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Detection of ten novel *FBN1* mutations in Chinese patients with typical or incomplete Marfan syndrome and an overview of the genotype-phenotype correlations☆

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ABSTRACT

Objective: The aim of this study is to identify the mutation spectrum of *FBN1* in patients with Marfan syndrome (MFS) or Marfan-Like Phenotypes and to analyze the genotype-phenotype correlations of existing literature.
Methods and results: A total of 21 unrelated patients with a definite or suspected clinical diagnosis of MFS were recruited for research. Eleven *FBN1* mutations were identified in 12 patients who strictly fulfilled the Ghent criteria for MFS, and 1 *FBN1* mutations were detected in 9 patients with suspected MFS by screening the mutations of *FBN1*. These *FBN1* mutations include 10 novel mutations (c.357 C>A, c.493 C>T, c.1374 T>A, c.4143 delG, c. 6987 C>G, c.7238 G>A, c. 7765 A>G, c.8200 A>G, c. 8431 G>A, c.8547 T>G,) and 2 previously reported mutations (c.4567 C>T, c.4615 C>T). By searching PubMed and Embase (from 1990 up to December 2018), twenty nine studies (including the present study) with 890 subjects with MFS or Marfan-like phenotypes were included to analyze the genotype-phenotype correlations. Several genotype-phenotype correlations were founded. Firstly, mutations of premature termination codons (PTC) were associated with an increased risk of major cardiovascular involvements. Secondly, the frequency of patients with major cardiovascular involvement in exons 43–65 group was as high as that in exons 24–32 group (71.4% vs. 77.0%; $p = 0.238$). Finally, cysteine missense mutations might be associated with major cardiovascular involvements.
Conclusions: These results extended the *FBN1* mutation spectrum of this rare disease and revealed the genotype-phenotype correlations in MFS by analyzing existing literature.

1. Introduction

Marfan syndrome (MFS) (*MIM# 154700*) is an autosomal dominant disorder of the connective tissue caused by mutations in the *FBN1* gene (*MIM# 134797*), which encodes an extracellular matrix protein fibrillin-1 [1,2]. Complications of MFS may involve the eyes, skeleton, and lungs, but the high mortality of untreated cases is mainly related to cardiovascular complications such as aortic dissection and rupture. MFS accounts for the majority of aortic dissections in patients < 40 years of age. Complications often occur randomly and children had similar high rates of aortic root dilatation [3]. Complications often occur randomly and the outcome is frequently fatal and life expectancy is reduced in MFS cohort [4]. Many patients with aortic dissection die before presentation to a hospital or prior to diagnosis [5].

FBN1 spans 233 kb on chromosome 15q21.1, including 66 exons of which 65 are coding. Fibrillin-1 is a large multi-domain glycoprotein (320 kDa) and the major component of extracellular microfibril, with important functions in elastic and nonelastic tissues. Fibrillin-1 serves two key physiological functions: participating in the assembly of specialized matrices that confer structural properties to connective tissues, and providing contextual specificity for transforming growth factor β (TGF-β) and bone morphogenetic protein (BMP) signals, which regulate matrix formation and remodeling [6]. It has been shown that excessive TGF-β activity contributes to the pathogenesis of MFS [7,8]. *FBN1* mutations result in the production of abnormal fibrillin, which leads to structurally inferior connective tissue [9,10].

Although aortic root dilatation and related complications represent the main cause of death in patients with MFS, the correlations between genotype and cardiovascular phenotype in MFS have not been established [11]. The purposes of this study were to identify the mutation spectrum of *FBN1* gene in Chinese MFS patients with aortic

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aneurysms/dissection and to explore the genotype-phenotype correlations by analyzing the data from existing literature.

2. Patients and methods

2.1. Patients and clinical data

The study was approved by the Ethics Committee of Fuwai Hospital at Peking Union Medical College in Beijing, China. A total of 21 unrelated patients with a definite or suspected clinical diagnosis of MFS were recruited for research. The informed consent was obtained from all participants prior to thorough physical, ophthalmic and cardiovascular examinations. Patients were evaluated for dolichostenomelia by measuring the upper-to-lower body-segment ratio (≤0.85 in dolichostenomelia) and the armspan-to-height ratio (>1.05 in dolichostenomelia). Arachnodactyly was assessed by hand measurements. Facial features, height and width of the palate, dental crowding, pectus deformities, scoliosis, contractures, hypermobility of the large and small joints, and the presence of striae atrophicae were scored using standardized criteria. Cardiology, echocardiography, ophthalmology, and orthopedic reports were reviewed and patients were asked to disclose any history of hernias or pneumothorax. No imaging was performed to look for dural ectasia or protrusio acetabuli.

The diagnosis of MFS depends primarily on clinical features that have been codified into the Ghent diagnostic nosology. The cardiovascular, ocular, skeletal systems and the dura and family/genetic history can provide major criteria, while system involvement of the pulmonary system and skin/integument can only provide system involvement. The diagnosis is made by identifying major criteria in two different organ systems and involvement of a third system. In the presence of a family history of MFS in a first-degree relative who independently meets the major criteria, the diagnosis of MFS can be made in the presence of one major criterion in one organ system and involvement of a second organ system. All the patients participating in this study showed signs of aortic dilatation and/or dissection, twelve patients fulfilled the clinical criteria of MFS according to the Ghent nosology, and other 9 patients showed clinical MFS features but did not fulfill the diagnostic criteria. Fifty subjects without diagnostic features of MFS were included as controls.

2.1.1. Genomic DNA preparation

Blood specimens (5 ml) were collected and genomic DNA was extracted from blood leucocytes. For mutation screening, all 65 exons of *FBN1* were amplified by PCR using a set of primer pairs as previously described [12] and followed by direct sequencing analysis. Genomic DNA from 50 unrelated control individuals was tested for the identified mutations to exclude polymorphisms and confirm their association with the pathological conditions.

Analysis of genotype and phenotype correlations.

The analysis of genotype-phenotype correlations in MFS patients was performed by using the data from this study and the previous articles. We systematically searched PubMed (http://www.ncbinlm.nih.gov/pubmed; from 1990 to December 2018), Embase (http://www.embase.com; from 1990 to December 2018) and reviews of relevant articles. The following terms were used: "Marfan syndrome OR Marfan syndrome and related disorder OR *FBN1* mutations OR fibrillin-1 mutations". Titles and abstracts were screened to exclude ineligible studies. The exclusion criteria of the publications were as follows: (i) Not reporting original data (reviews, editorials, commentaries/replies to commentaries, news, etc.); (ii.)Not reporting in English;(iii.)Mouse modle of Marfan syndrome; (iv) *FBN1* carriers without detailed molecular and phenotype informations. *FBN1* carriers with detailed molecular and phenotype were included for the analysis of genotype-phenotype correlations.

2.2. Statistical analysis

Chi-square tests were used to compare the frequency of clinical features between two groups. To study the impact of mutation types, we carried out the following comparisons, (1) patients with nonsense mutations versus patients with other type mutations, (2) patients with missense mutations versus patients with frameshift mutations, and (3) patients with missense mutations involved in eliminating or creating a cysteine versus patients without cysteine missense mutations. To explore the consequences of mutations in different structural and functional domains, we compared (1) patients with a mutation at the 5′ end of the FBN1 gene (exons 1–21) and patients with a mutation at the 3′ end of the gene (exons 43–65); (2) patients with a mutation located in the so-called neonatal region (exons 24–32) and patients with a mutation located in other exons; and (3) patients with cardiovascular phenotypes and patients with ocular and skeletal phenotypes in the groups with a particular mutation (by mutation type and by mutation distribution) 2 by 2.

SPSS software version 17.0 was used for all statistical analyses. P values <0.05 were considered significant.

3. Results

3.1. The molecular study of the patients with typical or incomplete MFS

Among 21 unrelated individuals (median age at diagnosis 29 years; range 14–53 years), the definitive diagnosis of MFS was made in 12 patients, and other 9 patients showed clinical MFS features but did not fulfill the diagnostic criteria. Aortic dilations and/or dissections as major cardiovascular manifestations were evident in all 21 patients. Mitral valve prolapse was observed in 2 patients. Aortic dissection was observed in 13 patients.

A summary of clinical phenotype and *FBN1* mutations in all 21 patients is shown in Table 1. Five patients had a major criterion in the skeletal system; four had ocular involvement; six had striae; and one had pneumothorax. The mutation detection rate was 11/12 (91.7%) in patients diagnosed as classical MFS. In contrast, a very low mutation yield (1/9, 11.1%) was observed in patients referred to as incomplete MFS. The efficacy of mutation screening was roughly comparable to previous studies [9,12–17] (Table 2). The observed *FBN1* mutations included 10 novel mutations (c.357 C>A, c.493 C>T, c.1374 T>A, c.4143 delG, c. 6987 C > G, c.7238 G>A, c. 7765 A>G, c.8200 A>G, c. 8431 G>A, c.8547 T>G) and 2 previously reported mutations (c.4567 C>T, c.4615 C>T). Among these mutations, we identified 5 missense (c.6987 C > G, c.7238 G>A, c.7765 A>G, c.8200 A>G, c.8431 G>A), 6 non-sense (c.357 C>A, c.493 C>T, c.1374 T>A, c.4567 C>T, c.4615 C>T, c.8547 T>G) and one frameshift (c.4143 delG). Eight mutations affect calcium-binding EGF modules (c.4143 delG, c. 357 C>A, c. 4567 C>T, c. 6987 C > G, c. 1374 T>A, c. 493 C>T, c. 5791 G>C, c. 7765 A>G). One substitution mutation involved in the highly conserved cysteine residue (c. 4615 C>T) and the other three substitution mutations involved in the COOH unique region (c. 8431 G>A, c. 8547 T>G, c. 8200 A>G).

The analysis of genotype-phenotype correlations by using data from existing studies.

To evaluate the genotype-phenotype correlations in MFS, we analyzed the data from the present study and reviewed previous studies. Initially, 914 articles were identified from the databases PubMed and EMBASE. Based on the predefined selection criteria, 886 papers were excluded for different reasons. As a result, twenty nine studies [13–41] with 890 subjects met all the inclusion criteria and were chosen for the analysis of genotype-phenotype correlations (including 12 *FBN1* carriers identified in the present study) (Fig. 1).

The distribution of clinical manifestations in 890 patients is listed in Table 3, including ectopia lentis in 486patients (54.6%), significant aortic dilatation or dissection in 634 patients (71.2%), and major skeletal involvement in 427 patients (48.0%). Overall, 379 patients (49.6%) had a

Table 1
Molecular and clinical details of 21 unrelated patients with a possible or definite clinical diagnosis of MFS.

Patient	Fulfill Ghent criteria	Sex	Age	Exon	Protein Change	Nucleotide change	Module	Oscular system	Skeletal system	Cardiovascular system	Dural ectasia	Skin	Lung	Family history	Scoring of systemic features[a]
1	Yes	M	25	5	Arg165X	493 C>T	EGF-like #03	m	nil	AD, A Dissect, moderate MR	nil	striae		+	3
2	Yes	M	20	11	Tyr458X	1374T>A	cb EGF-like #04	EL	m	AD,A Dissect	nil	nil	nil	+	6
3	Yes	M	21	33	Pro1381 Lys fs	4143delG	cb EGF-like #13	m	M	AD	nil	striae	Pnx	+	11
4	No	M	23	36	Arg1523X	4567C>T	cb EGF-like #22	m	m	AD,A Dissect	nil	nil	nil	−	3
5	Yes	F	48	37	Arg1539X	4615C>T	8-Cys #04	EL	m	AD, moderate MR	nil	nil	nil	+	5
6	Yes	F	25	4	Cys119X	357C>A	cb EGF-like #2	nil	M	AD,A Dissect, severe MR	nil	striae	nil	−	8
7	Yes	F	28	58	Cys2413Tyr	7238G>A	cb EGF-like #37	EL	M	AD, moderate MR	nil	nil	nil	−	9
8	Yes	F	44	56	Asp2329Glu	6987C>G	cb EGF-like #36	nil	M	AD,A Dissect	nil	striae	nil	+	10
9	Yes	F	14	62	Arg2589Gly	7765A>G	cb EGF-like #41	nil	M	AD, MVP	nil	nil	nil	+	9
10	Yes	M	30	64	Asn2734 Asp	8200A>G	COOH unique region	EL	m	AD	nil	striae	nil	−	5
11	Yes	F	31	65	Gly2811Arg	8431 G>A	COOH unique region	m	M	AD,A Dissect	nil	striae	nil	−	11
12	Yes	M	53	65	Tyr 2849X	8547 T>G	COOH unique region	m	m	AD	nil	nil	nil	+	7
13	No	M	31	−	−	−	−	nil	m	AD,A Dissect	nil	nil	nil	−	4
14	No	M	44	−	−	−	−	nil	m	AD,A Dissect	nil	nil	nil	−	5
15	No	M	23	−	−	−	−	nil	m	AD,A Dissect	nil	nil	nil	−	3
16	No	M	26	−	−	−	−	nil	nil	AD,A Dissect	nil	nil	nil	−	0
17	No	F	23	−	−	−	−	m	m	AD,MVP	nil	nil	nil	−	4
18	No	M	47	−	−	−	−	nil	m	AD,A Dissect	nil	nil	nil	−	3
19	No	M	16	−	−	−	−	nil	m	AD,A Dissect	nil	nil	nil	−	4
20	No	M	27	−	−	−	−	m	m	AD	nil	nil	nil	−	4
21	Yes	M	28	−	−	−	−	m	m	AD, A Dissect				+	5

EL, ectopia lentis; AD, Aortic Root Dilation; A Dissect, Aortic Dissection; MR: Mitral Regurgitation; MVP: Mitral Valve Prolapse; Pnx, pneumothorax; Nil, evaluated negative for the specific.
[a] The Marfan score was based on the"systemic criteria" in the Ghent II nosology [8].

positive family history. The proportion of each specific clinical feature was analyzed in different mutation groups. The following systems were considered to be involved in MFS, including skeleton, eye, heart, skin and dura. Collectively, the detailed information about molecular genotypes and clinical phenotypes was obtained and analyzed in the total of 890 *FBN1* carriers with MFS. (Table 4).

3.2. Type of mutations

3.2.1. Cysteine missense mutation

By analyzing data from existing studies, the association of cysteine missense mutation with ectopia lentis was revealed (77.5% vs. 50.3%; $p < 0.001$). The percentage of major cardiovascular involvement was slightly higher among patients with cysteine missense mutations compared to patients with other missense mutations (68.3% vs. 66.5%; $p = 0.596$), as well as that of major skeletal involvements (41.2% vs. 38.7%; $p = 0.629$), but did not reach the statistic significance.

Table 2
FBN1 mutations in MFS identified from different studies.

Previous reports	MFS	IM
Loeys [13]	62/94	7/52
Halliday [14]	17/22	2/6
Korkko [12]	18/20	0/1
Biggin [15]	26/29	9/13
Rommel [16]	37/60	16/36
Comeglio [17]	90/110	84/315
Stheneur [10]	193/266	61/105
Attanasio [20]	75/85	5/14
This study	11/12	1/9

Abbreviations: MFS, classical Marfan syndrome; IM, incomplete MFS.

3.2.2. PTC mutations

The frequency of ectopia lentis was significantly lower in patients with PTC mutations compared to patients with non-PTC mutations (28.8% vs. 66.4%; $p < 0.001$). However, PTC mutations were associated with an increased risk of major cardiovascular involvements compared to other mutations (78.3% vs. 68.1%; $p = 0.002$). Among patients with PTC mutations, the frequency of major cardiovascular involvements was significantly higher than that of major skeletal involvements (78.3% vs. 60.3%; $p < 0.001$), as well as that of major ocular involvements (78.3% vs. 28.8%; $p < 0.001$).

3.2.3. Frameshift mutations

The frequency of major cardiovascular involvements was much higher in patients with frameshift mutations compared to patients with missense mutations (77.5% vs. 67.6%; $p = 0.015$), as well as that of major skeletal involvements (56.1% vs. 40.3%; $p < 0.001$). The

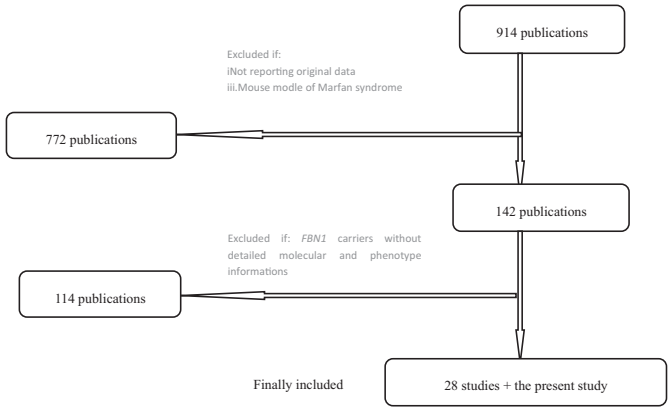

Fig. 1. Strategy of the systematic literature search and its results.

Table 3
Clinical Features of Different Systems in *FBN1* carriers.

System and clinical feature(s)	No. of events (n)	Percentage (%)
Skeletal		
M	427	48.0
m	398	44.7
not involved	65	7.3
Ocular		
M	486	54.6
m	122	13.7
not involved	282	31.7
Cardiac		
M	634	71.2
m	113	12.7
not involved	143	16.1
Skin		
m	413	46.4
not involved	452	50.8
n/a	25	2.8
Lung		
m	63	7.1
not involved	754	84.7
n/a	73	8.2
Dural ectasia		
M	129	14.5
not involved	360	40.4
n/a	401	45.1
Family history of MFS or *FBN1* mutation	379	49.6

m, minor involvement; M, major involvement; n/a, not available.

percentage of major ocular involvement was significantly lower among patients with frameshift mutations compared to patients with missense mutations (35.3% vs. 65.2%; $p < 0.001$).

3.2.4. Mutation distribution

The overview of the included twenty nine studies showed that the percentage of major cardiovascular involvements were higher in patients with mutations in exons 24–32 compared patients with mutations in exons 1–21 (77.0% vs. 68.1%; $p = 0.04$), but similar to patients with mutations in exons 43–65 (71.4% vs. 77.0%; $p = 0.238$). The frequency of ectopia lentis was significantly lower in patients with PTC mutations compared to patients with non-PTC mutations (28.8% vs. 66.4%; $p < 0.001$).

4. Discussion

In the present study, direct sequencing of the 65 exons of FBN1 was performed in 21 probands with typical or incomplete MFS, and 12 *FBN1* mutations were identified. Seven mutations detected in this study seemed causative because they fulfilled at least one of the following criteria: (1) involvement of a highly conserved cysteine residue, (2) nonsense mutation, and (3) frameshift mutation (reviewed by Robinson et al. [42]). The remaining five putative mutations that did not satisfy the above criteria were absent in 100 alleles from 50 normal individuals, so the five mutations in *FBN1* were not polymorphisms and their association with the pathological conditions were confirmed. As the probands came from remote areas, their families were recommended to go to local hospital for diagnosis and treatment.

The mutation detection rate was 11/12 (91.7%) in patients diagnosed as classical MFS. In contrast, a very low mutation yield (1/9, 11.1%) was observed in patients referred to as incomplete MFS. It is possible that one patient with "typical MFS" without any detected *FBN1* mutation and some of the patients with "incomplete MFS" have causal mutation outside of the coding region. Because the mutations in TGF-β signaling pathway-related genes (*TGFBR1* and *TGFBR2*) cause heritable disorders of the connective tissue, such as MFS, Loeys-Dietz syndrome (LDS), and Shprintzen-Goldberg syndrome (SGS) [43–45], and these syndromes may affect cardiovascular, ocular and skeletal systems. The variable phenotypic expression of the disorder and the age-related nature of clinical manifestations may result in some of the patients with "incomplete MFS" carrying causal mutation outside of the coding region [46].

The mutations detected in this study distributed throughout the *FBN1*gene. Nearly half of the mutations are missense mutations, in line with several other reports [28,47,48]. Our results indicate that the prevalence of major cardiovascular involvements is higher in MFS patients with cysteine substitution or PTC mutations, or *FBN1* mutations in exons 43–65. Previous studies have revealed the association of cysteine missense mutation with ectopia lentis [15–17,31,37,42]. The association of cysteine missense mutation with ectopia lentis was confirmed by our analysis of the existing studies. It has been reported that PTC mutations were associated with a reduction in risk of ectopia lentis [37], which was consistent with our finding.

Cardiovascular abnormalities are the most common cause of morbidity in MFS. Therefore, the correct diagnosis of MFS has important implications in appropriate cardiovascular and ophthalmologic follow-up. Genetic analysis has been widely accepted as a means to establish a diagnosis in uncertain cases and the detection of a mutation that has been found in other MFS patients has become a major diagnostic criteria. However, genetic counseling, and in particular the ability to predict phenotype on the basis of genotype in MFS, remains limited.

Despite the large number of FBN1 mutations reported in MFS, only a few genotype/phenotype relationships have been firmly established so far. For example, mutations leading to premature termination codons (PTC) are less frequently associated with ectopia lentis and retinal detachment than mutations that cause the substitution of a cysteine residue in a calcium-binding epidermal growth factor-like (cbEGF) domain [31]. One international study established several correlations in 1013 probands with a pathogenic *FBN1* mutation, found between different classes of mutation (types and locations). 1) A higher probability of ectopia lentis was found for patients with a missense mutation substituting or producing a cysteine, when compared with other

Table 4
Distribution of major clinical signs according to the type of *FBN1*mutations.

Mutation type and location	Skeletal system (*n* (%))			Ocular system (*n* (%))			Cardiovascular system		
	M	m	Not involved	M	m	Not involved	M	m	Not involved
Cys ($n = 306$)	126(41.2)	147(48.0)	33(10.8)	237(77.5)	20(6.5)	48(15.7)	209(68.3)	41(13.4)	56(18.3)
Non-Cys($n = 173$)	67(38.7)	95(54.9)	11(6.4)	87(50.3)	20(11.6)	66(38.2)	115(66.5)	17(9.8)	41(23.7)
PTC ($n = 267$)	161(60.3)	95(35.6)	11(4.1)	77(28.8)	54(20.2)	131(50.6)	205(78.3)	35(13.1)	23 (8.6)
Other ($n = 620$)	265(42.7)	302(48.7)	53(8.5)	412(66.4)	66(10.6)	142(22.9)	422(68.1)	78(12.5)	120(19.3)
Sub/Mis($n = 479$)	193(40.3)	242(50.5)	47(9.2)	312(65.2)	60(12.5)	107(22.3)	324(67.6)	58(12.1)	97(20.2)
Frameshift($n = 173$)	97 (56.1)	53(30.6)	23(13.3)	61(35.3)	22(12.7)	90(52.0)	134(77.5)	16(9.2)	23(13.3)
E 24–32 ($n = 125$)	57(46.0)	64(50.8)	4(3.2)	77(61.1)	12(10.3)	36(28.6)	98(77.0)	17(13.5)	12(9.5)
E1–21 ($n = 260$)	102(39.2)	127(48.8)	31(11.9)	166(63.8)	25(9.6)	69(26.5)	177(68.1)	33(12.7)	50(19.2)
E43–65 ($n = 315$)	174(55.2)	126(40.0)	15(4.8)	136(43.1)	49(15.6)	130(41.3)	225(71.4)	42(13.3)	48(15.2)

Cys: Cysteine missense mutations; Non-Cys:Non Cysteine missense mutations Sub: substitution; Mis: missense; E: Exons; M: major involvement; m: minor involvement.

missense mutations. 2) Patients with an *FBN1* premature termination codon had a more severe skeletal and skin phenotype than did patients with an inframe mutation. 3) Mutations in exons 24–32 were associated with a more severe and complete phenotype, including younger age at diagnosis of type I fibrillinopathy and higher probability of developing ectopia lentis, ascending aortic dilatation, mitral valve abnormalities, scoliosis, and shorter survival [11]. 4) One recent study suggested that FBN1 3'UTR mutations are involved in aortic aneurysm formation in MFS patients [49].

Our results revealed several genotype phenotype correlations for *FBN1* mutations. Firstly, it was demonstrated that PTC mutations were more frequently associated with aortic aneurysm and/or dissections than non-PTC mutations. This observation is consistent with the findings of Schrijver et al. [31], in which aortic dissection appeared to be more frequent in the PTC group. However, the studies conducted by Loeys et al. [48] and Waldmuller et al. [50] showed that the PTC mutation was not associated with the over-all risk of dissection in the ascending thoracic aorta.

Secondly, our systematical analyses demonstrated mutations in exons 24–32 of *FBN1* was associated with neonatal MFS and a more severe phenotype. One international research showed that exon 24–32 mutations defined a high-risk of cardiac manifestations associated with severe prognosis at all ages [31]. In addition, Schrijver et al. [31] found that cysteine substitutions in cbEGF domains encoded by FBN1 exons 26–32 were associated with early aorta dilatation in childhood.

Finally, our results showed that mutations in exons 43–65 were associated with substantially more cardiovascular manifestations, in line with a similar finding in 25 of 33 individuals [19] and in 33 of 37 individuals with mutations in the same exons [22]. Previously, this mutation location has been associated with mild or less cardiovascular manifestations [28]. One possibility for this discrepancy is a "milder" cardiac features has not been substantiated in our analysis.

In conclusion, these results expand the mutation spectrum of *FBN1* and help in the study of the molecular pathogenesis of Marfan syndrome. The systematic analyses enrich our knowledge of genotype-phenotype correlations related to *FBN1* mutations. These data collectively highlight the importance of correlation between genotype and phenotype in anticipating the clinical consequence of specific *FBN1* mutations in patients with MFS and may help to assist clinicians in tailor-made patient follow-up.

Declaration of Competing Interest

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.06.066.

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