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# Comparison of Clinical Presentations and Outcomes Between Patients With *TGFBR2* and *FBN1* Mutations in Marfan Syndrome and Related Disorders

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**Background**—*TGFBR2* mutations were recognized recently among patients with a Marfan-like phenotype. The associated clinical and prognostic spectra remain unclear.

**Methods and Results**—Clinical features and outcomes of 71 patients with a *TGFBR2* mutation (*TGFBR2* group) were compared with 50 age- and sex-matched unaffected family members (control subjects) and 243 patients harboring *FBN1* mutations (*FBN1* group). Aortic dilatation was present in a similar proportion of patients in both the *TGFBR2* and *FBN1* groups (78% versus 79%, respectively) but was highly variable. The incidence and average age for thoracic aortic surgery (31% versus 27% and  $35 \pm 16$  versus  $39 \pm 13$  years, respectively) and aortic dissection (14% versus 10% and  $38 \pm 12$  versus  $39 \pm 9$  years) were also similar in the 2 groups. Mitral valve involvement (myxomatous, prolapse, mitral regurgitation) was less frequent in the *TGFBR2* than in the *FBN1* group (all  $P < 0.05$ ). Aortic dilatation, dissection, or sudden death was the index event leading to genetic diagnosis in 65% of families with *TGFBR2* mutations, versus 32% with *FBN1* mutations ( $P = 0.002$ ). The rate of death was greater in *TGFBR2* families before diagnosis but similar once the disease had been recognized. Most pregnancies were uneventful (without death or aortic dissection) in both *TGFBR2* and *FBN1* families (38 of 39 versus 213 of 217;  $P = 1$ ). Seven patients (10%) with a *TGFBR2* mutation fulfilled international criteria for Marfan syndrome, 3 of whom presented with features specific for Loeys-Dietz syndrome.

**Conclusions**—Clinical outcomes appear similar between treated patients with *TGFBR2* mutations and individuals with *FBN1* mutations. Prognosis depends on clinical disease expression and treatment rather than simply the presence of a *TGFBR2* gene mutation.

**Key Words:** aorta ■ mitral valve ■ genetics ■ survival ■ sinus of Valsalva

Marfan syndrome and related diseases traditionally have been identified through combinations of clinical criteria such as the Ghent criteria.<sup>1</sup> Over time, it has become apparent that the background for Marfan syndrome and related diseases is genetic and related to mutations in genes

involved in connective tissue buildup and turnover such as, but not limited to, *FBN1*<sup>2</sup> and *TGFBR2*.<sup>3-5</sup> Although the Ghent criteria identify a patient population mostly harboring *FBN1* gene mutations,<sup>6</sup> the clinical spectrum and prognosis of patients with *TGFBR2* gene mutations are less well known.

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These mutations are found in patients with strongly overlapping connective tissue disorders, namely Marfan syndrome type 2,<sup>7</sup> the newly recognized Loey-Dietz syndrome,<sup>5</sup> and familial thoracic aneurysm and dissection.<sup>4</sup> The largest number of *TGFBR2* gene mutations has been reported in probands, mostly pediatric, displaying Loey-Dietz syndrome, characterized by arterial aneurysms, arterial tortuosity, Marfanoid habitus, and craniofacial features, and has been associated with a high rate of pregnancy-related complications.<sup>8,9</sup>

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## Clinical Perspective on p 2549

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We have assembled the largest-ever group of patients with *TGFBR2* gene mutations. Here, we describe the spectrum of clinical features and outcomes in this population, comparing this group with unaffected relatives and patients with classic Marfan syndrome related to *FBN1* gene mutations.

### Methods

The study population consisted of 3 groups: patients carrying a *TGFBR2* gene mutation identified through a Marfan clinic (*TGFBR2* group), patients carrying a *FBN1* gene mutation identified through a Marfan clinic (*FBN1* group), and a control group (first-degree relatives of patients from the *TGFBR2* group who were clinically evaluated but found not to carry the family mutation). The control group was chosen to match the *TGFBR2* group and to decrease genetic variability.

To evaluate the prognosis of the disease in the whole family (and to avoid excluding patients with fatal events), 2 additional cohorts were included, pooling all affected family members of a proband regardless of whether the diagnosis was available at the time of their first clinical event (which was often fatal). The *TGFBR2* cohort (or *FBN1* cohort) included all patients from the *TGFBR2* group (or *FBN1* group) and their affected relatives (obligate carriers, those who experienced sudden death, those who presented with vascular dissection, or those who had undergone aortic surgery).

### Clinical Screening

All patients underwent comprehensive clinical evaluation, including screening for the Ghent criteria for Marfan syndrome<sup>1</sup> and for features associated with Loey-Dietz syndrome once it was described.<sup>5</sup> All data were collected and assessed by one physician (D.A.) to ensure homogeneity across centers.

Cardiological screening included physical examination and trans-thoracic echocardiography. Aortic root dimensions were measured at the level of the aortic annulus, Valsalva sinuses, sinotubular junction, tubular ascending aorta, aortic arch, thoracic descending aorta, and abdominal aorta with the leading edge method. Aortic dilatation was considered when normalized diameters were greater than the mean plus 2 standard deviations, according to the criteria of Roman et al.<sup>10</sup> Aortic and mitral regurgitations were quantified into 4 grades.<sup>11</sup> Mitral valve was considered myxomatous when its thickness was  $\geq 4$  mm. Mitral valve prolapse was defined by a coaptation occurring 2 mm behind the mitral annulus in the parasternal long-axis view.<sup>12</sup> Associated congenital disorders (bicuspid aortic valve, atrial septal defect, patent ductus arteriosus<sup>13</sup>) were screened systematically. Additional examinations with aortic magnetic resonance imaging or an aortic computed tomography scan were performed as deemed necessary by the treating physician. Arterial tortuosity was recorded.

Skeleton, skin, integument, and lung features were screened systematically by a pediatrician, rheumatologist, or geneticist, depending on the patient and center. Ophthalmological examination (including split lamp examination) was performed in all patients. Dural ectasia was screened for diagnostic purposes.<sup>14</sup> Patients were classified according to whether they fulfilled the Ghent criteria<sup>1</sup> for Marfan syndrome or presented with a feature reported as specific for Loey-Dietz syndrome (cleft palate or bifid uvula, craniofacial abnormality, velvet skin, arterial tortuosity, congenital cardiopathy,

and skeletal features such as talipes equinovarus, camptodactyly, or cervical spine instability).<sup>8</sup>

For all patients carrying a mutation (regardless of whether *FBN1* or *TGFBR2*), the standard recommendations for lifestyle and management of Marfan syndrome were applied. Recommendations included exercise restriction, systematic  $\beta$ -blockade, yearly transthoracic echocardiography, and prophylactic aortic surgery when the aortic diameter exceeded 5.0 cm for adults or earlier in children.<sup>15,16</sup>

### Mutation Analysis

Blood samples were obtained after informed consent was provided by patients or parents, in agreement with French bioethics laws. Genomic DNA was isolated from peripheral blood leukocytes through standard procedures. All exons of the *TGFBR2* gene and large flanking intronic regions were amplified by polymerase chain reaction for direct bidirectional sequencing (Big Dye Terminators Kit, ABI 3100 Genetic Analyzer, Applied Biosystems, Warrington, Cheshire, UK), as reported previously,<sup>17</sup> and multiplex ligation-dependent probe amplification analysis (SALSA MLPA KIT P065/P066 MARFAN, MRC-Holland, Amsterdam, the Netherlands). When a mutation altered the regional restriction map, its presence was checked by polymerase chain reaction/digestion with the appropriate restriction enzyme. Mutation pathogenicity has been evaluated with UMD-Predictor and Human Splicing Finder.<sup>18,19</sup>

### Statistical Analysis

Because clinical features appear with increasing age in Marfan syndrome,<sup>16</sup> the analysis was repeated for all anthropometric parameters (height, weight, arm span) in both adults ( $\geq 18$  years of age) and children ( $< 18$  years of age). Data are presented as mean  $\pm$  standard deviation; qualitative variables are presented as frequency and percentage. Qualitative variables were compared by use of a  $\chi^2$  test or by the Fisher test when appropriate. Quantitative variables were compared by use of the Student *t* test. A mixed model for clustered data (for taking into account the correlation family relatedness) was used to compare aortic diameters in the different groups. The mixed model incorporates both random and fixed effects (age, height, weight). The model assumes that the random effects account for the correlation between measures from the same family. Pairwise comparisons were performed; values of  $P < 0.017$  were considered statistically significant (comparison of 3 groups). Survival curves were constructed through the use of Kaplan–Meier analysis and compared by use of a log-rank test, in which case values of  $P < 0.05$  were considered significant (comparison of 2 groups). Statistical analysis was performed with SAS 9.1 (SAS institute Inc, Cary, NC).

### Results

The *TGFBR2* group included 71 patients, 22 of whom were children (26 probands, 45 relatives). Twenty-four mutations were found, including 4 originally reported<sup>7</sup>: 17 missense mutations (p.T96I, p.S449F, p.R254H, p.L308P, p.H377P, p.R378G, p.C394W, p.M425V, p.A426T, p.D446N, p.D446H, p.R495Q, p.P498T, p.P525R, p.R528C, p.R528H, p.R537C [present in 3 families]), 1 in-frame deletion (p.A451\_L452del), 4 nonsense mutations (p.W521X, p.W504X, p.R497X, p.Q511X), and 2 splicing mutations (c.1525 to 1G>T [or IVS6 to 1G>T], p.Q508Q). Among these mutations, 3 (p.R528C, p.R528H, p.R537C) have also been reported in Loey-Dietz syndrome type 1 patients, and 2 (p.S449F, p.R497X) have been seen in Loey-Dietz syndrome type 2 patients.<sup>5,8,20</sup> Presumed spontaneous mutation was present in 15 of 26 probands (58%) from the *TGFBR2* group and in 45 of 122 probands (37%) from the *FBN1* group ( $P = 0.05$ ).

The *FBN1* group included 243 patients belonging to 122 families with 114 different *FBN1* gene mutations. The control group included 50 unaffected family members not carrying

**Table 1. Aortic Diameters in the 3 Groups**

|   | Diameter, mm  |            |              |            |            |            |
|---|---------------|------------|--------------|------------|------------|------------|
|   | Control Group | <i>P</i> * | TGFBR2 Group | <i>P</i> † | FBN1 Group | <i>P</i> ‡ |
| <b>Adults</b>   |               |            |              |            |            |            |
| Annulus   | 22.3±2.6      | 0.002      | 23.4±3.3     | 0.70       | 24.8±3.9   | 0.20       |
| Sinus of Valsalva   | 32.2±3.4      | <0.0001    | 44±10        | 0.0007     | 42.4±7.3   | <0.0001    |
| Standard deviation according to Roman et al <sup>10</sup> | 0.21±0.8      | <0.0001    | 5.4±4.4      | 0.0002     | 3.9±2.6    | <0.0001    |
| Sinotubular junction                                      | 26.9±3.5      | 0.0003     | 31.5±6.7     | 0.35       | 33±5.7     | <0.0001    |
| Tubular ascending aorta                                   | 28.5±3.5      | 0.02       | 30.4±6.4     | 0.71       | 31.6±5.1   | 0.0015     |
| Aortic arch   | 22.7±3.1      | 0.15       | 23.6±7.4     | 0.13       | 23.5±4.5   | 0.63       |
| Thoracic descending aorta                                 | 19.1±3.1      | 0.03       | 21.4±8.7     | 0.41       | 21.3±7.4   | 0.18       |
| Abdominal aorta   | 15.5±1.9      | 0.01       | 19.2±8.4     | 0.07       | 17.8±7.1   | 0.17       |
| <b>Children</b>   |               |            |              |            |            |            |
| Annulus   | 18.9±4.2      | 0.44       | 19.2±3.0     | 0.38       | 20.3±4.3   | 0.12       |
| Sinus of Valsalva   | 27.4±5.8      | 0.02       | 32±7.5       | 0.01       | 30.8±6.3   | 0.06       |
| Standard deviation according to Roman et al <sup>10</sup> | 1.05±1.4      | 0.002      | 6.2±3.8      | 0.005      | 4.2±2      | 0.01       |
| Sinotubular junction                                      | 21.8±3.4      | 0.31       | 22.6±2.1     | 0.65       | 23.5±4.9   | 0.24       |
| Tubular ascending aorta                                   | 22.9±8.5      | 0.6        | 21.4±3.2     | 0.44       | 22.5±4.8   | 0.45       |
| Aortic arch   | 14.4±2.4      | 0.01       | 17.1±2.9     | 0.64       | 17.2±4.2   | 0.03       |
| Thoracic descending aorta                                 | 12.3±3        | 0.51       | 13.3±2.5     | 0.93       | 13.8±2.7   | 0.05       |
| Abdominal aorta   | 10.7±3.6      | 0.40       | 11±2.6       | 0.66       | 10.7±2.4   | 0.55       |

\*Control vs TGFBR2 group.

†FBN1 vs TGFBR2 group.

‡Control vs FBN1 group.

the familial *TGFBR2* gene mutation. The TGFBR2 cohort included 22 additional relatives, ie, 93 subjects (46 men, 47 women; mean age, 33±17 years at last follow-up or age at death). The FBN1 cohort included 93 additional relatives, ie, 336 subjects (171 men, 165 women; mean age, 36.5±16.5 years at last follow-up or age at death).

### Cardiac Features

The aortic diameter was maximal at the level of the sinuses of Valsalva for all subjects and greater compared with control subjects in both the FBN1 and TGFBR2 groups (Table 1). The proportion of patients with aortic dilatation was similar in the TGFBR2 and FBN1 groups (78% [54 of 69] versus 79% [178 of 226], respectively; *P*=1) in both adults (74% [35 of 47] versus 76% [121 of 160]) and children (86% [19 of 22] versus 86% [57 of 66]). Great variability in aortic dilatation was observed in both groups (Figure 1). Aortic dilatation was more frequent in the probands for both the TGFBR2 group (probands, 22 of 22 [100%]; family members, 32 of 47 [68%]; *P*=0.003) and the FBN1 group (probands, 94 of 111 [85%]; family members, 84 of 115 [73%]; *P*=0.03).

A bicuspid aortic valve was observed in a small and similar proportion of patients in both the TGFBR2 and FBN1 groups (7% versus 4%, respectively; *P*=0.5) and was absent in the control group. In the TGFBR2 group, all patients with a bicuspid aortic valve also presented with thoracic aortic aneurysm and moderated skeletal features. A 3-year-old girl also presented with patent ductus arteriosus, atrial septal defect, and more pronounced skeletal involvement. In the FBN1 group, all pa-

tients with bicuspid aortic valve fulfilled international criteria for Marfan syndrome. Congenital cardiopathies were more frequent and mitral valve involvement was less severe in the TGFBR2 than in the FBN1 group, as reported in Table 2.

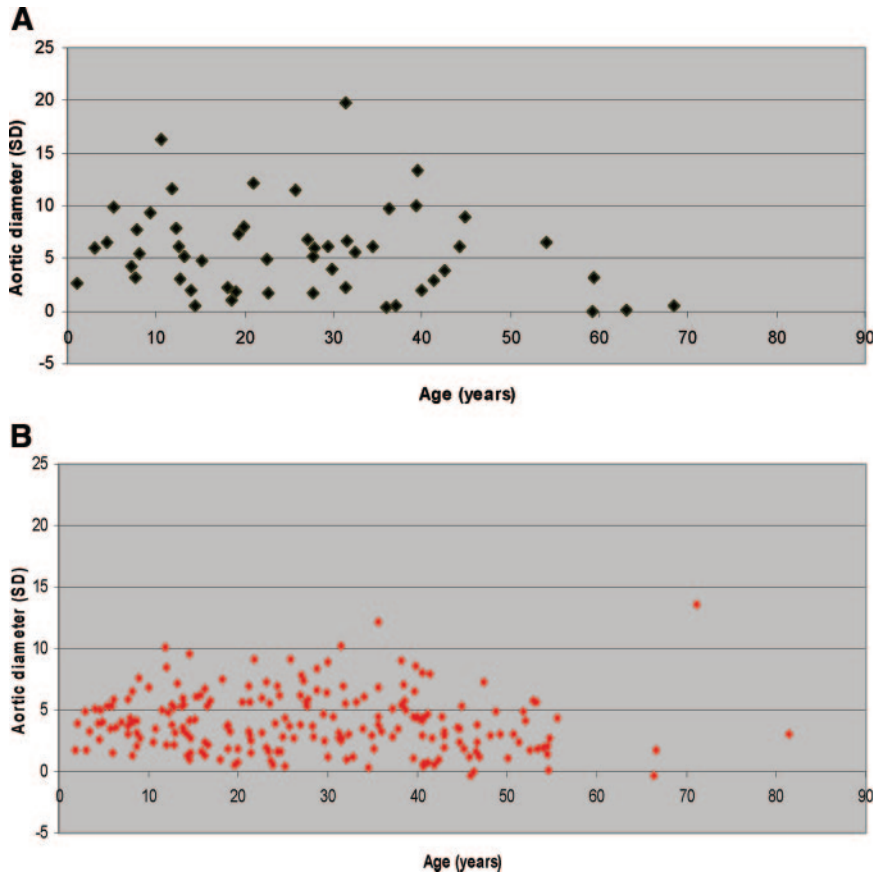
### Clinical Events

Surgery of the ascending aorta was performed at a similar frequency (31% [22 of 71] versus 27% [66 of 243]; *P*=0.53) and age (35±16 versus 39±13 years; *P*=0.23) in the TGFBR2 and FBN1 groups. Surgery was performed for aortic dilatation in 12 patients and aortic dissection in 10 patients in the TGFBR2 group (compared with 43 and 23 in the FBN1 group, respectively). Furthermore, 5 surgical procedures in 3 patients (4%) were performed on the descending aorta in the TGFBR2 group versus 5 in 5 patients (2%) in the FBN1 group.

Both the frequency and age of occurrence of aortic dissection were similar in the TGFBR2 and FBN1 groups for the ascending aorta (14% [10 of 71] versus 10% [23 of 243], *P*=0.26; 38±12 versus 39±9 years, *P*=0.82) and the descending aorta (3 of 71 versus 8 of 243, *P*=0.72; 34±6 versus 44±10 years, *P*=0.16). The average age of the first aortic dissection was also similar in the TGFBR2 and FBN1 groups (39±12 versus 41±9 years, respectively; *P*=0.56). Rates of survival appeared similar in the TGFBR2 and FBN1 groups when patients with a diagnosis made in their lifetime were considered (Figure 2B).

### Comparison Between TGFBR2 and FBN1 Cohorts

The feature revealing the presence of disease was predominantly aortic dilatation, dissection, or sudden death in the TGFBR2



**Figure 1.** Maximum aortic diameter expressed as the number of standard deviations above the mean according to Roman et al<sup>10</sup> in patients with (A) a *TGFBR2* or (B) an *FBN1* gene mutation illustrating the variability of the aortic dilatation.

families (65%) and was extra-aortic in *FBN1* families (skeletal in 34%, ophthalmological in 16%, both in 12%, pneumothorax in 2%). In the remaining *TGFBR2* families, skeletal features (35%) were the reasons for referral (Figure 3). Interestingly, in families referred for skeletal features, age at diagnosis was lower than in families referred after a cardiovascular event ( $8 \pm 5$  versus  $33 \pm 10$  years;  $P < 0.0001$ ).

The survival rate was lower in the *TGFBR2* cohort (Figure 2A). Five acute aortic events occurred before the age of 19 years: 2 aortic dissections leading to death in undiagnosed patients and 3 surgeries for dilatation of the ascending aorta. In the *FBN1* cohort, 5 acute aortic events occurred before the age of 19 years: 2 deaths in undiagnosed patients and 3 surgeries for dilatation of the ascending aorta.

**Table 2. Nonaortic Cardiac Features (Congenital Cardiopathies, Mitral Valve Disease) in the 3 Groups**

|                                  | Control Group | <i>P</i> * | <i>TGFBR2</i> Group | <i>P</i> † | <i>FBN1</i> Group | <i>P</i> ‡ |
|----------------------------------|---------------|------------|---------------------|------------|-------------------|------------|
| Mitral valve disease, % (n/N)    |               |            |                     |            |                   |            |
| Myxomatous degeneration          | 8 (2/25)      | 1          | 11 (5/44)           | 0.03       | 27 (50/183)       | 0.04       |
| Prolapse                         | 2 (1/50)      | 0.001      | 21 (15/66)          | 0.001      | 45 (105/232)      | <0.0001    |
| Mitral regurgitation             | 17 (8/50)     | 0.02       | 35 (23/66)          | 0.002      | 56 (129/230)      | <0.0001    |
| Mitral surgery                   | 0 (0/50)      | 1          | 0 (0/71)            | 0.12       | 4 (10/243)        | 0.22       |
| Congenital cardiopathy           |               |            |                     |            |                   |            |
| Existence, % (n/N)               | 0 (0/50)      | 0.04       | 8 (6/71)            | 0.002      | 1 (2/243)         | 1          |
| Isolated PDA, n                  | 0             |            | 2                   |            | 1                 |            |
| PDA+VSD, n                       | 0             |            | 1                   |            | 0                 |            |
| PDA+ASD+bicuspid aortic valve, n | 0             |            | 1                   |            | 0                 |            |
| ASD, n                           | 0             |            | 1                   |            | 1                 |            |
| Tetralogy of Fallot, n           | 0             |            | 1                   |            | 0                 |            |

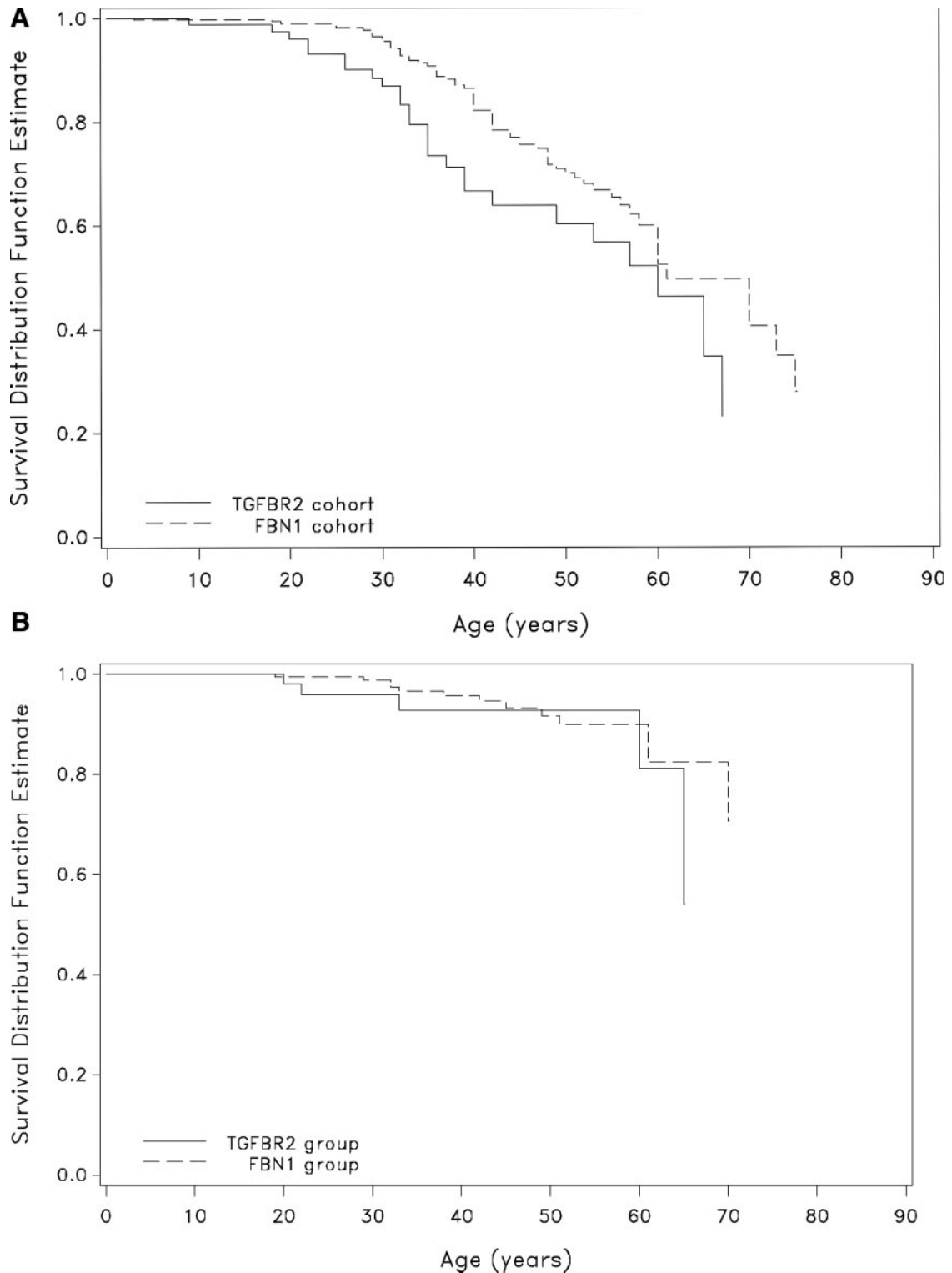
PDA indicates patent ductus arteriosus; VSD, ventricular septal defect; and ASD, atrial septal defect.

\*Control vs *TGFBR2* group.

†*FBN1* vs *TGFBR2* group.

‡Control vs *FBN1* group.



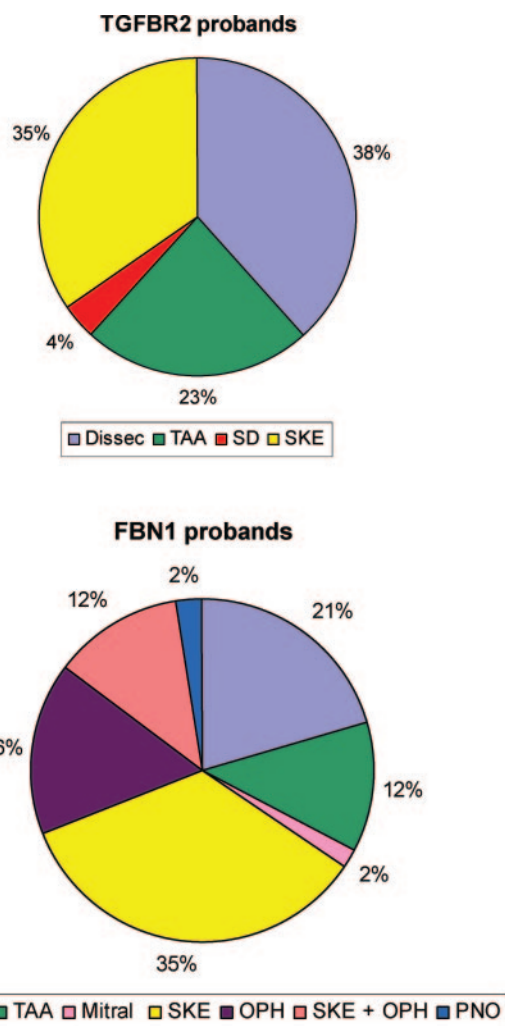


**Figure 2.** Kaplan–Meier survival curves. Survival rate of TGFBR2 and FBN1 cohorts including (A) all family members regardless of whether they were receiving medical care and (B) survival rate of TGFBR2 and FBN1 groups including only treated patients with a known *TGFBR2* or *FBN1* gene mutation. Survival rate of the TGFBR2 cohort was significantly worse than that of the FBN1 cohort ( $P=0.017$ ), whereas survival rate of the TGFBR2 group was similar to that of the FBN1 group ( $P=0.39$ ).

### Extracardiac Features

At least 1 phenotypic feature was present in all but 1 patient (nonproband) in the TGFBR2 group and in all patients in the FBN1 group. In the TGFBR2 group, 85% of patients (60 of 71) showed <3 major skeletal features, 31% (22 of 71)

showed no major skeletal features, and 9% (6 of 71) showed neither major nor minor skeletal features (Table 3). Joint hypermobility was the most frequent minor skeletal feature in patients without a major skeletal criterion (14 of 23, 61%). Overall, although 92% of the patients had some skeletal



**Figure 3.** Mode of entry into the study of probands from the TGFBR2 and FBN1 groups. Dissec indicates aortic dissection; TAA, thoracic aortic aneurysm; SD, sudden death; SKE, skeletal features; Mitral, mitral features; OPH, ophthalmologic features; SKE+OPH, both skeletal and ophthalmologic features; and PNO, pneumothorax.

involvement, it was milder than that in the FBN1 group. In the TGFBR2 group, at least 3 skeletal features or Loeys-Dietz syndrome-specific features were present in 1 member of each family except 2. These families included only the 2 probands: a 47-year-old man presenting with thoracic aortic aneurysm and 2 skeletal features and a 36-year-old woman with aortic dissection and ectopia lentis but no skeletal features.

Adults in the FBN1 group presented with greater arm span and height than adults from the control group, whereas adults from the TGFBR2 group did not. Ophthalmologic features were present in the TGFBR2 group but were less prominent than in the FBN1 group. In particular, ectopia lentis was found in 12% of patients (8 of 67) versus 65% in the FBN1 group ( $P < 0.0001$ ). It was described as mild in 5 patients, and surgery has not been required to date.

### Nosological Classification of Patients in the TGFBR2 Group

Seventeen of the 38 patients (45%) screened specifically for cleft palate or bifid uvula, hypertelorism, velvety translucent

skin, or a specific skeletal sign qualified for Loeys-Dietz syndrome (ie, they presented with at least one of these features). Arterial tortuosity was described in 5 of 25 patients; congenital cardiopathy was seen in 6 of 71. According to proposed criteria,<sup>8</sup> Loeys-Dietz syndrome was diagnosed in at least 1 member of 18 of the 26 families studied.

When each patient from the TGFBR2 group was considered independently of their family history, 10% of patients (7 of 71) fulfilled the Ghent criteria for Marfan syndrome (including 2 with ectopia lentis), compared with 58% (140 of 243) in the FBN1 group ( $P < 0.0001$ ). Three patients in the TGFBR2 group fulfilled the diagnostic criteria for both Loeys-Dietz and Marfan syndromes.

### Pregnancy

Thirty-nine pregnancies occurred among 17 women in the TGFBR2 cohort. One patient experienced sudden death in the immediate postpartum period (no diagnosis was made at that time), but no aortic complications were reported during pregnancy or postpartum in the others. Among 87 women in the FBN1 cohort, 217 pregnancies occurred. Four of these patients presented with aortic dissection or death during pregnancy ( $P = 1$ ).

### Discussion

This is the largest group ever reported of patients with a TGFBR2 gene mutation. Compared with patients with an FBN1 gene mutation, those with a TGFBR2 gene mutation showed less severe extra-aortic involvement but similar aortic dilatation, with wide interindividual variability. In contrast to initial reports that suggested dismal clinical outcomes for patients with a TGFBR2 mutation, outcomes appeared similar to those of patients with an FBN1 mutation once the diagnosis was made and medical care was given. Conversely, the spontaneous evolution of affected parents who were not medically followed up illustrates the severe prognosis in the absence of care. This finding emphasizes the importance of early identification, before the development of clinical events, by systematic screening of the family of affected members and by routine assessment of the mutation in patients with clinical features suggestive of Marfan syndrome.

### Cardiovascular Features

No specific aortic pattern could be recognized to differentiate patients with a TGFBR2 gene mutation from those with an FBN1 gene mutation. Indeed, maximal aortic diameters were found at the level of the sinuses of Valsalva in both groups, and diameters measured at the level of the annulus, at the sinotubular junction, or above were also identical. Similarly, aortic surgery of the ascending aorta was performed at a similar frequency and age in both groups.

In our population, the first aortic dissection occurred at a mean age of  $40 \pm 13$  years in the TGFBR2 cohort, including all family members, regardless of whether they were receiving medical care. This is much older than the age reported previously (cardiovascular surgery at a mean age of 19.8 years and first vascular dissection at 26.7 years).<sup>8</sup> Furthermore, in our cohort, vascular events appeared to be limited to

**Table 3. Selected Ghent Criteria in the 3 Groups**

|   | Control Group | <i>P</i> * | TGFBR2 Group | <i>P</i> † | FBN1 Group   | <i>P</i> ‡ |
|---|---------------|------------|--------------|------------|--------------|------------|
| n   | 50            |            | 71           |            | 243          |            |
| Age, y  | 27.9±16.5     | 0.79       | 28.8±17      | 0.5        | 30.2±16.2    | 0.37       |
| Men/women   | 29/21         | 0.12       | 31/40        | 0.43       | 119/124      | 0.24       |
| Skeletal features, % (n/N)                          |               |            |              |            |              |            |
| Pectus deformity                                    | 6 (3/50)      | <0.0001    | 45 (31/69)   | 0.03       | 59 (144/243) | <0.0001    |
| Carinatum   | 6 (3/50)      | 0.24       | 13 (9/69)    | 0.004      | 30 (74/243)  | 0.0002     |
| Excavatum requiring surgery                         | 0 (0/50)      | 1          | 0 (0/69)     | 0.59       | 2 (5/243)    | 0.59       |
| Excavatum of moderate severity                      | 0 (0/50)      | <0.0001    | 32 (22/69)   | 0.4        | 27 (65/243)  | <0.0001    |
| Arachnodactyly                                      | 10 (5/50)     | 0.0003     | 41 (28/70)   | 0.01       | 57 (137/240) | <0.0001    |
| Facial appearance                                   | 6 (2/32)      | 0.004      | 33 (20/60)   | 0.16       | 43 (102/236) | <0.0001    |
| Arched palate                                       | 12 (6/50)     | <0.0001    | 48 (32/67)   | 0.03       | 62 (151/243) | <0.0001    |
| Scoliosis   | 10 (5/50)     | 0.007      | 31 (21/68)   | 0.004      | 51 (122/240) | <0.0001    |
| Anthropometric data in adults                       |               |            |              |            |              |            |
| Men/women, n/N                                      | 15/15         | 0.54       | 21/28        | 0.43       | 87/90        | 0.93       |
| Height, cm  |               |            |              |            |              |            |
| Men   | 180.5±4.6     | 0.24       | 182.7±5.7    | 0.025      | 187.2±8.3    | 0.0001     |
| Women   | 167.9±5.4     | 0.49       | 169.2±6.3    | 0.001      | 174.1±6.7    | 0.0009     |
| Weight, kg  |               |            |              |            |              |            |
| Men   | 78.4±10       | 0.68       | 76.7±12.9    | 0.82       | 77.5±14      | 0.81       |
| Women   | 66.3±9.4      | 0.06       | 59.8±10.7    | 0.03       | 65.9±13      | 0.91       |
| Arm span, cm  |               |            |              |            |              |            |
| Men   | 184.3±5.3     | 0.16       | 187.8±8.3    | 0.02       | 194.2±11.4   | <0.0001    |
| Women   | 168±7.3       | 0.12       | 173.2±11.3   | 0.02       | 178.3±9      | <0.0001    |
| Arm span/height ratio                               |               |            |              |            |              |            |
| Men   | 1.03±0.02     | 0.42       | 1.03±0.03    | 0.3        | 1.04±0.04    | 0.10       |
| Women   | 1±0.03        | 0.13       | 1.02±0.04    | 0.54       | 1.02±0.03    | 0.01       |
| Ophthalmologic features, % (n/N)                    |               |            |              |            |              |            |
| Severe myopia                                       | 6 (3/50)      | 0.51       | 10 (7/67)    | <0.0001    | 32 (74/234)  | 0.0002     |
| Flat cornea   | 3 (1/32)      | 1          | 5 (3/58)     | <0.0001    | 43 (100/233) | <0.0001    |
| Ectopia lentis                                      | 2 (1/50)      | 0.08       | 12 (8/67)    | <0.0001    | 65 (149/229) | <0.0001    |
| Skin, pulmonary, and neurological features, % (n/N) |               |            |              |            |              |            |
| Striae atrophicae                                   | 16 (8/49)     | 0.01       | 36 (24/66)   | 0.0001     | 58 (139/241) | <0.0001    |
| Recurrent herniae                                   | 6 (3/49)      | 0.04       | 19 (13/67)   | 0.61       | 17 (40/239)  | 0.06       |
| Pneumothorax  | 0 (0/50)      | 0.26       | 4 (3/69)     | 1          | 4 (10/240)   | 0.22       |
| Lumbosacral dural ectasia                           | 0 (0/30)      | 0.13       | 10 (4/40)    | 0.01       | 29 (64/220)  | 0.0006     |

\*Control vs TGFBR2 group.

†FBN1 vs TGFBR2 group.

‡Control vs FBN1 group.

the aorta (both ascending and descending), in contrast to previous reports describing more extensive symptomatic peripheral vascular disease.<sup>8,21</sup> An older average age at the time of diagnosis may explain the apparent better survival rate and less aggressive aortic disease reported in our cohort compared with the largely pediatric cohorts of Loeys et al<sup>8</sup> and Williams et al,<sup>22</sup> who also pooled both *TGFBR1* and *TGFBR2* gene mutation carriers. Developmental defects for Loeys-Dietz syndrome are detected primarily by pediatricians, as opposed to the disease being revealed by cardiovascular complications in the adult population. In fact, 65% of

our families were recognized after a cardiovascular event or discovery of aortic dilatation.

Aortic dissection occurring later in life has been reported previously by Pannu et al<sup>4</sup> and Hasham et al,<sup>23</sup> who studied 4 families with isolated thoracic aneurysm and dissection, all of whom were carrying mutations affecting arginine 460 in *TGFBR2* (p.R460H and p.R460C). In these families, dissections occurred at a mean age of 46±16 years. Thus, our findings fill the gap that exists in the literature for clinical features and complications reported between syndromic populations and pure aortic aneurysm.<sup>4,8</sup> Therefore, as is now



well known in diseases associated with mutations in the *FBNI* gene,<sup>14</sup> the clinical spectrum associated with *TGFBR2* gene mutations ranges from severe neonatal forms to isolated and moderate aortic dilatation in late adulthood. Thus, our key finding is that the prognosis of a patient depends on the clinical expression of the disease and not solely on the presence of a mutation in the *TGFBR2* gene. Further genotype/phenotype correlations obtained in larger populations may also help to refine this prognosis, like mutations of exon 24–32 in the *FBNI* gene associated with neonatal forms of Marfan syndrome.<sup>24</sup>

In our centers, patients with a *TGFBR2* gene mutation were managed according to the rules developed for Marfan syndrome.<sup>15,16</sup> Our results show that adhering to these rules did not cause excess deaths (Figure 2). Interestingly, no ascending aortic dissection occurred in our patients with normal aortic diameters, in contrast to previous reports.<sup>8,25</sup> Finally, no aortic dissection occurred in women during pregnancy or postpartum when the diagnosis was documented and prevention rules recommended in Marfan syndrome applied.<sup>15</sup>

The importance of molecular biological data for determining the best care for a patient is debated. This report supports previous data that suggested that aortic fragility is the main and more consistent feature associated with the presence of a mutation in the *TGFBR2* gene. Nevertheless, it is apparent from Figure 1 that great variability exists in this feature, as in others, between members of different families (and therefore carrying generally different mutations) and in patients in the same family (ie, carrying the same mutation), so strict management rules appear difficult to determine. Only 78% of patients with *TGFBR2* gene mutations presented with aortic dilatation. The incidence of aortic dilatation has been reported to be 98% (patients with Loeys-Dietz syndrome)<sup>8</sup> or even 100%.<sup>20</sup> In some studies, dilatation of the aorta was a selection criterion.<sup>4,26</sup> However, in another group of patients,<sup>25</sup> 6 of 14 patients (43%) with a *TGFBR2* gene mutation who were not selected according to these criteria did not present with an aortic aneurysm.

It therefore appears sensible to propose surgery on an individual basis, being more interventional in patients with aortic dilatation occurring at a young age with developmental defects, whereas rules developed for Marfan syndrome should be used in patients diagnosed during adulthood without specific Loeys-Dietz syndrome features. Although complete vascular screening should be mandatory today on the basis of previous reports, it remains to be established in which subgroup this will be useful because no widespread or aggressive vascular disease was observed in our population of patients 1 to 68 years of age with a mean follow-up period of 7 years.

### Extra-Aortic Features

Patients carrying a *TGFBR2* gene mutation also presented with extra-aortic features. As described by Loeys et al,<sup>8</sup> congenital heart disease is far more frequent in patients carrying a *TGFBR2* gene mutation than in the general population and in patients with *FBNI* gene mutations. Mitral valve disease may be present, at most mild mitral regurgitation, never requiring surgery. Of the noncardiovascular fea-

tures, the most significant were found in the skeleton, notably pectus deformities, arachnodactyly, joint hypermobility, and scoliosis, among others. These features clearly define a disease that is different from isolated thoracic aneurysm and dissection<sup>4</sup>; one third of our families were discovered because of skeletal features. Compared with *FBNI* gene mutations, however, skeletal involvement associated with *TGFBR2* mutations is usually less severe. Finally, occasional co-occurrence of ocular, skin, integument, and central nervous system features reveals the existence of a true clinical overlap for diseases associated with *FBNI* and *TGFBR2* gene mutations.

### Conclusions

Great clinical heterogeneity exists in patients with *TGFBR2* gene mutations, which underscores the importance of molecular biology for early diagnosis. A patient's prognosis depends on the clinical expression of the disease and not solely on the presence of a mutation in the *TGFBR2* gene. Indeed, regular follow-up and individualized care improve the prognosis for patients with a *TGFBR2* gene mutation compared to the prognosis of patients with an *FBNI* gene mutation. Finally, pregnancy is not necessarily associated with an ominous prognosis but warrants specific care as recommended for Marfan syndrome.

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### Disclosures

None.

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## CLINICAL PERSPECTIVE

Marfan syndrome has been related to mutations in the *FBNI* gene coding for fibrillin. More recently, mutations in the *TGFBR2* gene coding for transforming growth factor- $\beta$  receptors have been associated with overlapping phenotypes, familial thoracic aortic aneurysms, and the newly described Loeys-Dietz syndrome characterized by arterial aneurysms, arterial tortuosity, Marfanoid habitus, and craniofacial features. We report here the findings of a study of a large group of patients with *TGFBR2* mutations, including probands and affected relatives, and compare them with nonaffected relatives and patients with classic Marfan syndrome related to *FBNI* mutation. We show the following: Aortic dilatation is variable among patients even within the same family; skeletal features are also variable, usually that of a mild Marfan phenotype without excessive height; ophthalmological features are mild if present; and early diagnosis is crucial because medical care (regular follow-up and individualized care) is associated with an improved survival rate, similar to that of patients with classic Marfan syndrome related to a mutation in the *FBNI* gene. In contrast, in the absence of diagnosis, the spontaneous prognosis is poor. Systematic screening of the family and routine assessment of the mutation in patients with clinical features suggestive of Marfan syndrome are therefore mandatory.