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# Clinical and Molecular Study of 320 Children With Marfan Syndrome and Related Type I Fibrillinopathies in a Series of 1009 Proband With Pathogenic *FBNI* Mutations

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## ABSTRACT

From a large series of 1009 probands with pathogenic *FBNI* mutations, data for 320 patients <18 years of age at the last follow-up evaluation were analyzed (32%). At the time of diagnosis, the median age was 6.5 years. At the last examination, the population was classified as follows: neonatal Marfan syndrome, 14%; severe Marfan syndrome, 19%; classic Marfan syndrome, 32%; probable Marfan syndrome, 35%. Seventy-one percent had ascending aortic dilation, 55% ectopia lentis, and 28% major skeletal system involvement. Even when aortic complications existed in childhood, the rates of aortic surgery and aortic dissection remained low (5% and 1%, respectively). Some diagnostic features (major skeletal system involvement, striae, dural ectasia, and family history) were more frequent in the 10- to <18-year age group, whereas others (ascending aortic dilation and mitral abnormalities) were more frequent in the population with neonatal Marfan syndrome. Only 56% of children could be classified as having Marfan syndrome, according to international criteria, at their last follow-up evaluation when the presence of a *FBNI* mutation was not considered as a major feature, with increasing frequency in the older age groups. Eighty-five percent of child probands fulfilled international criteria after molecular studies, which indicates that the discovery of a *FBNI* mutation can be a valuable diagnostic aid in uncertain cases. The distributions of mutation types and locations in this pediatric series revealed large proportions of probands carrying mutations located in exons 24 to 32 (33%) and in-frame mutations (75%). Apart from lethal neonatal Marfan syndrome, we confirm that the majority of clinical manifestations of Marfan syndrome increase with age, which emphasizes the poor applicability of the international criteria to this diagnosis in childhood and the need for follow-up monitoring in cases of clinical suspicion of Marfan syndrome.

### Key Words

Marfan syndrome, *FBNI*, childhood, international criteria

### Abbreviations

AAD—ascending aortic dilation  
CI—confidence interval  
EL—ectopia lentis  
MFS—Marfan syndrome  
PTC—premature termination codon

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**M**ARFAN SYNDROME (MFS) (MIM 154700) is a connective tissue disorder with autosomal dominant inheritance that has a prevalence of 1 case per 5000 to 10 000 individuals<sup>1</sup> and is caused mainly by *FBNI* mutations.<sup>2,3</sup> The cardinal features of MFS involve the ocular, cardiovascular, and skeletal systems.<sup>4</sup> The skin, lung, and dura also may be involved.<sup>5</sup> In addition to classic MFS, *FBNI* mutations are responsible for a large phenotypic spectrum ranging

from neonatal MFS to mild clinical entities.<sup>6</sup> Because of the high population frequency and the nonspecific nature of many of the clinical findings in MFS, clinical diagnostic criteria have been established, that is, the Ghent criteria,<sup>7</sup> which have superseded the previous Berlin criteria.<sup>8</sup>

The phenotype in adults is well documented, and diagnosis of MFS in the context of classic multisystem involvement is relatively straightforward.<sup>9–11</sup> Diagnosis of MFS in childhood may be problematic, however, because many manifestations are age-dependent, which diminishes the utility of the international criteria.<sup>7</sup> The marked phenotypic heterogeneity both between and within families and the high incidence of sporadic cases also contribute to the diagnostic difficulties. From a large, collaborative, international study including 1009 probands, all carrying a pathogenic *FBNI* mutation, we analyzed the clinical and molecular characteristics of a pediatric subgroup of probands who were <18 years of age at their last follow-up evaluation. Our results provide a better description of MFS in childhood and the presenting features at different ages.

## METHODS

A total of 1191 probands carrying a *FBNI* mutation who were registered between 1995 and 2005 were identified through the Universal Marfan database-*FBNI* ([www.umd.be](http://www.umd.be))<sup>2,12</sup> and the network of participating centers. Inclusion criteria in the present study were (1) heterozygosity for a pathogenic *FBNI* gene mutation and (2) the availability of clinical information. Of 1191 probands with a *FBNI* mutation, 182 probands were excluded from the study (no clinical data available,  $n = 129$ ; insufficient data on cardiovascular, ocular, or skeletal involvement,  $n = 44$ ; autosomal dominant Weill-Marchesani syndrome,  $n = 4$ ; 2 *FBNI* mutations on the same allele,  $n = 4$ ; compound heterozygosity,  $n = 1$ ). The pathogenic nature of a putative mutation was assessed by using recognized criteria. In brief, all nonsense mutations, deletions, and insertions (in or out of frame) were considered pathogenic; for all splice mutations, the wild-type and mutant strength values of the splice sites were compared by using genetic algorithms, and only mutations displaying significant deviation from the normal value were included. Missense mutations were considered pathogenic when  $\geq 1$  of the following features was found: (1) de novo missense mutation; (2) missense mutation substituting or creating a cysteine; (3) missense mutation involving a consensus calcium-binding residue; (4) substitution of glycines implicated in correct domain-domain packing; or (5) intrafamilial segregation of a missense mutation involving a conserved amino acid.<sup>13</sup> The patients included in the study originated from 38 countries, on 5 continents. The clinical data were collected either from a questionnaire sent to referring physicians and clinical investigators or from previous publications in which sufficient information was available. The clinical information included a range of qualitative and quantitative clinical parameters, including the age at the diagnosis of MFS or another type I fibrillinopathy and the presence or absence of clinical fea-

tures, including cardiovascular, ocular, skeletal, cutaneous, pulmonary, and dural manifestations.

Data for 320 probands (32%) who were <18 years of age at the last follow-up evaluation were extracted for the study. To describe this population, the frequency of each specific clinical feature or system involvement was studied in the overall population of children and then in 3 subgroups, that is, neonates, children <10 years of age at the last follow-up evaluation, and children 10 to <18 years of age at the last follow-up evaluation. The clinical features studied in each system are listed in Table 1. The ages at diagnosis and at surgery were collected for scoliosis, ectopia lentis (EL), ascending aortic dilation (AAD), and aortic dissection. For each child, major and/or minor system features were defined for skeletal, ocular, cardiovascular, pulmonary, cutaneous, and dural manifestations, according to the Ghent criteria.<sup>7</sup> Ghent criteria were defined as positive for isolated cases that presented with 2 major system manifestations and involvement of  $\geq 1$  other organ system. In familial cases, the presence of a major criterion finding in 1 organ system and the involvement of a second organ system were sufficient for the diagnosis of MFS if another family member was diagnosed independently as having MFS. To reproduce the situation that clinicians face in clinical practice, the presence of a *FBNI* mutation was not considered as a major feature initially. For the group of patients who did not fulfill clinical international criteria, we evaluated the proportions of patients who demonstrated positive results for international criteria when the presence of the *FBNI* mutation was considered as a major feature for the general population and for the different groups. Because some of the clinical or radiologic features that are part of the international criteria (including protrusio acetabulae, dural ectasia, flat cornea, iris or ciliary muscle hypoplasia, dilation of the pulmonary artery, mitral annular calcification, and apical blebs) were investigated only occasionally, unmentioned clinical features had to be considered absent for determination of patients' status with respect to the international criteria.

The first presenting diagnostic feature was determined for each patient. For descriptive purposes, the overall population was classified as having neonatal MFS (defined in this study as a diagnosis of type I fibrillinopathy with severe valvular involvement before 4 weeks of age), severe MFS (defined by the diagnosis of MFS according to clinical international criteria, including AAD, before 10 years of age), classical MFS (defined by the diagnosis of MFS according to clinical international criteria in other patients), or probable MFS (defined on the basis of unfulfilled clinical international criteria in childhood, ie, before 18 years of age). Mutation types and locations were compared for the different presentation types.

The Kaplan-Meier method<sup>14</sup> was used to estimate the cumulative probabilities (and their confidence intervals [CIs]) of diagnoses of clinical features at 10 years of age when the ages at diagnosis were known (AAD, dissection, and surgery; EL and surgery for EL; and scoliosis). The  $\chi^2$  test was used to analyze the distribution of mutations (locations and types) according to MFS presentation. Only  $P$

**TABLE 1** Frequency of Clinical Features of the Ghent Criteria for the 320 Child Probands

Clinical Features	Frequency, %			
	Total (N = 320)	Neonatal MFS (N = 45)	<10 y (N = 111) <sup>a</sup>	10 to <18 y (N = 164) <sup>a</sup>
Skeletal system				
Pectus carinatum or excavatum requiring surgery	27	14	26	31
Dolichostenomelia	52	41	48	58
Positive wrist and thumb sign	83	100	79	81
Scoliosis of >20° or spondylolisthesis	43	33	35	52
Limited elbow extension (<170°)	21	81	11	12
Pes planus	48	22	46	55
Protrusio acetabulae	9	0	6	12
Facial appearance	58	82	52	55
Joint hypermobility	67	64	68	67
Moderate pectus excavatum	32	14	32	31
High arched palate	70	68	61	73
Major skeletal system involvement	28	24	20	34
Minor skeletal system involvement	63	69	67	59
Ocular system				
EL	55	38	63	55
Myopia	42	31	44	44
Flat cornea	NI	NI	NI	NI
Iris or ciliary muscle hypoplasia	NI	NI	NI	NI
Major ocular system involvement	55	38	63	55
Cardiovascular system				
AAD, with or without aortic regurgitation	71	93	66	68
Ascending aortic dissection	1	0	1	1
Dilation or dissection of descending aorta or abdominal aorta	2	4	1	2
Mitral valve prolapse	62	73	62	59
Mitral annulus calcification	NI	NI	NI	NI
Dilation of pulmonary artery	NI	NI	NI	NI
Major cardiac system involvement	71	93	66	68
Minor cardiac system involvement	14	2	19	15
Pulmonary system				
Pneumothorax or apical blebs	4	7	3	4
Minor lung system involvement	4	7	3	4
Skin				
Striae atrophicae	19	2	7	32
Recurrent or incisional hernia	7	16	4	7
Minor skin involvement	23	18	9	34
Dura				
Lumbosacral dural ectasia	26	0	11	35
Major central nervous system involvement	5	0	2	9
Family				
First-degree family member fulfilling diagnostic criteria	29	0	22	43
Pathogenic <i>FBN1</i> mutation	100	100	100	100
Clinical Ghent criteria positive	56	36	52	64
Ghent criteria positive after <i>FBN1</i> mutation screening	85	93	80	85

NI indicates not investigated.

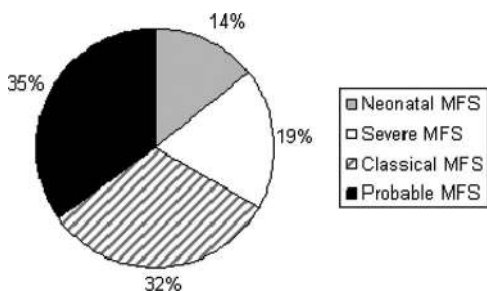
<sup>a</sup> At last follow-up evaluation.

values of <.001 were considered significant, because multiple tests were performed. Analyses were performed by using Stata 9.0 (Stata Corp, College Station, TX).

## RESULTS

Of the 320 child probands, 55% were male and 45% were female. Only 94 patients (30%) had a family history of MFS or other type I fibrillinopathy. The median age at diagnosis was 6.5 years (interquartile range: 3–11

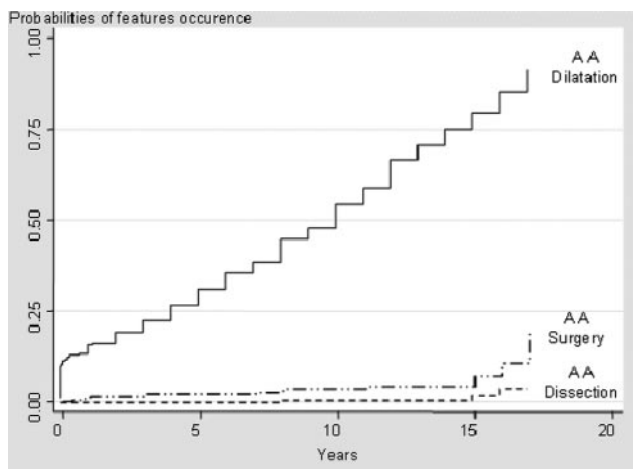
years). Forty-five patients (14%) had a neonatal MFS presentation. Of the remaining patients, 111 (35%) were <10 years of age at their last follow-up evaluation and 164 (51%) were between 10 and 18 years of age. Thirty-six children (11%) were dead at the last follow-up evaluation (29 as a result of cardiac failure, including 25 with neonatal MFS; 3 in the context of cardiac surgery, at birth, 4 years, and 16 years; 1 as a result of respiratory insufficiency in the context of severe



**FIGURE 1**  
Type of MFS presentation in the pediatric population with MFS ( $N = 320$ ), when the presence of a *FBN1* mutation was not taken into account (see "Methods" for definitions of the different types of presentation).

emphysema; 1 as a result of aortic dissection at 16 years of age; 1 as a result of another cause, independent of MFS; and 1 as a result of termination of pregnancy for a fetus with severe prenatally ultrasonographically detected features and asymptomatic parents, which suggested neonatal MFS). The population was classified as follows: neonatal MFS, 14%; severe MFS, 19%; classic MFS, 32%; probable MFS, 35% (Fig 1). The frequencies of the clinical manifestations that are part of the international criteria are presented in Table 1 for the overall population of probands and the different groups.

Figure 2 shows Kaplan-Meier estimates of the probability of diagnosing an aortic event in this population. The cumulative probability of AAD diagnosed at 10 years was 53% (99.9% CI: 44%–63%). The probability of aortic surgery was 5% (99.9% CI: 1%–14%), and the probability of ascending aortic dissection was 1% (99.9% CI: 0%–11%). Aortic surgery was necessary for 14 probands with severe aortic dilation and 3 probands with aortic dissection. Of the 3 patients with ascending aortic dissections, at 8, 15, and 16 years of age, 2 patients also had involvement of the descending and/or abdominal aorta. The cumulative probabilities of mitral valve



**FIGURE 2**  
Kaplan-Meier analysis of the probability of diagnosing an aortic event in the pediatric population with MFS ( $N = 320$ ). The probabilities of ascending aortic surgery and ascending aortic dissection were determined in the overall population of child probands. AA indicates ascending aortic.

prolapse, mitral insufficiency, aortic insufficiency and valvular surgery independent of aortic surgery at 10 years were 49% (99.9% CI: 40%–59%), 34% (99.9% CI: 25%–44%), 10% (99.9% CI: 5%–18%), and 6% (99.9% CI: 2%–13%), respectively. Congenital structural heart disease was found for 6 probands. When results were stratified for the different groups, the frequencies of AAD and valvular abnormalities were higher among those with neonatal MFS (Table 1).

With respect to ocular manifestations, the cumulative probability of EL diagnosed at  $\leq 10$  years was 52% (99.9% CI: 42%–62%) and that for eye surgery was 24% (99.9% CI: 14%–39%). With stratification into different age groups, the frequency of EL was higher in the  $< 10$ -year age group (63%) and lower in the neonatal MFS group (Table 1). Myopia was diagnosed for 42% of patients, whereas cataracts, retinal detachment, and glaucoma each were diagnosed for 1% of children.

With respect to skeletal manifestations, 28% of probands had major skeletal system involvement and 63% had minor skeletal system involvement at their last follow-up evaluation. The cumulative probability of scoliosis diagnosed at  $\leq 10$  years was 47% (99.9% CI: 37%–59%). Orthopedic surgery was performed for 8% of probands (scoliosis,  $n = 14$ ; pectus carinatum or excavatum,  $n = 5$ ; other indications,  $n = 8$ ). One hundred five (52%) of 203 probands had heights  $> 3$  SDs above the mean. Three probands had craniosynostosis. The frequencies of most skeletal features (pectus carinatum or excavatum requiring surgery, dolichostenomelia, scoliosis, pes planus, and protrusio acetabulae) increased with age (Table 1).

With respect to other manifestations, the proportions of patients with striae, dural ectasia, and family history increased with age (Table 1). A diaphragmatic hernia was noted for 7 patients with neonatal MFS. Hydrocephalus was described in 1 case of neonatal MFS. Other features (polymicrogyria, mitochondrial complex I deficiency, and epidermolysis bullosa) were described only once, which indicates a coincidental association.

As expected for the general population,<sup>15</sup> 10 probands (3%) had developmental delay/mental retardation. The presence of mental retardation could be considered coincidental for 3 patients, because 1 patient also had mitochondrial complex I deficiency and 2 patients had a family history of MFS without mental retardation. Mental retardation also was described for 2 patients with neonatal MFS and long survival times (3 and 4 years) and 1 patient with craniosynostosis reported as Shprintzen-Goldberg syndrome. The 4 remaining patients represented sporadic cases or had unknown family history, with presentation as severe MFS in 3 cases and classic MFS in 1 case. The patients with polymicrogyria and hydrocephalus were not included in the number of patients with developmental delay/mental retardation because the patients died at 1 day and 2 months of life.

The majority (85%) of patients could be classified as having MFS according to international criteria at their last follow-up evaluation when the presence of a *FBN1* mutation was considered as a major feature, but only 56% of the children met the clinical international criteria when the

**TABLE 2** First Diagnostic Manifestation in the Overall Population of Child Probands and in the Different Age Groups at the Time of MFS (or Other Type I Fibrillinopathy) Diagnosis

First Diagnostic Manifestation	Proportion, %		
	Total (N = 320)	<10 y (N = 166)	10 to <18 y (N = 109)
EL + AAD	29	30	34
AAD	27	19	30
Skeletal	24	25	20
EL	20	27	16

presence of a *FBNI* mutation was not considered as a major feature. When the populations of children in the different age groups were considered, 36% in the neonatal MFS group, 52% in the <10-year group, and 64% in the 10- to <18-year group met the clinical international criteria (Table 1). Table 1 also shows the proportion of patients who could be diagnosed as having MFS when the presence of the *FBNI* mutation was considered. Of the patients with ascending aortic dissection or surgery, 4 (24%) did not fulfill the clinical international criteria.

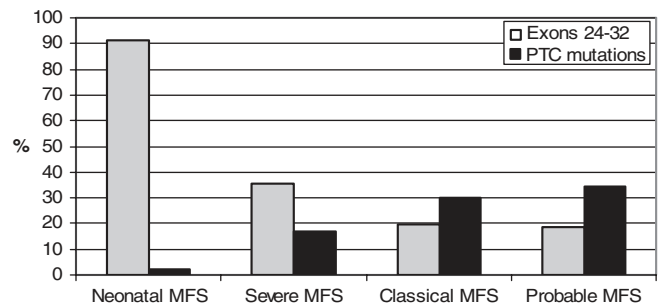
Table 2 shows that the first diagnostic features leading to the diagnosis of MFS were divided fairly evenly between AAD, EL, both EL and AAD, and skeletal involvement in the overall population of child probands. Results also are presented according to the age at diagnosis.

The distribution of mutations in the proband cohort was as follows: 232 mutations (75%) were in-frame mutations, whereas 78 (25%) generated a premature termination codon (PTC). Ten splice site mutations were not classified because the consequences at the mRNA level could not be determined unambiguously. Within the missense mutations, 130 (66%) of 196 involved a cysteine (111 replacing and 19 creating a cysteine). Most mutations (79%;  $n = 252$ ) were located in an epidermal growth factor domain, 241 (75%) were in a calcium-binding epidermal growth factor domain, and 38 (12%) were in a transforming growth factor  $\beta_1$ -binding protein domain. One hundred four mutations (33%) were lo-

cated in exons 24 to 32. A  $\chi^2$  analysis for the distribution of mutations according to the type of presentation revealed significant differences for children with mutations in exons 24 to 32, compared with children with mutations located elsewhere ( $P < .001$ ) (Fig 3). Indeed, a larger proportion of mutations in exons 24 to 32 was found for patients with a neonatal presentation, compared with children with classic or probable MFS. Two of the 3 probands who developed aortic dissection and 9 of the 14 probands who underwent surgery because of aortic dilation had mutations in the exon 24 to 32 region. Significant results also were found for PTC mutations versus in-frame mutations, with the proportion of PTC mutations decreasing with the severity of the presentation ( $P < .001$ ) (Fig 3).

## DISCUSSION

The literature description of MFS at pediatric ages is scanty. Previous reports of children with MFS included only small numbers of patients, with a strong bias in clinical presentation. Authors have concentrated mainly on severely affected individuals with prominent cardiovascular involvement.<sup>16-21</sup> The 2 largest studies included 40 and 52 children.<sup>22,23</sup> Lipscomb et al<sup>22</sup> focused on the evolution of the physical characteristics of MFS throughout childhood. By studying probands and relatives <16 years of age who were identified through a regional MFS registry and excluding neonatal MFS, the authors showed that musculoskeletal features predominated in and evolved throughout childhood. The most frequent musculoskeletal findings at presentation were a combination of tall stature, limb disproportion, pectus deformity, classic facial features, high arched palate, and arachnodactyly. Only 15% of patients had EL, 18% had mitral valve prolapse, and 43% had AAD, which usually became evident at ~9 to 15 years of age. The authors concluded that the absence of aortic root enlargement could not be used to exclude a diagnosis of MFS for a "marfanoid" child before skeletal growth was complete.<sup>22</sup> Very different cardiovascular values were described in the study by van Karnebeek et al,<sup>23</sup> in which



**FIGURE 3**

Distributions of locations (mutations located in exons 24–32) and types of *FBNI* mutations (mutations leading to a PTC) depending on the presentation of MFS or type I fibrillinopathy in the pediatric population with MFS (N = 320). <sup>a</sup>  $\chi^2$  test P value.

	Neonatal MFS vs other MFS presentations	Severe MFS vs other MFS presentations	Classical MFS vs other MFS presentations	Probable MFS vs other MFS presentations
Exon 24-32 vs other exons	<.0001 <sup>a</sup>	.5764 <sup>a</sup>	.0021 <sup>a</sup>	.0001 <sup>a</sup>
PTC vs missense mutations	.0002 <sup>a</sup>	.1062 <sup>a</sup>	.1755 <sup>a</sup>	.0070 <sup>a</sup>

52 children who were referred to their pediatric department and fulfilled the international criteria were investigated, with exclusion of patients with neonatal MFS. Eighty-eight percent of those children had mitral valve prolapse, 77% AAD, 48% mitral regurgitation, and 25% aortic regurgitation. Aortic surgery was performed for 23% of children with AAD (after aortic dissection for 2 patients), and mitral valve surgery was performed for 13% of patients with mitral valve abnormalities. In addition, 62% of patients had EL.<sup>23</sup> The methods for ascertainment and referral of patients might represent the main explanation for these differences.

Our larger sample size, different method of ascertainment through a mutation database, inclusion of only probands, and molecular confirmation of the diagnosis of MFS or type I fibrillinopathy allow a more-accurate description of the organ involvement of MFS at pediatric ages. The large patient number allowed us to stratify the cohort into different groups on the basis of neonatal status and age at last follow-up evaluation, for descriptive and prognostic purposes. We showed that the frequency of AAD was higher in neonatal MFS (Table 1). We also showed that aortic complications were rare in childhood, because aortic dissection occurred in only 3 probands and aortic surgery needed to be performed for 14 patients. As noted in previous publications,<sup>16,18,21,24</sup> valvular involvement was frequent among the children in our series. The frequency of EL was higher in the <10-year age group (Table 1). Finally, the frequencies of many skeletal features, dural ectasia, minor cutaneous involvement, and family history increased with age (Table 1). Therefore, MFS in childhood seems to be represented by differing features, depending on the age at diagnosis. An early-onset presentation can be described in de novo cases, with predominantly a severe aortic and mitral valve phenotype and a high mortality rate. When patients are diagnosed between 10 and 18 years of age, their presentation seems to be similar to that of patients with classic MFS, with increasing frequencies of skeletal features, striae, dural ectasia, and family history. Not surprisingly, because 23% of the series was represented by neonatal or severe MFS, we found a higher rate of de novo mutations than usually described.

Three patients in this series had craniosynostosis, 1 of whom was described previously.<sup>25</sup> All 3 patients had mutations located in the exon 24 to 32 region. The possible association between MFS and craniosynostosis is important to note, because it can be a confounder in the diagnosis of Loeys-Dietz syndrome or Shprintzen-Goldberg syndrome.<sup>26–28</sup> Only the patient reported by Sood et al<sup>25</sup> also had mental retardation. There were 7 patients (2% of the population) with mental retardation that could not be stated as being coincidental. The presence of mental retardation usually turns clinicians to alternative diagnoses, such as Lujan-Fryns syndrome.<sup>29</sup> We do not provide arguments in favor of an association between MFS and mental retardation because the rate of mental retardation in this series was similar to that in the general population.<sup>15</sup>

We were able to determine the more-frequent diagnostic features at initial presentation in this cohort. In

the overall population of children, the rates of the main diagnostic presentations (AAD and EL, AAD, EL, and skeletal features) were quite similar (Table 2). Results did not vary considerably when the population was stratified according to age at the time of diagnosis. However, the retrospective design of our study and the nature of MFS itself preclude accurate definition of the ages at which manifestations arose. Only the age at first detection of a specific feature, which was necessarily older than the true age of occurrence, could be used. Also, these results remain artificial; because the findings of EL and AAD require additional examinations, the diagnosis is usually triggered by skeletal features.

Results regarding the proportion of patients with positive clinical results for the international criteria confirmed the limited utility of the international criteria in infancy and childhood. Indeed, only 56% of children would have been diagnosed on clinical grounds alone, compared with 79% in adulthood.<sup>11</sup> Although some minor features (eg, mitral valve prolapse, with or without mitral regurgitation, and dysmorphic facial features) were overrepresented in childhood, compared with the adult cohort, the lower rate of positive clinical results for the international criteria in children is explained mainly by the underrepresentation of dural ectasia, minor cutaneous involvement, and family history.<sup>11</sup> Because only child probands were selected, the absence of a family history is clearly a selection bias. Indeed, milder cases presenting later more frequently have a family history, because the milder mutations permit survival into the reproductive period. Children with new mutations tend to be more seriously affected and may not survive to reproduce. The dura was assessed only occasionally (62 of 320 patients), because evaluation might require anesthesia in young children, access to MRI studies often is limited, and no normal values are readily available.<sup>30</sup> It is well known that striae usually appear during growth and puberty.<sup>5</sup> The frequencies of AAD, EL, and major skeletal features were comparable for the child and adult cohorts.<sup>10</sup> When the population was stratified according to the age at the last follow-up evaluation, we clearly showed that the rate of positive clinical results for the international criteria increased with age (Table 1). Therefore, in cases in which MFS or another type I fibrillinopathy is suspected for a child, one could advocate long-term, clinical, follow-up monitoring in search of developing features suggesting a diagnosis of MFS. Alternatively, because the diagnosis of MFS leads to aortic risk and the identification of a *FBNI* mutation leads to the diagnosis of MFS for an additional 29% of pediatric patients, *FBNI* screening could be offered in this population, to limit the risk of loss to follow-up monitoring. It must be emphasized strongly that negative screening results should not indicate discharge of patients from follow-up monitoring.

One limitation of the study could be related to the fact that we selected only child probands. This does not entirely match the clinical situation of caring for children of adult probands, because child probands are more likely to have severe forms of MFS. A *FBNI* mutation search as an inclusion criterion might be another bias



toward severe cases. Nevertheless, our results are intermediate between the results obtained by Lipscomb et al,<sup>22</sup> whose patients were recruited through a regional registry, and those obtained by van Karnebeek et al,<sup>23</sup> whose patients were recruited through a pediatric clinic. Also, for determination of the patients' status with respect to the international criteria, we had to consider unmentioned clinical features as absent, which might have biased our results.

In addition to the description of clinical manifestations, we took advantage of our large sample size to study the molecular characteristics of the cohort. Thirty-three percent of mutations were located in the exon 24 to 32 region. This frequency was significantly higher than that in the adult population (14%)<sup>13</sup> and was largely explained by the neonatal MFS cases (Fig 3). In addition, the proportion of mutations leading to PTC in children (25%) was significantly smaller than that in the adult cohort (36%). This finding may be partly linked to the large proportion of mutations in the exon 24 to 32 region, because we showed previously that PTC mutations were underrepresented in this region.<sup>13</sup>

## CONCLUSIONS

We present a comprehensive clinical and molecular description of a large series of pediatric cases with a *FBNI* mutation. Besides lethal neonatal MFS, which represents a genuine entity, we confirm that the majority of clinical manifestations of MFS increase with age, highlighting the limited usefulness of international criteria for diagnosis in early infancy and emphasizing the value of *FBNI* mutation screening, which not only confirms the diagnosis but also facilitates determination of prognosis and timely management.

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