FLNA</i>	100.00%	53.5832
A451	<i>ACTA2</i>	99.87%	28.7851
A457	<i>FBN2</i>	99.88%	24.9377
A457	<i>NOTCH1</i>	99.99%	53.8418
A458	<i>COL5A1</i>	99.98%	37.4503
A458	<i>FBN1</i>	99.89%	25.9181
A459	<i>COL5A1</i>	99.95%	34.3485
A476	<i>ACTA2</i>	99.91%	33.03
A480	<i>COL3A1</i>	99.66%	21.5959
A480	<i>MYLK</i>	99.94%	31.0416
A483	<i>FBN1</i>	99.87%	28.056
A483	<i>MYH11</i>	99.99%	32.7046
A485	<i>MYH11</i>	99.97%	28.121
A486	<i>FBN1</i>	99.86%	25.8944
A486	<i>MYH11</i>	99.97%	33.7559
A58	<i>PLOD3</i>	100.00%	27.2218
A64	<i>TGFBR1</i>	99.92%	28.6646
A65	<i>COL1A1</i>	100.00%	31.4589
A65	<i>FBN1</i>	99.98%	29.6789
A73	<i>FBN1</i>	99.93%	31.129
A79	<i>FBN2</i>	99.38%	21.545
A95	<i>ELN</i>	99.95%	47.263

Table S3 Summary of the Quality Control for WGS

Sample name	Raw reads	Raw data(G)	Effective(%)	Error(%)	Q20(%)	Q30(%)	GC(%)
A234	68242360	112.47	99.72	0.03;0.06	95.99;90.46	90.86;80.95	42.42;42.53
A234	64207401		99.77	0.02;0.05	96.39;92.12	91.73;83.19	42.47;42.59
A234	65852300		99.76	0.02;0.05	96.48;92.09	91.89;83.18	42.50;42.63
A234	66726903		99.76	0.02;0.05	96.27;91.96	91.43;83.08	42.48;42.58
A234	109876053		99.75	0.02;0.05	96.27;92.15	91.62;83.43	42.43;42.57
A131	53392265	115.13	99.93	0.02;0.04	98.09;95.16	94.45;87.25	41.86;41.79
A131	85589822		99.35	0.02;0.06	96.28;90.90	91.59;81.43	42.31;42.39
A131	88670286		99.34	0.02;0.06	96.38;90.94	91.77;81.52	42.32;42.41
A131	85990756		99.33	0.02;0.06	96.17;90.76	91.31;81.36	42.32;42.37
A131	70107025		99.34	0.02;0.06	96.15;90.86	91.45;81.60	42.29;42.34
A130	44030048	100.21	99.35	0.02;0.03	97.22;94.28	93.60;87.77	43.81;43.79
A130	41734353		99.49	0.02;0.04	96.69;92.25	92.44;84.46	43.51;43.54
A130	50701573		98.99	0.02;0.03	97.15;94.17	93.23;87.28	43.67;43.69
A130	67145722		99.52	0.02;0.03	97.34;94.97	93.42;88.41	43.23;43.37
A130	66333103		99.47	0.02;0.03	97.16;94.21	93.09;87.60	43.25;43.33
A130	64086096		99.4	0.02;0.03	97.43;95.56	93.68;89.55	43.26;43.38
A137	36344886	95.98	99.1	0.03;0.06	96.18;91.02	91.24;81.53	41.80;41.75
A137	27100252		99.92	0.02;0.04	97.87;95.15	93.81;86.72	41.54;41.51
A137	33367492		98.77	0.03;0.07	95.68;90.69	90.28;80.89	41.93;42.05
A137	58010578		98.55	0.02;0.05	97.17;92.50	93.38;83.91	41.75;41.80
A137	53610876		98.65	0.02;0.04	97.57;93.17	94.18;84.95	41.74;41.75
A137	57610035		99.9	0.02;0.05	98.74;95.22	95.85;85.26	41.38;41.36
A137	53898804		98.8	0.02;0.04	96.87;92.87	92.65;84.57	41.77;41.81
A239	18725303	106.09	99.56	0.02;0.02	97.75;96.86	94.37;92.50	42.81;42.86
A239	87333011		99.56	0.02;0.02	98.07;96.75	95.08;92.14	42.82;42.91
A239	53408888		99.55	0.02;0.02	98.08;96.64	95.08;92.03	42.79;42.88
A239	53320486		99.55	0.02;0.02	98.09;96.55	95.12;91.81	42.77;42.84
A239	53488462		99.55	0.02;0.02	98.07;96.69	95.07;92.10	42.80;42.88
A239	33972412		99.56	0.02;0.02	97.76;96.78	94.39;92.25	42.83;42.90
A239	34447609		99.57	0.02;0.02	97.85;96.90	94.61;92.66	42.82;42.89
A239	18934867		99.56	0.02;0.02	97.78;96.83	94.48;92.59	42.76;42.83
A79	30485312	96.35	95.76	0.02;0.05	96.45;92.14	91.97;83.65	45.24;45.30
A79	80103931		96	0.02;0.05	96.82;92.17	92.60;83.48	45.27;45.35
A79	84538747		95.81	0.02;0.04	97.03;93.19	93.08;85.19	45.27;45.36
A79	48911286		96.5	0.02;0.05	96.52;91.51	92.27;83.07	45.34;45.49
A79	77118243		96.08	0.02;0.05	96.67;92.28	92.40;83.92	45.24;45.29
A73	50458521	99.34	99.22	0.02;0.03	96.97;93.87	92.87;86.62	41.87;41.98
A73	63529197		99.18	0.02;0.03	97.18;94.12	93.29;87.03	41.80;41.87
A73	70076687		99.17	0.02;0.03	97.37;93.73	93.75;86.48	41.78;41.84
A73	48992172		99.24	0.02;0.03	97.17;94.50	93.28;87.66	41.75;41.86
A73	52790685		99.27	0.02;0.03	96.97;94.14	92.71;86.90	41.62;41.72
A73	45281135		99.12	0.02;0.03	96.98;94.13	92.76;86.87	41.46;41.56

A436	40976015	97.66	98.89	0.02;0.04	96.68;93.40	92.32;86.26	42.69;42.72
A436	45213994		98.84	0.02;0.04	96.76;93.57	92.36;86.43	42.73;42.77
A436	45563698		98.85	0.02;0.04	96.73;93.61	92.33;86.46	42.73;42.78
A436	60721181		98.92	0.02;0.03	97.02;94.15	92.96;87.46	42.66;42.68
A436	45679411		98.99	0.02;0.04	96.53;93.58	92.16;86.63	42.67;42.73
A436	87673017		99.28	0.03;0.10	95.05;88.37	88.57;77.18	42.58;42.71
A437	44356511	94.64	99.89	0.02;0.05	98.13;94.85	94.36;86.29	40.93;40.83
A437	48293615		99.89	0.02;0.05	98.08;94.81	93.67;85.23	40.96;40.88
A437	50094644		99.89	0.02;0.05	98.12;94.67	93.77;84.95	40.92;40.84
A437	49957020		99.89	0.02;0.05	98.03;94.71	93.59;84.96	40.93;40.84
A437	41487112		99.91	0.02;0.05	98.21;94.41	94.55;85.44	41.02;40.89
A437	81274497		99.2	0.03;0.11	95.72;87.52	90.17;75.97	41.63;41.73
A434	70584320	122.7	99.49	0.02;0.06	96.27;91.14	91.65;81.83	41.37;41.47
A434	69666916		99.35	0.02;0.07	96.57;90.63	92.17;81.19	41.41;41.53
A434	54375032		99.4	0.02;0.06	96.62;91.32	92.33;82.42	41.38;41.51
A434	74718728		99.4	0.02;0.06	96.68;91.52	92.38;82.72	41.46;41.54
A434	73089078		99.41	0.02;0.06	96.68;91.46	92.38;82.61	41.42;41.48
A434	66562983		99.48	0.03;0.07	95.22;90.14	89.42;80.45	41.36;41.47
A432	71505018	100.98	99.91	0.02;0.04	97.99;95.20	94.18;87.27	42.86;42.82
A432	87397410		99.15	0.02;0.06	96.20;91.15	91.41;81.74	43.29;43.37
A432	90155159		99.12	0.02;0.06	96.31;91.17	91.59;81.79	43.32;43.41
A432	87536087		99.11	0.02;0.06	96.10;91.01	91.14;81.66	43.31;43.37
A433	49548787	94.42	99.31	0.02;0.06	96.57;90.06	91.96;80.22	42.66;42.71
A433	57683603		99.47	0.02;0.06	96.96;92.20	92.53;82.49	42.71;42.82
A433	55880619		99.49	0.02;0.06	96.62;91.18	91.85;80.95	42.66;42.78
A433	55857603		99.47	0.02;0.06	96.79;91.92	92.10;81.96	42.67;42.79
A433	49468402		99.5	0.02;0.04	97.19;93.36	93.28;85.46	42.70;42.73
A433	46295831		99.57	0.03;0.10	95.76;89.17	90.15;78.42	42.88;43.16
A430	67698907	109.18	98.74	0.02;0.04	96.61;93.49	91.77;86.24	44.08;44.18
A430	74706659		98.7	0.02;0.04	97.25;94.27	92.99;87.11	44.09;44.14
A430	73653106		98.67	0.02;0.03	97.41;95.55	93.34;89.23	44.11;44.18
A430	75389941		98.76	0.02;0.03	97.24;94.90	93.00;88.42	44.09;44.15
A430	72472325		98.73	0.02;0.03	97.23;95.30	93.07;89.02	44.03;44.11
A438	71118424	102.92	99.38	0.02;0.02	97.68;96.60	94.30;92.09	42.93;42.99
A438	70682552		99.39	0.02;0.02	97.73;96.75	94.42;92.37	42.88;42.95
A438	35391375		99.24	0.02;0.03	96.56;94.43	91.95;88.07	43.09;43.12
A438	39135906		99.24	0.02;0.03	96.59;94.95	92.06;88.96	43.11;43.16
A438	39831610		99.21	0.02;0.03	96.12;93.62	91.17;86.91	43.17;43.21
A438	54072627		99.22	0.02;0.04	96.28;93.18	91.54;86.28	43.17;43.22
A438	32829562		99.34	0.03;0.04	95.62;91.70	90.55;84.83	43.14;43.31
A454	77236638	91.76	99.2	0.03;0.07	95.44;90.16	89.85;80.26	41.44;41.60
A454	69457963		99.37	0.03;0.07	95.62;90.47	90.05;80.61	41.39;41.54
A454	71388505		99.32	0.03;0.06	95.76;91.04	90.43;81.49	41.44;41.57
A454	75414241		99.31	0.03;0.06	95.62;91.12	90.19;81.60	41.38;41.51
A454	12373885		99.37	0.03;0.09	95.67;89.02	90.07;78.31	41.32;41.31

A457	79579423	99.23	95.49	0.02;0.06	96.26;90.83	91.62;81.39	43.84;43.91
A457	85985447		95.81	0.02;0.06	96.59;90.81	92.14;81.17	43.86;43.95
A457	87890450		95.54	0.02;0.05	96.81;91.98	92.63;83.04	43.85;43.95
A457	47542559		96.21	0.02;0.06	96.54;91.39	92.08;82.08	43.87;43.97
A457	29781659		95.87	0.02;0.06	96.47;90.91	92.05;81.61	43.84;43.89
A451	30004365	92.14	99.61	0.02;0.04	97.07;92.02	93.32;83.75	42.36;42.52
A451	50796087		99.61	0.02;0.05	96.91;91.91	93.05;83.64	42.39;42.63
A451	60405535		99.6	0.02;0.05	96.72;91.07	92.81;82.63	42.43;42.73
A451	33002594		99.61	0.02;0.06	96.20;89.36	91.98;80.37	42.39;42.76
A451	36170805		99.92	0.02;0.03	98.81;96.23	96.30;89.27	42.17;42.12
A451	26592627		99.92	0.02;0.03	98.82;96.24	96.35;89.35	42.18;42.13
A451	25585068		99.92	0.02;0.03	98.75;96.13	96.16;89.17	42.14;42.09
A451	29905036		99.58	0.02;0.05	96.74;91.02	92.74;82.31	42.38;42.59
A451	14682947		99.59	0.02;0.06	95.93;90.96	90.97;81.50	42.54;42.68
A452	61387344	93.82	98.31	0.02;0.03	96.10;94.05	90.92;86.88	42.28;42.34
A452	53040159		98.23	0.02;0.04	96.32;94.12	91.36;86.72	42.28;42.38
A452	52831078		98.31	0.02;0.04	96.67;93.64	92.01;86.29	42.26;42.33
A452	56251942		98.31	0.02;0.04	96.84;93.75	92.37;86.41	42.29;42.36
A452	55036401		98.29	0.02;0.04	96.61;93.77	91.96;86.37	42.25;42.28
A452	34246412		99.12	0.03;0.14	95.64;85.82	90.01;73.78	42.15;42.22
A453	76970385	98.25	99.56	0.02;0.05	97.16;92.23	93.32;83.33	43.10;43.33
A453	56129530		99.86	0.02;0.05	98.78;94.96	95.92;84.65	42.63;42.67
A453	71164280		99.56	0.02;0.05	96.83;92.60	92.58;84.01	43.10;43.28
A453	61393979		99.67	0.02;0.05	96.32;90.74	92.18;82.62	43.12;43.46
A453	61836793		99.65	0.02;0.05	96.33;90.33	92.15;82.01	43.18;43.54
A458	39043563	92.5	99.6	0.02;0.05	97.24;92.56	93.50;83.97	42.76;42.88
A458	61485237		99.86	0.02;0.05	98.98;94.91	96.48;84.38	42.28;42.32
A458	57215545		99.87	0.02;0.05	98.88;94.89	96.18;84.24	42.31;42.35
A458	74389398		99.59	0.02;0.05	97.28;93.09	93.40;84.53	42.72;42.81
A458	76202971		99.61	0.02;0.04	97.32;93.38	93.52;85.13	42.72;42.81
A459	47152897	94.68	98.57	0.02;0.04	97.39;93.18	93.81;84.97	43.05;43.08
A459	63363532		99.21	0.02;0.05	98.82;95.00	96.06;84.61	42.41;42.43
A459	59263627		99.55	0.02;0.05	98.71;94.98	95.74;84.44	42.51;42.52
A459	71913221		98.75	0.02;0.05	97.05;93.03	92.93;84.46	43.02;43.04
A459	73897448		98.76	0.02;0.04	97.09;93.31	93.05;85.07	43.02;43.04
A349	98406592	108.16	99.6	0.02;0.03	97.68;94.96	94.13;88.38	43.83;43.96
A349	89846107		99.48	0.02;0.03	97.70;95.59	94.26;89.57	43.83;43.97
A349	106733071		99.39	0.02;0.03	97.32;95.62	93.45;89.87	44.10;44.20
A349	65539061		99.37	0.02;0.03	97.35;96.00	93.46;90.58	44.08;44.18
A223	73301572	92.49	99.55	0.02;0.05	97.15;92.33	93.33;83.52	43.64;43.79
A223	91020493		99.54	0.02;0.05	97.53;92.89	94.09;84.41	43.65;43.72
A223	48900977		99.86	0.02;0.05	98.76;95.03	95.86;84.84	43.18;43.19
A223	70329257		99.56	0.02;0.05	96.82;92.67	92.54;84.13	43.64;43.76
A223	24764326		99.63	0.03;0.12	95.45;87.73	89.61;76.36	43.70;43.79
A340	57098550	94.77	99.13	0.02;0.04	96.71;93.64	92.21;86.51	42.80;42.87

A340	68838906		99.12	0.02;0.03	96.65;93.61	92.29;86.97	42.78;42.92
A340	71025028		99.09	0.02;0.03	97.22;95.01	93.26;88.81	42.77;42.86
A340	69301301		99.14	0.02;0.04	96.78;92.20	92.54;85.08	42.80;42.96
A340	49630265		99.12	0.02;0.03	97.29;94.44	93.50;88.42	42.79;42.90
A342	51958685	91.3	99.55	0.02;0.04	96.55;93.14	91.98;85.85	42.44;42.49
A342	50929933		99.56	0.02;0.04	96.27;92.12	91.49;84.35	42.43;42.54
A342	51483409		99.57	0.02;0.05	96.14;91.16	91.33;83.12	42.39;42.57
A342	36597423		99.61	0.02;0.02	97.74;96.80	94.36;92.38	42.23;42.29
A342	76086767		99.61	0.02;0.02	98.00;96.56	94.94;91.79	42.25;42.32
A342	37274956		99.61	0.02;0.02	97.77;96.75	94.46;92.42	42.17;42.25
A343	85082996	112.38	99.09	0.02;0.02	97.69;96.21	94.32;91.29	43.36;43.44
A343	104140588		99.08	0.02;0.02	97.75;96.38	94.44;91.58	43.31;43.39
A343	124507160		99.07	0.02;0.02	97.48;95.66	93.97;90.56	43.29;43.36
A343	60871862		99.06	0.02;0.03	96.79;94.09	92.70;87.57	43.34;43.41
A229	59632846	93.17	99.61	0.02;0.06	96.84;91.51	92.29;81.22	41.93;42.08
A229	47578910		99.91	0.02;0.04	98.59;95.50	95.32;86.52	41.42;41.37
A229	57415113		99.62	0.02;0.06	96.66;91.19	91.84;80.61	41.89;42.05
A229	50995314		99.66	0.02;0.06	96.55;91.25	91.64;80.80	41.90;42.06
A229	49937486		99.68	0.02;0.06	96.54;91.18	91.63;80.95	41.92;42.10
A229	45015187		99.63	0.03;0.09	95.83;89.04	90.36;78.23	42.03;42.11
A228	72175632	97.11	99.91	0.02;0.05	97.95;94.94	93.96;86.26	43.02;43.03
A228	71565360		99.93	0.02;0.05	98.01;94.79	94.06;86.08	42.98;43.01
A228	89609552		98.46	0.03;0.07	95.88;90.29	90.63;80.22	43.52;43.74
A228	90355432		98.44	0.03;0.07	95.69;90.29	90.30;80.22	43.47;43.68
A69	40969558	96.77	99.65	0.02;0.04	96.45;93.14	91.74;85.65	42.34;42.42
A69	51677202		99.6	0.02;0.04	96.41;93.09	91.84;86.06	42.30;42.47
A69	52720145		99.58	0.02;0.03	96.98;94.50	92.81;87.89	42.28;42.40
A69	51712430		99.63	0.02;0.04	96.52;91.52	92.06;83.97	42.32;42.52
A69	36394820		99.59	0.02;0.03	97.04;93.82	93.02;87.38	42.31;42.44
A69	89104327		99.7	0.03;0.10	94.97;88.87	88.48;77.88	42.30;42.48
A64	42148707	92.57	99.93	0.02;0.04	98.67;95.23	95.71;86.55	41.77;41.71
A64	71112238		99.66	0.02;0.05	97.09;92.09	93.00;82.76	42.17;42.28
A64	63750299		99.93	0.02;0.04	98.56;95.30	95.24;86.08	41.73;41.69
A64	63625095		99.93	0.02;0.04	98.60;95.40	95.34;86.42	41.77;41.74
A64	57194843		99.68	0.02;0.05	97.11;91.98	93.14;83.02	42.20;42.29
A64	10741781		99.68	0.03;0.11	95.85;88.13	90.40;76.86	42.33;42.45
A65	37370914	95.55	99.92	0.02;0.05	98.33;94.84	94.91;85.61	40.96;40.82
A65	65198722		99.61	0.02;0.06	96.53;90.66	91.84;80.46	41.34;41.35
A65	57701595		99.91	0.02;0.05	98.19;94.95	94.37;85.24	40.90;40.82
A65	57545782		99.91	0.02;0.05	98.28;95.05	94.57;85.60	40.95;40.87
A65	52708754		99.63	0.02;0.06	96.65;90.70	92.19;80.97	41.38;41.39
A65	47972906		99.67	0.03;0.14	95.01;86.15	88.82;74.05	41.44;41.52
A66	34818045	104.89	99.94	0.02;0.04	98.02;95.33	94.28;87.57	40.94;40.88
A66	80564078		99.52	0.02;0.06	96.34;91.56	91.71;82.50	41.32;41.36
A66	86566901		99.52	0.02;0.06	96.58;91.81	92.18;82.93	41.32;41.35

A66	80614429		99.55	0.02;0.05	96.48;91.87	91.90;82.94	41.32;41.37
A66	67075416		99.5	0.02;0.06	96.41;91.42	91.79;82.22	41.37;41.42
A67	63343821	95.54	99.12	0.02;0.03	96.99;93.98	92.89;86.89	44.09;44.23
A67	84938828		99.06	0.02;0.03	97.21;94.74	93.42;88.32	44.13;44.23
A67	60412548		99.16	0.02;0.03	97.19;94.60	93.30;87.91	43.95;44.09
A67	53514731		99.19	0.02;0.03	96.99;94.24	92.74;87.15	43.80;43.93
A67	56260722		99.02	0.02;0.03	97.01;94.23	92.79;87.11	43.61;43.75
A60	46115073	98.37	99.85	0.02;0.05	98.18;94.72	94.49;86.01	41.47;41.35
A60	52712389		99.87	0.02;0.05	98.43;94.86	95.07;86.26	41.54;41.42
A60	45005418		99.87	0.02;0.05	98.29;94.26	94.73;85.12	41.56;41.44
A60	47197675		99.9	0.02;0.06	98.09;94.04	94.16;84.01	41.63;41.60
A60	56407763		99.91	0.02;0.05	98.17;94.94	94.45;86.17	41.81;41.78
A60	80448967		99.06	0.02;0.06	96.08;91.25	91.25;82.11	42.26;42.32
A62	60496294	91.6	98.9	0.02;0.04	96.95;93.47	92.53;85.99	43.54;43.77
A62	59405872		98.92	0.02;0.05	96.86;92.91	92.26;84.67	43.52;43.74
A62	59865007		98.93	0.02;0.05	96.85;92.85	92.14;84.23	43.54;43.76
A62	59603505		98.93	0.02;0.05	96.89;92.58	92.27;83.99	43.54;43.75
A62	55604155		99.03	0.02;0.04	97.03;94.35	92.71;87.38	43.63;43.68
A62	10371652		98.85	0.02;0.03	97.36;94.90	93.81;88.74	44.04;44.10
A174	45232840	97.03	98.86	0.03;0.04	94.89;92.59	88.74;84.58	41.10;41.32
A174	54341336		98.84	0.03;0.04	94.71;92.44	88.66;84.87	41.03;41.32
A174	55724264		98.8	0.03;0.04	95.53;93.85	89.95;86.65	41.10;41.33
A174	54999223		98.87	0.03;0.05	94.94;90.78	89.01;82.62	41.09;41.24
A174	38759974		98.87	0.02;0.04	95.90;93.34	90.75;86.39	41.16;41.26
A174	74383191		99.44	0.04;0.10	94.35;88.44	87.14;77.32	40.99;41.19
A426	46715327	91.57	99.22	0.02;0.03	97.04;93.77	93.03;86.57	41.51;41.55
A426	57002980		99.18	0.02;0.03	97.24;93.98	93.44;86.94	41.44;41.41
A426	64456435		99.18	0.02;0.03	97.43;93.58	93.89;86.37	41.42;41.40
A426	49467035		99.24	0.02;0.03	97.24;94.43	93.44;87.64	41.39;41.43
A426	42759560		99.28	0.02;0.03	97.03;93.99	92.86;86.76	41.26;41.28
A426	44815745		99.15	0.02;0.03	97.04;93.91	92.89;86.57	41.09;41.12
A445	60265322	92.3	98.94	0.02;0.04	96.84;93.34	92.28;85.74	41.56;41.77
A445	59031384		98.95	0.02;0.05	96.75;92.78	92.00;84.42	41.54;41.74
A445	59806014		98.97	0.03;0.05	96.74;92.71	91.87;83.96	41.56;41.76
A445	59477532		98.97	0.02;0.05	96.78;92.44	92.02;83.72	41.55;41.74
A445	53619763		99.09	0.02;0.04	97.05;94.16	92.88;87.48	41.56;41.60
A445	15494701		98.83	0.02;0.03	97.37;94.63	93.85;88.28	41.79;41.77
A444	73611017	100.37	99.58	0.02;0.05	97.09;92.67	93.05;83.88	41.21;41.26
A444	74225278		99.56	0.02;0.06	96.87;91.26	92.42;80.92	41.25;41.38
A444	58506713		99.91	0.02;0.04	98.67;95.52	95.57;86.59	40.79;40.72
A444	71471047		99.57	0.02;0.06	96.70;90.92	91.98;80.32	41.22;41.37
A444	56762889		99.6	0.02;0.05	97.10;92.56	93.16;84.10	41.26;41.30
A443	84939399	101.01	99.11	0.02;0.05	96.52;91.28	92.30;82.74	43.97;44.09
A443	85546135		99.03	0.02;0.05	96.41;91.16	92.20;82.76	43.95;44.12
A443	84723962		99.04	0.02;0.05	96.80;92.51	92.67;84.23	43.96;44.05

A443	81503177		99.07	0.02;0.05	96.74;92.43	92.49;83.96	43.98;44.05
A292	20227761	120.56	99.84	0.02;0.05	98.12;94.84	94.57;86.34	43.23;43.27
A292	46426827		99.61	0.03;0.07	96.03;91.04	90.78;81.19	43.62;43.78
A292	48061716		99.56	0.02;0.06	96.36;91.35	91.55;81.87	43.74;43.91
A292	65050307		99.63	0.03;0.06	96.06;92.16	90.79;83.27	43.64;43.80
A292	64970999		99.66	0.03;0.07	95.72;91.30	90.21;81.99	43.71;43.92
A292	68397107		99.72	0.03;0.06	95.82;92.09	90.22;83.02	43.80;43.98
A292	63740406		99.7	0.03;0.06	95.91;92.38	90.40;83.42	43.66;43.82
A292	25003084		99.69	0.03;0.06	95.90;91.18	90.57;81.48	43.64;43.80
A290	55490379	100.31	99.21	0.02;0.03	96.74;93.93	92.46;87.26	41.50;41.51
A290	59284945		99.17	0.02;0.03	96.84;94.12	92.51;87.44	41.55;41.58
A290	59777664		99.18	0.02;0.03	96.81;94.16	92.50;87.49	41.55;41.58
A290	77937953		99.14	0.02;0.03	97.01;94.35	92.68;87.51	41.48;41.57
A290	82364194		99.53	0.03;0.12	96.06;87.25	90.80;75.83	41.20;41.24
A291	58944404	96.36	99.89	0.03;0.05	96.72;95.12	90.94;86.59	42.55;42.60
A291	57735056		99.91	0.03;0.05	96.66;94.94	90.79;86.33	42.49;42.55
A291	73530165		99.6	0.03;0.07	93.86;90.10	86.63;80.03	42.71;43.04
A291	73743514		99.6	0.04;0.07	93.60;90.09	86.19;80.00	42.65;42.99
A291	57236205		99.61	0.04;0.13	93.73;87.09	86.07;75.48	42.59;42.76
A448	78658710	98.28	96.41	0.02;0.05	96.53;92.40	92.14;84.10	43.96;44.00
A448	33444254		96.69	0.02;0.05	96.84;92.31	92.65;83.77	44.00;44.04
A448	86836918		96.49	0.02;0.04	97.06;93.33	93.16;85.48	43.99;44.03
A448	47319611		96.69	0.02;0.05	96.45;91.55	92.28;83.38	44.00;44.16
A448	81325690		96.7	0.02;0.05	96.72;92.49	92.52;84.30	43.98;44.01
A55	85507896	92.28	99.59	0.02;0.03	97.15;95.59	93.28;90.24	41.40;41.52
A55	65265470		99.54	0.02;0.03	96.60;95.43	92.04;89.70	41.43;41.60
A55	71654354		99.55	0.02;0.03	96.73;95.60	92.31;89.97	41.38;41.55
A55	75994716		99.55	0.02;0.03	96.57;94.89	92.07;89.06	41.35;41.49
A55	9188768		99.68	0.04;0.12	93.80;87.10	86.29;75.37	40.87;41.02
A217	45764082	96.16	98.95	0.02;0.03	96.72;93.76	92.43;86.90	42.59;42.62
A217	51765485		98.91	0.02;0.03	96.84;93.98	92.51;87.14	42.63;42.68
A217	52213970		98.92	0.02;0.03	96.82;94.02	92.50;87.18	42.63;42.68
A217	66045940		98.98	0.02;0.03	96.99;94.49	92.92;88.11	42.57;42.59
A217	54874038		99.05	0.02;0.03	96.57;93.90	92.25;87.22	42.57;42.63
A217	50198327		99.39	0.03;0.11	95.72;88.14	90.15;76.82	42.39;42.51
A58	32339828	94.67	99.87	0.02;0.04	97.66;95.03	93.05;86.56	40.71;40.60
A58	60189837		99.89	0.02;0.05	97.99;95.12	93.76;86.74	40.77;40.66
A58	46402991		99.91	0.02;0.05	97.41;94.29	92.32;84.48	40.75;40.73
A58	53923353		99.93	0.02;0.04	97.45;95.22	92.53;86.68	40.93;40.91
A58	65311817		99.76	0.03;0.06	95.25;90.94	89.14;81.31	41.11;41.14
A58	57391637		99.76	0.03;0.05	95.16;91.86	89.28;83.11	41.21;41.37
A185	87652540	97.35	99.35	0.02;0.04	96.62;93.15	92.23;85.89	41.91;41.99
A185	65181576		99.26	0.02;0.03	96.99;94.14	92.92;87.47	41.95;41.99
A185	66399814		99.28	0.02;0.03	97.07;94.11	93.08;87.37	41.95;41.98
A185	105433869		99.31	0.02;0.03	96.93;94.79	92.85;88.66	41.98;42.06

A180	62874875	92.64	98.22	0.02;0.04	97.20;92.39	93.25;85.48	43.32;43.49
A180	62134799		98.23	0.02;0.03	97.01;93.73	92.94;86.97	43.33;43.42
A180	62974113		98.27	0.02;0.03	97.20;94.84	93.20;88.48	43.34;43.39
A180	94797573		98.33	0.02;0.03	97.24;94.47	93.36;88.43	43.34;43.45
A180	26014252		99.15	0.03;0.10	95.77;88.55	90.21;77.46	43.41;43.54
A476	46140806	105.47	99.94	0.02;0.04	98.07;95.02	94.40;86.77	43.20;43.20
A476	65125280		99.72	0.03;0.07	95.67;90.53	90.19;80.59	43.61;43.84
A476	66639856		99.73	0.03;0.06	95.98;91.18	90.82;81.63	43.61;43.83
A476	65730241		99.73	0.03;0.07	95.76;90.70	90.41;80.87	43.59;43.81
A476	65658958		99.74	0.03;0.07	95.76;90.83	90.33;81.10	43.55;43.75
A476	42260341		99.94	0.02;0.04	98.34;94.91	95.10;86.90	43.12;43.12
A479	56168197	99.57	98.83	0.03;0.05	95.70;91.78	90.09;83.26	44.88;44.89
A479	65313247		98.84	0.03;0.07	96.11;90.13	90.97;81.10	44.95;44.96
A479	61123951		98.88	0.03;0.05	96.21;92.52	91.27;84.74	44.82;44.79
A479	61240648		98.64	0.03;0.06	96.07;91.09	90.92;82.36	44.87;44.88
A479	88048236		98.79	0.03;0.05	95.89;92.61	90.22;84.19	44.82;44.86
A209	39822275	93.85	99.9	0.02;0.04	98.10;94.93	94.27;86.40	41.54;41.45
A209	37419019		99.91	0.02;0.05	98.18;94.52	94.45;85.61	41.60;41.50
A209	38147058		99.92	0.02;0.05	97.98;94.28	93.89;84.47	41.67;41.65
A209	54566834		99.34	0.03;0.07	95.94;90.51	90.58;80.26	42.21;42.33
A209	65559960		99.35	0.02;0.06	96.31;91.44	91.47;82.06	42.16;42.18
A209	77329906		99.39	0.02;0.05	96.10;92.17	91.27;83.44	42.31;42.39
A162	57508826	95.13	99.87	0.02;0.04	98.10;95.12	94.29;86.91	41.98;41.90
A162	75323999		99.16	0.02;0.07	96.36;90.62	91.53;80.95	42.44;42.43
A162	53304429		99.89	0.02;0.05	98.17;94.73	94.45;86.14	42.06;41.96
A162	55063802		99.91	0.02;0.05	98.01;94.47	93.97;84.94	42.13;42.11
A162	75898987		99.38	0.03;0.06	96.10;90.99	90.87;81.11	42.66;42.76
A163	33780640	94.83	99.87	0.02;0.04	98.51;95.44	95.29;87.06	43.43;43.41
A163	61411886		99.38	0.02;0.05	96.97;92.75	92.73;83.90	43.89;44.01
A163	63259030		99.38	0.02;0.06	96.74;91.29	92.09;80.85	43.91;44.11
A163	50155893		99.85	0.02;0.04	98.55;95.35	95.20;86.22	43.34;43.32
A163	60790553		99.39	0.02;0.07	96.56;90.98	91.62;80.26	43.87;44.08
A163	46687789		99.5	0.03;0.11	95.49;87.99	89.63;76.52	44.09;44.53
A204	82350990	113.1	99.94	0.02;0.04	97.95;95.20	93.99;86.93	41.65;41.63
A204	96498393		99.58	0.03;0.07	95.84;90.27	90.47;80.35	42.06;42.25
A204	97360153		99.54	0.03;0.07	95.98;90.86	90.84;81.25	42.09;42.24
A204	100806843		99.55	0.03;0.07	95.82;90.90	90.55;81.31	42.03;42.17
A168	60638187	123.18	99.59	0.03;0.06	95.92;90.67	90.78;81.25	42.03;42.03
A168	72071129		99.53	0.02;0.06	96.46;91.86	91.75;82.83	42.11;42.13
A168	65295372		99.58	0.02;0.06	96.47;90.73	91.77;81.14	42.13;42.13
A168	71683807		99.65	0.02;0.06	96.71;91.31	92.45;82.40	42.01;42.03
A168	73254777		99.63	0.02;0.06	96.92;91.88	92.83;83.08	41.99;42.00
A168	67652442		99.54	0.02;0.05	97.08;92.70	93.13;84.50	42.01;42.00
A203	74685353	96.77	98.92	0.02;0.03	96.54;94.29	91.71;87.26	41.74;41.80
A203	74401428		98.9	0.02;0.03	96.49;94.36	91.64;87.26	41.73;41.81

A203	74189331		98.94	0.02;0.04	96.34;93.95	91.31;86.61	41.76;41.82
A203	99281239		98.95	0.02;0.04	96.87;94.07	92.52;86.88	41.60;41.65
A199	60582267	90.1	98.23	0.02;0.03	96.17;94.23	91.01;87.16	44.52;44.59
A199	58127804		98.14	0.02;0.03	96.50;94.41	91.64;87.18	44.54;44.64
A199	62381961		98.2	0.02;0.03	96.82;93.94	92.25;86.77	44.50;44.64
A199	61392228		98.21	0.02;0.04	96.98;94.00	92.60;86.81	44.54;44.66
A199	57851980		98.18	0.02;0.04	96.78;94.10	92.25;86.88	44.48;44.56
A197	42799115	91.16	96.78	0.02;0.05	97.47;92.66	93.96;84.10	43.98;44.03
A197	53352087		99.83	0.02;0.06	98.93;94.64	96.33;83.87	43.47;43.50
A197	53778708		99.85	0.02;0.06	98.83;94.62	96.01;83.71	43.49;43.52
A197	66119798		97.32	0.02;0.05	97.09;92.50	93.01;83.57	43.94;44.00
A197	67771280		97.32	0.02;0.05	97.14;92.81	93.15;84.21	43.94;44.00
A197	20061294		97.09	0.03;0.11	95.63;88.06	90.00;76.84	44.06;44.17
A469	50099365	92.95	99.56	0.03;0.07	95.69;89.96	90.44;80.14	42.45;42.60
A469	70996205		99.41	0.02;0.05	97.26;92.79	93.56;84.42	42.26;42.42
A469	65358506		99.44	0.02;0.04	97.62;93.33	94.31;85.28	42.25;42.34
A469	57360815		99.9	0.02;0.05	98.76;95.33	95.90;85.62	41.91;41.93
A469	66024033		99.45	0.02;0.04	96.95;93.19	92.83;85.14	42.28;42.42
A462	54503285	100.06	99.45	0.03;0.05	96.29;92.43	90.58;83.45	44.16;44.53
A462	97918149		99.42	0.03;0.04	96.64;94.18	91.95;87.56	44.17;44.27
A462	57208165		99.39	0.03;0.05	96.35;91.90	91.20;82.98	44.15;44.57
A462	54428307		99.39	0.03;0.06	96.36;91.59	90.96;82.35	44.15;44.58
A462	69488103		99.36	0.03;0.04	96.67;94.02	91.86;87.19	44.22;44.30
A299	54806065	106.03	99.87	0.02;0.04	98.59;95.53	95.50;87.36	43.18;43.09
A299	82263068		99.34	0.02;0.06	96.83;91.41	92.34;81.22	43.59;43.72
A299	65387728		99.86	0.02;0.04	98.62;95.48	95.42;86.63	43.10;43.02
A299	79830849		99.36	0.02;0.06	96.67;91.12	91.91;80.69	43.56;43.69
A299	71160128		99.39	0.02;0.05	97.10;92.76	93.14;84.49	43.61;43.63
A173	47105648	109.58	99.93	0.02;0.04	98.22;95.12	94.81;87.07	41.28;41.21
A173	66768882		99.72	0.03;0.07	95.96;90.54	90.82;80.77	41.62;41.73
A173	68458214		99.72	0.02;0.06	96.26;91.21	91.42;81.84	41.62;41.72
A173	67389621		99.73	0.03;0.07	96.05;90.72	91.02;81.07	41.60;41.69
A173	67644381		99.74	0.03;0.06	96.05;90.86	90.95;81.28	41.57;41.66
A173	47892741		99.92	0.02;0.04	98.47;94.98	95.48;87.15	41.23;41.14
A273	86338593	127.88	99.63	0.02;0.04	97.19;92.93	93.54;85.31	42.69;42.86
A273	84537843		99.64	0.02;0.04	97.00;92.72	93.21;85.08	42.72;42.93
A273	85881277		99.62	0.02;0.05	96.23;89.94	92.08;81.53	42.79;43.23
A273	83662995		99.64	0.02;0.06	96.12;89.81	91.79;81.27	42.74;43.12
A273	85829744		99.61	0.02;0.05	96.87;91.99	92.98;83.94	42.70;42.93
A201	33158849	100.78	99.64	0.02;0.04	97.18;92.73	93.52;84.95	42.60;42.73
A201	54091273		99.65	0.02;0.04	96.98;92.52	93.19;84.73	42.63;42.83
A201	62501077		99.64	0.02;0.05	96.84;91.81	93.03;83.87	42.65;42.93
A201	34945135		99.64	0.02;0.05	96.32;90.12	92.18;81.64	42.63;42.98
A201	49368816		99.62	0.02;0.06	96.32;89.71	92.16;81.03	42.68;43.05
A201	35024882		99.63	0.02;0.06	96.21;89.66	92.06;81.10	42.70;43.12

A201	33826138		99.64	0.02;0.06	96.09;89.53	91.75;80.85	42.64;43.01
A201	33001646		99.62	0.02;0.05	96.86;91.78	92.97;83.57	42.61;42.81
A287	78811916	94.45	99.44	0.03;0.03	94.67;94.05	88.18;86.87	42.59;42.81
A287	53396181		99.41	0.03;0.03	95.02;94.24	88.77;87.15	42.68;42.92
A287	53128639		99.38	0.03;0.03	94.90;94.33	88.59;87.16	42.67;42.93
A287	53174874		99.4	0.03;0.04	94.66;93.94	88.08;86.53	42.68;42.93
A287	76321064		99.63	0.04;0.09	94.52;89.16	87.42;78.44	42.54;42.76
A281	57404866	92.25	98.82	0.03;0.05	96.47;92.34	91.66;83.73	42.27;42.58
A281	53516448		98.83	0.03;0.05	96.47;92.31	91.66;83.68	42.26;42.56
A281	68522999		98.82	0.02;0.04	96.74;94.49	92.41;88.06	42.28;42.28
A281	32344704		99.07	0.02;0.05	96.88;93.23	92.37;85.57	42.27;42.47
A281	31672702		99.08	0.02;0.05	96.78;92.66	92.05;84.24	42.24;42.44
A281	32146532		99.09	0.03;0.05	96.77;92.60	91.94;83.79	42.26;42.46
A281	31890461		99.1	0.02;0.05	96.81;92.33	92.07;83.56	42.25;42.44
A280	77131738	92.78	99.91	0.02;0.04	97.74;95.22	93.50;87.23	42.19;42.18
A280	63010732		99.64	0.03;0.06	95.22;91.02	89.37;81.55	42.39;42.59
A280	67258546		99.64	0.03;0.06	95.28;91.17	89.44;81.79	42.41;42.62
A280	63626022		99.66	0.03;0.06	95.40;91.35	89.65;81.99	42.40;42.60
A280	38228664		99.62	0.03;0.06	95.41;90.69	89.69;81.12	42.45;42.60
A283	54507270	103.77	99.06	0.02;0.04	96.96;93.37	92.88;85.92	42.55;42.61
A283	65263796		99.04	0.02;0.04	97.18;93.69	93.33;86.41	42.46;42.52
A283	72474862		99.02	0.02;0.04	97.36;93.24	93.76;85.79	42.43;42.48
A283	55053332		99.11	0.02;0.03	97.16;94.04	93.30;87.00	42.42;42.48
A283	50353411		99.14	0.02;0.04	96.96;93.64	92.74;86.18	42.28;42.34
A283	48232453		98.96	0.02;0.04	96.97;93.64	92.78;86.17	42.11;42.16
A282	34084404	94.51	99.93	0.02;0.05	98.73;94.95	95.85;85.88	41.52;41.41
A282	59612476		99.6	0.02;0.06	97.00;91.11	92.82;81.17	41.94;41.99
A282	52309765		99.92	0.02;0.05	98.61;95.03	95.36;85.43	41.47;41.40
A282	52205909		99.92	0.02;0.05	98.65;95.13	95.46;85.79	41.51;41.45
A282	47640848		99.63	0.02;0.06	97.01;91.06	92.94;81.52	41.98;42.02
A282	69193153		99.64	0.03;0.13	95.28;86.79	89.23;74.75	42.03;42.20
A295	62563020	94.04	98.51	0.02;0.05	97.04;90.50	92.97;82.25	43.02;42.86
A295	61796800		98.5	0.02;0.05	96.85;91.54	92.66;83.38	43.03;43.13
A295	62739418		98.54	0.02;0.04	97.05;93.28	92.94;85.57	43.03;43.10
A295	89497292		98.6	0.02;0.04	96.34;91.75	91.72;83.72	43.03;43.20
A295	36910985		99.24	0.03;0.17	95.53;84.30	89.80;71.51	43.14;43.35
A288	57677418	93.24	97.65	0.02;0.04	96.44;93.06	91.93;85.77	43.56;43.62
A288	45960513		97.36	0.02;0.04	96.64;93.30	92.28;86.09	43.62;43.65
A288	52233798		97.3	0.02;0.04	96.76;93.50	92.36;86.30	43.67;43.71
A288	52630672		97.31	0.02;0.04	96.72;93.54	92.32;86.33	43.66;43.71
A288	69531596		97.58	0.02;0.03	96.86;94.81	92.72;88.71	43.65;43.72
A288	33249101		98.46	0.03;0.15	95.60;85.47	89.93;73.24	43.61;43.74
A416	71631036	95.8	99.42	0.02;0.03	96.76;93.83	92.32;86.89	43.38;43.43
A416	88973331		99.37	0.02;0.03	97.35;94.63	93.63;88.78	43.35;43.46
A416	76938124		99.93	0.02;0.05	98.20;94.82	94.56;86.23	43.09;43.03

A416	81806101		99.93	0.02;0.05	98.24;94.71	94.64;86.06	43.04;42.95
A302	70541260	92.65	97.53	0.02;0.04	97.23;92.67	93.33;85.95	45.68;45.68
A302	69720337		97.55	0.02;0.03	97.07;94.04	93.05;87.49	45.69;45.75
A302	70700480		97.62	0.02;0.03	97.25;95.10	93.30;88.95	45.70;45.75
A302	97857716		97.75	0.02;0.04	96.74;92.42	92.45;85.44	45.73;45.81
A303	54019758	95.27	99.03	0.02;0.03	96.23;94.22	91.19;87.24	41.60;41.64
A303	51492570		98.98	0.02;0.03	96.52;94.28	91.71;87.07	41.63;41.70
A303	53969272		99.03	0.02;0.03	96.83;93.89	92.33;86.77	41.57;41.68
A303	56578654		99.03	0.02;0.04	97.00;94.01	92.68;86.91	41.63;41.71
A303	53667688		99.01	0.02;0.04	96.80;94.05	92.34;86.89	41.56;41.60
A303	47896447		99.43	0.03;0.12	95.93;86.56	90.59;74.90	41.36;41.38
A263	91836498	108.28	97.29	0.02;0.05	96.57;92.33	92.25;84.08	43.26;43.26
A263	91468114		97.48	0.02;0.05	96.91;92.30	92.80;83.83	43.31;43.32
A263	39235771		97.37	0.02;0.04	97.10;93.26	93.26;85.45	43.29;43.30
A263	49512780		97.6	0.02;0.04	96.88;92.84	92.84;84.86	43.31;43.36
A263	88888646		97.54	0.02;0.05	96.77;92.43	92.64;84.29	43.29;43.29
A260	57470547	93.8	99.14	0.02;0.05	96.85;92.87	92.32;84.96	41.39;41.60
A260	56462069		99.15	0.02;0.05	96.76;92.28	92.04;83.61	41.35;41.56
A260	57075156		99.16	0.03;0.05	96.75;92.20	91.92;83.10	41.38;41.59
A260	56896011		99.17	0.02;0.06	96.79;91.93	92.07;82.87	41.36;41.56
A260	50575076		99.25	0.02;0.04	97.04;93.76	92.88;86.77	41.37;41.40
A260	34239410		98.87	0.02;0.03	97.33;94.17	93.76;87.46	41.54;41.49
A308	37638611	93.95	96.57	0.02;0.05	97.18;92.57	93.35;83.86	44.22;44.27
A308	49745288		99.86	0.02;0.06	98.75;94.65	95.84;83.83	43.72;43.76
A308	44839095		99.87	0.02;0.06	98.64;94.64	95.54;83.69	43.73;43.77
A308	59822565		97.12	0.02;0.05	96.85;92.36	92.49;83.29	44.17;44.23
A308	61752009		97.11	0.02;0.05	96.89;92.69	92.61;83.94	44.17;44.23
A308	59358400		96.91	0.03;0.12	95.13;87.52	89.01;76.04	44.23;44.34
A309	51476318	92.09	99.1	0.02;0.04	96.89;93.22	92.70;85.53	43.50;43.60
A309	62636862		99.05	0.02;0.03	97.25;93.99	93.56;86.98	43.52;43.57
A309	53666031		99.14	0.02;0.03	97.11;93.90	93.15;86.59	43.37;43.47
A309	48380820		99.18	0.02;0.04	96.90;93.45	92.56;85.71	43.23;43.33
A309	46669670		99.01	0.02;0.04	96.90;93.41	92.60;85.63	43.03;43.14
A309	44140201		99.44	0.02;0.03	97.23;95.72	93.21;90.02	43.31;43.41
A403	87540298	100.89	98.15	0.02;0.05	97.09;91.99	93.17;82.87	43.81;43.96
A403	110425348		98.27	0.02;0.05	97.47;92.63	93.94;83.86	43.82;43.92
A403	55788399		99.89	0.02;0.05	98.74;94.77	95.77;84.19	43.31;43.34
A403	82546449		98.51	0.02;0.05	96.72;92.32	92.33;83.46	43.80;43.92
A402	62617139	98.89	98.44	0.03;0.05	96.26;93.01	90.84;84.60	44.89;45.18
A402	65855738		98.39	0.03;0.05	96.25;92.42	91.20;83.92	44.91;45.24
A402	66720767		98.36	0.03;0.05	96.41;92.16	91.50;83.39	44.92;45.26
A402	64088633		98.37	0.03;0.06	96.41;92.10	91.49;83.29	44.92;45.25
A402	70352156		98.38	0.02;0.04	96.73;94.42	92.35;87.94	44.96;45.01
A406	64697139	92.32	98.19	0.02;0.03	96.64;94.85	91.90;88.29	43.54;43.62
A406	64238817		98.2	0.02;0.03	96.60;94.95	91.84;88.36	43.55;43.64

A406	64098613		98.25	0.02;0.03	96.45;94.55	91.51;87.72	43.57;43.65
A406	87716825		98.22	0.02;0.03	97.01;94.45	92.69;87.78	43.44;43.57
A406	26969409		99.05	0.03;0.10	95.80;88.73	90.30;77.87	43.44;43.57
A315	38553795	117.65	99.85	0.02;0.03	97.35;94.02	93.86;87.22	42.13;42.22
A315	63355658		99.86	0.02;0.03	97.19;93.88	93.59;87.12	42.15;42.29
A315	73341920		99.85	0.02;0.04	97.03;93.16	93.41;86.22	42.17;42.36
A315	39926014		99.85	0.02;0.04	96.54;91.63	92.60;84.17	42.15;42.40
A315	58459544		99.85	0.02;0.05	96.58;91.33	92.64;83.68	42.19;42.45
A315	40959485		99.85	0.02;0.05	96.45;91.20	92.50;83.64	42.20;42.51
A315	39451829		99.85	0.02;0.05	96.34;91.12	92.21;83.44	42.16;42.42
A315	38130710		99.84	0.02;0.04	97.05;93.17	93.34;85.98	42.13;42.26
A313	60087533	92.07	99.17	0.02;0.04	96.59;93.07	92.15;86.05	42.28;42.43
A313	61381713		99.15	0.02;0.03	97.15;94.54	93.12;87.95	42.26;42.36
A313	55700176		99.19	0.02;0.04	96.69;91.51	92.35;83.96	42.30;42.47
A313	73534081		99.16	0.02;0.03	97.23;93.96	93.37;87.55	42.28;42.40
A313	25817080		99.17	0.02;0.04	96.83;93.93	92.38;86.63	42.40;42.45
A313	30376721		99.49	0.03;0.11	95.80;87.94	90.31;76.62	42.20;42.32
A311	62640469	93.72	97.71	0.03;0.05	96.21;92.98	90.76;84.52	44.46;44.75
A311	65530224		97.66	0.03;0.05	96.18;92.46	91.09;83.99	44.48;44.81
A311	60300055		97.64	0.03;0.05	96.38;92.24	91.45;83.49	44.49;44.83
A311	59868661		97.64	0.03;0.06	96.37;92.14	91.44;83.34	44.48;44.81
A311	64063917		97.62	0.02;0.04	96.68;94.27	92.28;87.65	44.50;44.56
A95	57884321	97.06	98.59	0.02;0.03	97.17;95.11	93.20;89.26	45.01;45.10
A95	67067866		98.1	0.02;0.05	96.97;93.19	92.58;85.47	45.00;45.24
A95	65789794		98.12	0.02;0.05	96.89;92.60	92.30;84.12	44.98;45.21
A95	66539902		98.15	0.02;0.05	96.88;92.54	92.20;83.68	45.01;45.23
A95	66255579		98.12	0.02;0.05	96.91;92.27	92.31;83.45	45.01;45.22
A93	66495934	92.56	99.85	0.02;0.05	98.38;94.69	94.92;85.93	44.48;44.44
A93	32468080		99.85	0.02;0.06	98.24;94.15	94.59;84.92	44.49;44.43
A93	53537002		99.89	0.02;0.06	98.05;93.87	94.03;83.69	44.58;44.57
A93	62453520		99.9	0.02;0.05	98.13;94.80	94.31;85.88	44.76;44.75
A93	76577702		99.49	0.02;0.07	96.28;90.71	91.37;80.92	45.17;45.23
A93	16991166		99.47	0.02;0.06	96.03;91.40	91.12;82.25	45.30;45.40
A242	17521421	97.32	99.91	0.02;0.05	96.88;94.61	91.61;85.87	42.38;42.45
A242	31769206		99.91	0.02;0.05	97.11;94.92	91.84;86.31	42.42;42.46
A242	33224845		99.9	0.02;0.05	97.20;95.12	92.07;86.76	42.56;42.59
A242	54612435		99.72	0.03;0.07	94.78;90.92	88.16;81.44	42.60;42.84
A242	55033676		99.75	0.04;0.08	94.34;89.96	87.40;80.05	42.65;42.96
A242	59815231		99.78	0.04;0.07	94.27;90.73	87.09;80.99	42.72;43.02
A242	53990602		99.77	0.03;0.07	94.87;91.14	88.27;81.58	42.67;42.91
A242	18445612		99.94	0.03;0.05	96.70;95.00	90.97;86.54	42.46;42.53
A246	56576192	90.68	99.1	0.02;0.04	96.54;93.49	91.97;86.07	42.63;42.74
A246	73225376		99.05	0.02;0.03	96.85;94.49	92.65;87.92	42.66;42.76
A246	56376677		99.15	0.02;0.03	96.76;94.19	92.43;87.21	42.52;42.64
A246	48671668		99.18	0.02;0.03	96.59;93.76	91.93;86.36	42.39;42.49

A246	52336899		99.02	0.02;0.03	96.72;93.78	92.22;86.35	42.24;42.33
A246	15070294		99.26	0.02;0.03	96.32;95.49	91.37;89.61	42.38;42.59
A89	67114262	100.9	98.24	0.02;0.04	96.85;92.57	92.60;84.31	45.13;45.27
A89	71239340		98.25	0.02;0.04	97.07;92.90	93.04;84.80	44.99;45.14
A89	69099007		98.38	0.02;0.04	97.06;93.26	93.04;85.38	44.96;45.10
A89	67670015		98.34	0.02;0.04	96.86;92.80	92.47;84.48	44.77;44.91
A89	61207399		97.99	0.02;0.04	96.88;92.68	92.52;84.28	44.59;44.73
A320	39423649	93.92	99.08	0.03;0.06	95.79;90.09	90.36;80.77	42.20;42.15
A320	44077981		99.18	0.03;0.06	95.61;91.75	89.63;82.66	42.10;42.12
A320	22141511		99.25	0.02;0.05	96.59;91.34	91.91;83.53	41.85;41.83
A320	69967251		99.28	0.02;0.05	96.87;90.93	92.48;82.90	41.99;42.25
A320	54695410		99.25	0.02;0.04	96.92;92.28	92.59;84.97	41.90;41.92
A320	25172723		99.25	0.02;0.04	96.94;92.30	92.43;84.84	41.88;41.85
A320	25073561		99.21	0.02;0.05	96.92;92.27	92.36;84.25	41.90;41.91
A320	35334890		98.96	0.02;0.03	97.16;94.03	93.34;87.11	42.13;42.10
A321	63518371	95.18	98.86	0.02;0.03	96.52;94.50	91.66;87.68	43.02;43.09
A321	63198667		98.84	0.02;0.03	96.47;94.59	91.60;87.71	43.02;43.10
A321	62975838		98.89	0.02;0.03	96.32;94.18	91.25;87.06	43.05;43.11
A321	87848889		98.85	0.02;0.03	96.62;94.59	91.92;87.62	42.95;43.04
A321	39772714		99.34	0.03;0.13	95.86;86.58	90.47;74.97	42.75;42.83
A125	36195845	94.01	99.37	0.02;0.04	96.24;93.74	91.16;86.61	42.55;42.67
A125	35559953		99.35	0.03;0.04	96.00;93.20	90.74;85.82	42.58;42.75
A125	35949453		99.37	0.03;0.06	94.89;89.59	89.01;81.03	42.62;42.98
A125	23518027		99.22	0.02;0.04	96.00;92.18	90.93;84.40	42.66;42.79
A125	44795551		99.26	0.02;0.04	96.05;92.51	91.13;85.00	42.64;42.78
A125	44096967		99.28	0.03;0.05	95.34;90.06	89.99;81.72	42.69;42.99
A125	43831137		99.31	0.03;0.05	95.37;89.97	90.08;81.72	42.67;42.99
A125	49429451		99.55	0.03;0.11	95.70;87.76	90.09;76.18	42.13;42.38
A483	62222610	93.76	99.3	0.02;0.04	97.25;92.16	93.39;85.06	42.86;43.04
A483	61424350		99.28	0.02;0.04	97.07;93.46	93.08;86.50	42.87;42.96
A483	62313263		99.33	0.02;0.03	97.26;94.59	93.35;88.04	42.88;42.93
A483	91268876		99.32	0.02;0.03	97.26;94.83	93.33;88.46	42.86;42.97
A483	35294769		99.5	0.03;0.10	95.21;88.97	88.89;78.07	43.00;43.16
A482	35103842	93.03	99.39	0.03;0.03	95.96;94.33	90.67;87.34	43.59;43.66
A482	61221673		99.35	0.02;0.03	96.24;94.44	91.11;87.47	43.69;43.76
A482	60925035		99.32	0.02;0.03	96.20;94.55	91.04;87.52	43.69;43.78
A482	60906840		99.35	0.03;0.04	96.02;94.14	90.65;86.87	43.71;43.78
A482	51169820		99.39	0.02;0.04	96.60;93.93	91.94;86.71	43.59;43.61
A482	40774791		99.58	0.03;0.11	95.34;87.93	89.44;76.61	43.52;43.64
A480	97898812	93.22	99.46	0.02;0.06	96.15;90.81	91.31;81.19	42.71;42.86
A480	90962719		99.43	0.03;0.07	95.93;90.24	90.80;80.36	42.62;42.74
A480	27240605		99.92	0.02;0.04	97.93;95.15	93.93;86.75	42.20;42.20
A480	30500203		99.48	0.03;0.07	95.77;90.11	90.31;80.02	42.62;42.80
A480	31088966		99.43	0.03;0.07	95.91;90.68	90.68;80.91	42.66;42.81
A480	33041988		99.44	0.03;0.07	95.72;90.71	90.36;80.95	42.60;42.73

A486	66906491	96.54	99.82	0.02;0.05	98.55;94.99	95.37;84.57	43.61;43.63
A486	59696978		99.84	0.02;0.05	98.43;94.97	95.05;84.41	43.64;43.66
A486	77090922		99.39	0.02;0.05	96.79;92.88	92.33;84.14	44.01;44.06
A486	79085988		99.41	0.02;0.05	96.81;93.16	92.40;84.75	44.00;44.06
A486	39034169		99.38	0.02;0.05	96.40;92.68	91.66;84.23	44.07;44.11
A485	41957523	100.44	99.91	0.02;0.04	98.13;95.07	94.39;86.83	40.94;40.83
A485	57277173		99.39	0.02;0.07	96.36;90.43	91.55;80.68	41.41;41.37
A485	46888449		99.9	0.02;0.05	98.28;94.90	94.34;85.46	40.93;40.83
A485	40518575		99.91	0.02;0.05	98.08;94.40	93.81;84.70	40.92;40.82
A485	42562430		99.92	0.02;0.05	98.22;94.65	94.58;86.01	41.04;40.91
A485	105588866		99.53	0.03;0.11	95.58;87.80	89.87;76.52	41.58;41.62
A484	101690315	100.92	99.22	0.02;0.03	96.78;93.78	92.34;86.74	43.42;43.48
A484	78531901		99.15	0.02;0.04	97.33;92.55	93.54;85.77	43.38;43.54
A484	77477531		99.13	0.02;0.03	97.16;93.91	93.25;87.28	43.39;43.48
A484	78691558		99.18	0.02;0.03	97.34;95.00	93.50;88.76	43.40;43.45
A488	44688311	89.79	99.6	0.02;0.04	97.00;92.36	93.12;84.02	43.62;43.49
A488	72294544		99.57	0.02;0.05	97.05;92.28	93.21;83.80	43.59;43.41
A488	95459483		99.59	0.02;0.04	97.29;92.56	93.79;84.33	43.49;43.32
A488	86857359		99.6	0.02;0.05	97.03;92.03	93.14;83.36	43.55;43.38

Note: Raw reads: The total number of double-ended read pair in the original sequence (i.e., logarithm of reads); Raw data(G) : the amount of data per sample. Effective: The proportion of Clean reads used for subsequent bioinformatics analysis after filtration in Raw data. Error: the average Error rate of all bases calculated by read1 and read2 respectively;

Q20: The percentage of bases with Phred value greater than 20 in the total bases was calculated. Read1 and read2 were calculated respectively; Q30: The percentage of bases with Phred value greater than 30 in the total number of bases was calculated. Read1 and read2 were calculated respectively; GC content: The percentage of nitrogenous bases on a DNA molecule that are either guanine or cytosine, and calculated by read1 and read2 respectively.

Table S4 Allelic frequency for the identified variants in healthy control

GeneName	Transcription	Exon	Variant (DNA level)	AA change	Allelic frequency in the 568 healthy control	Allelic frequency in 1000 Genomes Project
<i>ACTA2</i>	NM_001141945	exon7	c.G635A	p.R212Q	0	0
<i>ACTA2</i>	NM_001141945	exon5	c.G446A	p.R149H	0	0
<i>ACTA2</i>	NM_001141945	exon3	c.G133T	p.V45L	0	0
<i>COL1A1</i>	NM_000088	exon30	c.G2005A	p.A669T	0.00088183	0
<i>COL1A1</i>	NM_000088	exon37	c.C2573G	p.A858G	0.00088339	0
<i>COL1A2</i>	NM_000089	exon40	c.G2456A	p.R819H	0	0
<i>COL1A2</i>	NM_000089	exon44	c.G2905A	p.V969M	0	0
<i>COL3A1</i>	NM_000090	exon42	c.C3061A	p.L1021I	0.00440141	0.0009
<i>COL3A1</i>	NM_000090	exon20	c.1348-3C>T	-	0	0
<i>COL5A1</i>	NM_000093	exon9	c.C1388T	p.P463L	0.00088028	0.0005
<i>COL5A1</i>	NM_000093	exon65	c.A5335G	p.N1779D	0.00530035	0
<i>COL5A1</i>	NM_000093	exon2	c.C200T	p.S67F	0	0
<i>COL5A1</i>	NM_000093	exon3	c.G401A	p.R134H	0	0
<i>COL5A1</i>	NM_000093	exon42	c.C3364A	p.P1122T	0	0
<i>COL5A1</i>	NM_000093	exon43	c.C3428T	p.P1143L	0	0
<i>COL5A2</i>	NM_000393	exon37	c.C2488T	p.R830W	0	0
<i>EFEMP2</i>	NM_016938	exon10	c.G1102A	p.V368I	0	0
<i>EFEMP2</i>	NM_016938	exon5	c.G485A	p.C162Y	0	0
<i>ELN</i>	NM_001278939	exon26	c.G1883C	p.G628A	0.00264085	0.0009
<i>ELN</i>	NM_001278918	exon9	c.C449T	p.P150L	0.00088028	0
<i>ELN</i>	NM_000501	exon2	c.G104C	p.G35A	0.00088028	0
<i>ELN</i>	NM_001278913	exon17	c.G1108A	p.G370S	0.00176056	0
<i>ELN</i>	NM_001278913	exon14	c.C806T	p.A269V	0	0
<i>FBN1</i>	NM_000138	exon66	c.T8597A	p.I2866N	0	0
<i>FBN1</i>	NM_000138	exon60	c.T7408G	p.C2470G	0	0
<i>FBN1</i>	NM_000138	exon57	c.G6914C	p.G2305A	0	0
<i>FBN1</i>	NM_000138	exon48	c.G5855A	p.G1952E	0	0
<i>FBN1</i>	NM_000138	exon34	c.C4162T	p.R1388C	0	0
<i>FBN1</i>	NM_000138	exon22	c.G2639A	p.G880D	0	0
<i>FBN1</i>	NM_000138	exon22	c.A2613C	p.L871F	0	0
<i>FBN1</i>	NM_000138	exon14	c.C1693T	p.R565X	0	0
<i>FBN1</i>	NM_000138	exon10	c.G1007C	p.C336S	0	0
<i>FBN1</i>	NM_000138	exon47	c.5778delT	p.N1926fs	0	0
<i>FBN2</i>	NM_001999	exon12	c.A1643C	p.D548A	0.00088028	0
<i>FBN2</i>	NM_001999	exon30	c.G3889A	p.G1297S	0.00176056	0
<i>FBN2</i>	NM_001999	exon6	c.G809T	p.R270L	0	0
<i>FLNA</i>	NM_001110556	exon20	c.G2876A	p.S959N	0	0
<i>MYH11</i>	NM_002474	exon33	c.G4604A	p.R1535Q	0.00264085	0.0005
<i>MYH11</i>	NM_002474	exon34	c.G4843A	p.A1615T	0	0.0005
<i>MYH11</i>	NM_002474	exon33	c.G4735A	p.D1579N	0	0
<i>MYH11</i>	NM_002474	exon32	c.A4442T	p.K1481M	0	0
<i>MYH11</i>	NM_002474	exon28	c.A3766C	p.K1256Q	0	0
<i>MYH11</i>	NM_001040113	exon2	c.A268G	p.M90V	0	0
<i>MYH11</i>	NM_002474	exon28	c.3757_3759del	p.1253_1253del	0	0
<i>MYLK</i>	NM_053026	exon14	c.G1816A	p.G606R	0.00528169	0.0009
<i>MYLK</i>	NM_053026	exon28	c.G4675A	p.V1559M	0.00528169	0.0014
<i>MYLK</i>	NM_053026	exon14	c.C1747G	p.P583A	0.00088028	0
<i>MYLK</i>	NM_053026	exon17	c.C2653T	p.R885C	0	0
<i>MYLK</i>	NM_053031	exon2	c.113_114insTG	p.A38fs	0	0
<i>MYLK</i>	NM_053025	exon10	c.1179_1181del	p.393_394del	0	0
<i>NOTCH1</i>	NM_017617	exon32	c.C5944T	p.R1982W	0	0
<i>PLOD1</i>	NM_000302	exon7	c.C710T	p.P237L	0	0
<i>PLOD3</i>	NM_001084	exon17	c.C1904T	p.T635I	0.00440917	0.0005
<i>PLOD3</i>	NM_001084	exon12	c.G1315A	p.A439T	0	0.0014
<i>PLOD3</i>	NM_001084	exon6	c.G670A	p.G224R	0	0
<i>TGFB3</i>	NM_003239	exon6	c.C1007T	p.P336L	0	0
<i>TGFBR1</i>	NM_001130916	exon4	c.C695T	p.T232M	0	0.0005
<i>TGFBR1</i>	NM_001130916	exon8	c.G1190A	p.C397Y	0	0
<i>TGFBR2</i>	NM_003242	exon7	c.G1564A	p.D522N	0	0
<i>TGFBR2</i>	NM_003242	exon4	c.871_873del	p.291_291del	0	0

Table S5 Clinical characteristics of subjects with top 3 frequent gene mutations

	<i>FBN1</i> N=10	<i>MYH11</i> N=9	<i>MYLK</i> N=7	P value
Onset Age, years	44.7±11.0	62.9±12.2	53.0±16.5	0.021
Male, n (%)	7 (70.0)	5 (55.6)	5 (71.4)	0.747
Height, cm	172.5±5.3	166.2±9.9	169.6±7.9	0.240
Weight, kg	68.5±15.1	69.1±14.3	69.4±11.1	0.991
BMI, kg/m ²	23.0±4.7	24.8±3.8	24.1±2.9	0.598
DeBakey type I, n (%)	8 (80.0)	7 (77.8)	6 (85.7)	0.917
Hypertension, n (%)	4 (40.0)	7 (77.8)	4 (57.1)	0.238
Diabetes mellitus, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Coronary artery disease, n (%)	1 (10.0)	0 (0.0)	0 (0.0)	0.372
Smoke, n (%)	6 (60.0)	2 (22.2)	2 (28.6)	0.194
Alcohol history, n (%)	3 (30.0)	3 (33.3)	0 (0.0)	0.110
SBP, mmHg	118.5±18.4	115.3±14.3	128±19.1	0.344
DBP, mmHg	66.3±12.5	60.6±12.6	73.7±16.2	0.181
Heart rate, bpm	86.9±7.6	85.1±8.9	76.7±9.3	0.061
Ascending aorta diameter, mm	50.0±16.1	49.6±13.1	48.5±9.0	0.972
Surgical intervention, n (%)	6 (60.0)	5 (55.6)	5 (71.4)	0.880

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure

Table S6 Reasons account for in-hospital mortality in type A AAD

No.	Age, Gender	Cause of death	Treatment	No. of mutation	Mutation involved genes
1	49, male	aortic rupture	conservative	1	<i>COL5A2</i>
2	58, male	aortic rupture	conservative	0	
3	20, female	aortic rupture	conservative	3	<i>FBN1, COL1A2, TGFBR2</i>
4	32, male	cardiac death	conservative	0	
5	49, female	cardiac death	surgical	0	
6	67, male	aortic rupture	surgical	1	<i>MYH11</i>
7	66, male	aortic rupture	conservative	1	<i>COL5A1</i>
8	63, male	aortic rupture	conservative	1	<i>MYH11</i>
9	53, female	aortic rupture	conservative	1	<i>FLNA</i>
10	76, female	cardiac death	conservative	1	<i>ACTA2</i>
11	59, female	cardiac death	conservative	2	<i>FBN1, MYH11</i>
12	45, male	aortic rupture	conservative	1	<i>FBN1</i>