**Value of Molecular Diagnosis in a Family With Marfan Syndrome and an Atypical Vascular Phenotype**

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Aortic dissection or rupture is the cause of death in over 90% of untreated patients with Marfan syndrome (MFS). Diagnosis is usually based on clinical criteria, but the phenotypic presentation varies widely among affected individuals. Early recognition of at-risk MFS patients is important in view of available medical and surgical treatments that can significantly improve life-expectancy. Molecular testing could provide an etiologic diagnosis in patients who present with milder or atypical clinical forms of the disease. Moreover, it could contribute to preventive treatment in carriers, inform genetic counseling, and offer reassurance to unaffected individuals. By describing a family with Marfan syndrome in whom the disease presented in an atypical aggressive form, this article highlights the value of testing for FBN1 mutations in selected cases.

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**INTRODUCTION**

Aortic dissection or rupture is the main cause of death in over 90% of untreated patients with Marfan syndrome (MFS), but in about 18% the first aortic event (i.e. dilatation or dissection) occurs in the distal aorta.

In general, MFS is caused by mutations in the fibrillin-1 (FBN1) gene, a large gene located on chromosome 15. More than 600 pathogenic mutations were reported in the last update of the Universal Marfan Database, and most of these are unique to individual families.

To date, there is no established genotype–phenotype correlation. Nevertheless, the relative risk of specific organ involvement differs significantly between different types of mutations.

Early recognition of at-risk MFS patients is important in view of available medical and surgical treatments that can significantly improve life-expectancy.

In this paper, we describe a family that includes several members with clinical features compatible with MFS but who have peculiar phenotypic characteristics. In this family, molecular diagnosis provided a definitive diagnosis and could be used for family screening.
The aortic root was considered dilated when Fig. 1, II:19), had a Bentall composite graft, III:6) had mild aortic root dilatation (40 mm), a normal-sized descending aorta had a diameter of 42 mm. The aortic root was considered dilated when the maximum diameter at the sinuses of Valsalva exceeded the upper normal limit for the patient’s age and body surface area.7 Magnetic resonance angiography (MRA) using a 3-T whole-body magnet (Siemens Magnetom Trio) was performed in some patients. Transverse, longitudinal, coronal and oblique sagittal scans encompassing the ascending aorta, aortic arch, and descending aorta were acquired. Multiplanar reconstructions were also analyzed. The only ocular criterion considered was ectopia lentis. Magnetic resonance was not used to look for dural ectasia.

Molecular Data

After appropriate written informed consent was obtained, DNA was extracted from peripheral blood samples and all 65 exons of FBN1 were amplified. Mutation screening of the entire coding sequence of the FBN1 gene was then performed using the polymerase chain reaction. All positive results were confirmed by repeated analysis.

RESULTS

Family Description

Our proband (Fig. 1, III:7, arrowed), a 37-year-old female, was referred to our center after experiencing a type-B aortic dissection that started 60 mm after the origin of left subclavian artery and extended distally to the iliac arteries. The dimensions of the ascending aorta and aortic arch were within normal limits, while the descending thoracic aorta had a diameter of 42 mm.

Family history at that time revealed that the patient’s father (Fig. 1, II:3) had died suddenly at the age of 48 years (after a type-B aortic dissection) and two uncles (Fig. 1, II:19 and II:21) were already being monitored for aortic disease. The older of these, a 53-year-old male (Fig. 1, II:19), had a Bentall composite graft implanted at the age of 50 years because of progressive aortic root dilatation (60 mm). The second uncle, who was 48 years old (Fig. 1, II:21), presented with generalized arterial disease. His left leg had been amputated because of occlusive arterial disease at the age of 45 years, and a popliteal aneurysm on the right leg had been excluded when he was aged 46 years. He also had mild dilatation of the abdominal aorta and an aortic root aneurysm, of diameters 34 mm and 46 mm, respectively.

By that time, family screening had been started and our patient’s brothers were called in for clinical evaluation. Three of them (two females and one male) were evaluated: a 43-year-old sister (Fig. 1, III:4) had a normal-sized aorta but peculiar post-isthmic ectasia was found on MRA (Fig. 2A); a 39-year-old sister (Fig. 1, III:6) had mild aortic root dilatation (40 mm), a normal-sized descending aorta and the same peculiar post-isthmic ectasia (Fig. 2B); and the youngest brother, a 36-year-old patient (Fig. 1, III:8), presented with aortic root dilatation (47 mm) and discrete aortic ectasia (31 mm) of the descending aorta just after the isthmus (Fig. 2C). Four days after clinical and imaging evaluations, this patient was admitted for acute type-B aortic dissection, which started immediately after the origin of the subclavian artery. A CT scan revealed aortic dilatation (44 mm) at the level of the aortic dissection.

A first-degree cousin of the patient, a 19-year-old (Fig. 1, III:33), had acute type-A dissection at the age of 19 years, which extended throughout the entire aorta. The ascending aorta was markedly dilated (82 mm) and he underwent emergent surgical aortic root and valve replacement.

Another of the proband’s aunts, a 61-year-old (Fig. 1, II:14), was found to have aortic root dilatation (43 mm).

The clinical features of affected family members are depicted in Table 1. The other family members evaluated (i.e. 12 subjects) showed no clinical or molecular evidence of MFS.

Molecular Study

A new pathogenic FBN1 mutation was identified in all affected members of this family. The mutation was a nonsense mutation, with a C1995G substitution in exon 16 of FBN1, which led to the formation of a stop codon in position 665 of tyrosine (i.e. Tyr665X).
Table 1
Clinical Features of Affected Family Members

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Cardiovascular system</th>
<th>Skeletal system</th>
<th>Ocular system (ectopia lentis)</th>
<th>Lung (spontaneous pneumothorax)</th>
<th>Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>ADil</td>
<td>ADis</td>
<td>MVP</td>
<td>PCar</td>
<td>PEcT</td>
</tr>
<tr>
<td>II:14</td>
<td>F</td>
<td>61</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>II:19</td>
<td>M</td>
<td>53</td>
<td>+</td>
<td>/Surg</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>II:21</td>
<td>M</td>
<td>48</td>
<td>+</td>
<td>–</td>
<td>na</td>
<td>na</td>
<td>1.03</td>
</tr>
<tr>
<td>III:4</td>
<td>F</td>
<td>43</td>
<td>–</td>
<td>–</td>
<td>+</td>
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<td>+</td>
</tr>
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<td>III:6</td>
<td>F</td>
<td>39</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>III:7</td>
<td>F</td>
<td>37</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>1.04</td>
</tr>
<tr>
<td>III:8</td>
<td>M</td>
<td>36</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>1.06</td>
<td>+</td>
</tr>
<tr>
<td>III:33</td>
<td>M</td>
<td>19</td>
<td>+</td>
<td>/Surg</td>
<td>–</td>
<td>–</td>
<td>1.08</td>
</tr>
</tbody>
</table>

Abbreviations: ADil, aortic dilatation; ADis, aortic dissection; Asp/H, arm-span-to-height ratio; F, female; FacF, facial features; JointH, joint hypermobility; M, male; MVP, mitral valve prolapse; na, not available; PAcet, protusio acetabulae; PCar, pectus carinatum; PEcT, pectoral excavatum; PPlan, pes planus; Scol, scoliosis; Surg, surgery; W&T, wrist and thumb signs; –, not present; +, present.

Figure 2. Three-dimensional reconstruction of magnetic resonance angiography images of patients III:4 (A), III:6 (B) and III:8 (C) in Figure 1, showing peculiar mild narrowing at the level of the isthmus and post-isthmic aortic ectasia (arrows).

In conclusion, in this family, detection of a FBN1 mutation was a determinant of a definitive diagnosis of MFS in this family. In general, FBN1 gene mutations are found in about 90% of MFS patients who fulfill Ghent’s criteria, but patients with classic MFS phenotypes have also been found to be carriers of TGFβ1 and TGFβ2 mutations (MFS type 2), the same mutations that cause Loeys–Dietz syndrome (LDS). These patients typically present at an early age with generalized arterial tortuosity and aneurysms and aortic dissection and have smaller aortic diameters. A broad clinical overlap has been found among MFS, MFS type 2 and LDS.

In this family, we found a new FBN1 mutation that leads to an early protein sequence truncation and which is associated with a particularly aggressive cardiovascular phenotype in most affected individuals. The nonsense mutation found was located in the exon encoding the second of seven TGFβ1-binding protein-like modules of fibrillin-1, a domain present only in FBN1 and latent TGF-beta binding proteins (LTBPs). These globular domains have no known specific function, although they may mediate specific protein–protein interactions.

Currently, increased TGFβ activity is thought to be a major contributor to the pathogenesis of both MFS and LDS.

In the future, better understanding of the genetic background and molecular pathways involved may change our approach to aortic disease in MFS. Meanwhile, currently accepted criteria for surgical aortic intervention in MFS patients are an ascending aorta diameter of 5.0 cm or more and a descending aorta diameter of at least 6.0 cm. These values are far from the aortic dimensions presented by our proband and her brother, yet this did not prevent them developing type-B aortic dissection. The questions of whether and when to intervene in the other two sisters who have similar aortic morphologies are difficult, and these individuals are now under close clinical and imaging surveillance to detect any increase in aortic dimensions.

Funding

This study was supported by a grant from the Research Department of Hospital S. João, Porto, Portugal.

Conflicts of Interest

None declared.

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