The c.7409G>A (p.Cys2470Tyr) Variant of FBN1: Phenotypic Variability across Three Generations

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Abstract

Marfan syndrome is an autosomal dominant connective tissue disorder caused by mutations in the fibrillin gene FBN1, which encodes an extracellular matrix glycoprotein. Major features of Marfan syndrome occur in the ocular, cardiovascular, and skeletal systems as well as in the dura mater. Approximately 60% of known disease-causing mutations are missense mutations of single amino acid residues. Effects on the cardiovascular system are classically associated with mutations in exons 24–32 of the 65 FBN1 exons and many, though not all, reports associate missense mutations in exons 59–65 with a mild cardiovascular phenotype. Here we present 5 related individuals among whom a c.7409G>A (p.Cys2470Tyr) missense variant in exon 59 of FBN1 is associated with significant cardiovascular features. The index case also had an apparently de novo 46,XX,del(5)(q33.1q33.3) deletion on chromosome 5. This family demonstrates skeletal, dermatological and neurological features consistent with Marfan syndrome but lacks significant ophthalmological findings to date. These findings suggest that FBN1 C-terminal missense mutations may not confer the ophthalmological features of Marfan syndrome, but they also confer a more significant risk for cardiovascular pathology than that suggested by previous studies. Furthermore, clinical data from this family supports the previously reported association of dural ectasia with C-terminal mutations.

Key Words
Cardiovascular phenotype · Diagnostic criteria · FBN1 · Marfan syndrome · Novel mutation

Marfan syndrome is an autosomal dominant connective tissue disorder with an incidence of between 1 and 3 per 10,000 individuals [Gray et al., 1994; Ramirez et al., 2007]. The disease predominantly manifests in the cardiovascular, skeletal and ocular systems as well as in the dura mater. Prominent cardiovascular features include dilatation of the aorta and proximal pulmonary artery as well as prolapse of the mitral and tricuspid valves. Musculoskeletal manifestations include joint laxity, chest deformities and overgrowth of tubular bones. Myopia is common and lens displacement is thought to occur in over 60% of affected individuals throughout their lifetime [Maumenee, 1981; Dietz, 1993; Ammash et al., 2008; Datta Kanjilal and Datta, 2009]. The recently revised Ghent
criteria establish the clinical diagnosis of Marfan syndrome [Loeys et al., 2010]. The revised criteria place a stronger emphasis on the cardiovascular manifestations of the disease. Briefly, individuals with aortic root dilatation/dissection and any one of (a) ectopia lentis, (b) a pathogenic FBN1 mutation or (c) a systemic score ≥7 points are considered to have Marfan syndrome, as are patients with ectopia lentis and an FBN1 mutation that is known from other evidence to be associated with aortic root dilatation or dissection. Some individuals who meet the previous criteria will no longer meet the current criteria. For example, the dura mater was formerly considered on an equal footing with aortic root dilatation for diagnostic purposes; each was a separate organ system for which ‘major involvement’ contributed equally. Currently, dural ectasia contributes a maximum of 2 out of 7 or more points in the ‘systemic score,’ which now encompasses skeletal, pulmonary and skin manifestations that were previously considered separately.

The phenotypic presentation and severity of Marfan syndrome varies broadly, both between and within families. Not all ‘classical’ features appear in every affected individual, and not all individuals who inherit the same pathogenic variant will manifest the same features. Phenotypic effects are known to vary within the same family, a phenomenon referred to as ‘variable expressivity’. Over 80% of cases of Marfan syndrome have been associated with rare variants affecting Fibrillin-1 (FBN1) [Pepe et al., 2011], which encodes for a large glycoprotein that assembles into extracellular matrix microfibrils. FBN1 is located on chromosome 15q21.1 and has 65 exons that encode a protein of 2,871 amino acids [Maslen et al., 1991; Corson et al., 1993; Pereira et al., 1993]. Rare DNA variants that alter single amino acid residues within the coding sequence of the protein (missense mutations) are the cause of 50–66% of cases of Marfan syndrome [Attanasio et al., 2008; Turner et al., 2009]. Though fewer than 15% of documented cases are the result of deletion/insertion mutations [Pepe et al., 2001; Turner et al., 2009], this proportion is expected to increase as high-throughput methodologies that detect these variants become more widespread.

The region of the fibrillin protein that is affected by a coding variant correlates with overall disease severity and, in certain cases, with specific effects in individual organ systems. Clear genotype-phenotype correlations have been made between mutations in exons 24–32 and severe neonatal Marfan syndrome [Palz et al., 2000; Attanasio et al., 2008; Turner et al., 2009], and with increased risk for cardiovascular manifestations at a later age [Faivre et al., 2007]. Genotype-phenotype correlations are less strong for rare variants found in the C-terminal region of fibrillin, perhaps indicating the involvement of interacting proteins in disease pathogenesis. According to several reports [Palz et al., 2000; Comeglio et al., 2007], missense mutations within exons 59–65 present with a relatively mild Marfan phenotype, with a lower risk of aortic involvement. Turner et al. [2009] reported a trend toward a lack of ectopia lentis. In contrast, other studies [Arbustini et al., 2005; Rand-Hendriksen et al., 2007] failed to associate missense mutations within this region with a milder cardiovascular phenotype. We present 4 generations of a family in which a C-terminal p.Cys2470Tyr mutation is associated with significant cardiovascular risk.

Material and Methods

The index case was patient IV-5 (fig. 1), who presented at age 6 months with hypotonia and poor head control. She was noted to have unusually long fingers by a clinical geneticist at 12 months of age. This finding triggered an echocardiogram assessment, which found aortic ectasia and mild mitral valve prolapse. The family history was then re-evaluated with a view toward complications of connective tissue disorders, and several at-risk individuals were identified and offered clinical assessment and Sanger sequencing of FBN1. Familial testing identified several people with clinical features of Marfan syndrome. All evaluations and procedures were undertaken with individual informed consent, consistent with Helsinki principles.

Genome and Candidate Gene Analysis of the Family

All tests were performed according to accepted clinical standards. Standard karyotyping and fluorescence in situ hybridization (FISH) was performed at British Columbia Children’s Hospital. Sequencing of the FBN1 gene was performed at the John Welsh Cardiovascular Diagnostic Laboratory, Baylor College of Medicine, Houston, Tex., USA.

Results

Clinical Evaluation of the Family

The pedigree for the family is shown in figure 1. In the index case IV-5, a standard karyotype revealed a deletion approximately 10 Mb in size on chromosome 5, (46,XX,del(5)(q33.1q33.3)) subsequently shown by FISH in her parents III-3 and III-4 to be apparently de novo. Neither parent was found to carry the deletion; independent molecular confirmation of stated relationships was not sought. She was also found to have a c.7409G>A transition in FBN1, which would be predicted to be a missense mutation encoding p.Cys2470Tyr. Sanger sequencing
chromatographs that show the presence or absence of the variant are shown next to the family members tested.

**Physical Features among c.7409G>A Heterozygotes**

The index case, patient IV-5, is now 9 years old. Birth weight at term was 4,310 g (98th centile). Her first recorded length was 68 cm at 4.5 months of age (98th centile). Craniofacial examination revealed right-sided plagiocephaly and a flattened occiput. She had mild ptosis with short, downslanting palpebral fissures (fig. 2a). She also had a wide forehead, long nose and overfolded superior helices of the ears (fig. 2b, c). At age 4 years, malar hypoplasia had become apparent (fig. 2d, e), as had scoliosis and thoracolumbar lordosis (fig. 2f) and a milder pectus deformity (fig. 2g). These features remained apparent at 6 years, 11 months (fig. 2h–l). She had a high arched palate (fig. 2m) with a normal uvula and malar hypoplasia with crowding of the lower teeth. She had long fingers (fig. 2n–q), pes planus and long toes with contractures (fig. 2r, s). She demonstrated joint hypermobility with a Beighton score of 6/9, with elbows hyperextending to 190°, positive thumb-to-arm and little finger signs. Wrist signs were positive bilaterally and thumb signs negative bilaterally. Subcutaneous veins were prominent on her thorax and upper back. She did not have any striae or scarring. Her blood pressure was 85/90 in the left arm and she had a regular heart rate of 90/min with normal heart sounds. She takes atenolol for cardioprotection. Ophthalmological examination was normal. Her measurements are summarized in table 1.

Patient III-4 (mother of the index case) was 181 cm tall as an adult and had mild ptosis and downslanting palpebral fissures (fig. 3a). She also had dolichocephaly, malar hypoplasia (fig. 3a, b), a narrow nasal bridge and a deep oropharynx with a high arched, narrow palate (fig. 3c). However, she had no dental crowding or retrognathia.

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**Fig. 1.** Pedigree. Successive generations are indicated by Roman numerals (I–IV) and individuals by Arabic numerals (1–6). Members with clinical features of Marfan syndrome are indicated by half-filled symbols, and those who have tested positive for the familial c.7409G>A (p.C2470Y) variant are starred (*); those who have tested negative are indicated by open circles (○).
Fig. 2. Clinical photos of IV-5, affected with an apparently de novo chromosome 5 microdeletion and an inherited p.C2470Y variant in FBN1. Face (a, b) and profile (c) at 12 months of age. Face (d), profile (e), back (f), and pectus excavatum (g) at 4 years of age. Face (h), profiles (i, j), chest (k), back (l) and palate (m) at ~7 years (6 years and 11 months) of age. Hands are shown at 4 (n, o, p) and ~7 years of age (q). Pes planus (r) and long feet with contractures of toes 2–5 (s) are shown at ages 4 years and ~7 years, respectively.
Table 1. Clinical manifestations of Marfan syndrome associated with the c.7409G>A (p.C2470Y) missense variant

| System and feature | Patient of Attanasio et al. [2008] | Patient III-1 | Patient III-4 | Patient IV-2 | Patient IV-5 | Patient IV-6 |
|--------------------|------------------------------------|--------------|--------------|--------------|--------------|--------------|
| **Skeletal**       |                                    |              |              |              |              |              |
| Height (centile)   | >97th                             | 97th         | >97th        | >97th        | 80th         | 97th         |
| Weight (centile)   | >97th                             | 91st         | >97th        | >97th        | 20th         | 97th         |
| Pectus carinatum   | –                                 | –            | +            | –            | –            | –            |
| Pectus excavatum (not requiring surgery) | – | – | + | – | + | – |
| Pectus excavatum (requiring surgery) | + | + | – | – | – | – |
| US:LS ratio <0.86  | *+                               | –            | +            | +            | –            | –            |
| AX:height ratio >1.05 | +* | – | + | + | – | + |
| Wrist sign         | –                                 | +            | –            | +            | +            | –            |
| Thumb sign (Steinberg sign) | – | – | – | – | – | – |
| Elbow extension <170° | – | – | – | – | – | – |
| Joint hypermobility | –                                 | upper normal | –            | +            | –            | +            |
| Pes planus         | +                                 | +            | partial      | –            | +            | +            |
| Hindfoot valgus    | –                                 | –            | –            | –            | –            | –            |
| Forefoot abduction and lowering of the midfoot | – | – | – | – | – | – |
| Protrusio acetabulae | +                               | –            | +            | –            | –            | –            |
| Scoliosis >20°     | +                                 | –            | –            | +            | –            | –            |
| Spondylolisthesis  | –                                 | –            | –            | +            | –            | +            |
| **Ocular**         |                                    |              |              |              |              |              |
| Ectopia lenti      | –                                 | –            | –            | –            | –            | –            |
| Flat cornea        | –                                 | –            | –            | –            | –            | –            |
| Increased axial globe length | – | – | – | – | – | – |
| Hypoplastic iris   | –                                 | –            | –            | –            | –            | –            |
| Myopia             | –                                 | –            | –            | –            | –            | –            |
| Hypertelorism       | –                                 | –            | –            | –            | –            | –            |
| **Cardiovascular** |                                    |              |              |              |              |              |
| Aortic root dilatation above indicated Z-score | + | + | – | + | + | + |
| Aortic dissection  | –                                 | –            | –            | –            | –            | –            |
| Mitral valve prolapse | –                              | leaflets mildly calcified but not prolapsed | slight but not meeting criteria for diagnosis | – | mild | – |
| Mitral valve calcification | +                              | –            | –            | –            | –            | –            |
| **Facial features**|                                    |              |              |              |              |              |
| Facial dysmorphism  | +                                 | +            | –            | +            | +            | +            |
| Dolichocephaly     | –                                 | +            | –            | –            | +            | –            |
| Enophthalmos       | –                                 | –            | +            | –            | +            | +            |
| Downsloping PFs    | +                                 | +            | –            | +            | –            | +            |
| Malar hypoplasia   | +                                 | +            | –            | +            | –            | –            |
| Retroglossa         | +                                 | –            | –            | –            | –            | –            |
| High arched palate | +                                 | +            | +            | –            | +            | +            |
| Crowded teeth      | +                                 | –            | –            | –            | +            | –            |
| **Dermatological** |                                    |              |              |              |              |              |
| Striae atrophicae  | +                                 | +            | +            | –            | –            | –            |
| **Respiratory**    |                                    |              |              |              |              |              |
| Spontaneous pneumothorax | –                              | –            | –            | –            | –            | –            |
| **Neurological**   |                                    |              |              |              |              |              |
| Dural ectasia      | +                                 | +            | –            | –            | –            | –            |
| **Family history** |                                    |              |              |              |              |              |

* US:LS ratio = Upper segment/lower segment; AR:height ratio = arm span/height; PFs = palpebral fissures.
Fig. 3. Clinical photos of affected family members. a–d Patient III-4 at 35 years of age. Shown are face (a), profile (b), palate (c). Distal limbs are shown at 36 years (d). Patient III-1 is also shown at 38 years of age. His face (e), profile (f), palate (g), widening of scars of the chest (h) and anterior abdomen (i) and flexion contractures of toes 2–5 (j) are shown. Photos k–q depict IV-6, the son of III-4, at 3 months of age (k, l) and at 3 years and 3 months of age (m–q). Photos r–v depict IV-2, the son of III-1 at 8 years of age: face (r), profile (s), palate (t), body (u) and hands (v).
Eye exam was normal. Anthropometric measurements are shown in table 1. She had pectus carinatum but no excessive spinal curvature. She did not have arachnodactyly, but her thumb joints were hyperextensible and swan-necking occurred at the base of the thumbs (fig. 3d). Her feet had partially collapsed arches and her great toes deviated in a valgus direction bilaterally (fig. 3d). Her Beighton score was 1/9, with the thumb-to-arm sign being positive on the left. There was no restriction of extension of the lower extremities. Thumb sign was negative bilaterally. She had horizontal striae on her lower flanks and back and vertical striae on her abdomen and anterior flanks. She had no herniae. Varicose veins were present particularly on the posterior calves. Her cardiac sounds were normal.

Patient III-1 (maternal uncle of the index case and brother to III-4) was 194.5 cm tall. He had bilateral ptosis, with downsloping palpebral fissures, malar flattening, large ears, and a prominent nasal bridge (fig. 3e, f). He had a long, deep philtrum and a high palate (fig. 3g). He has had surgery correction of a pectus deformity and a Bentall procedure with aortic valve replacement to correct a progressively dilated aortic root. A residual pectus excavatum has persisted despite surgical repair (fig. 3h), and he had striae in the axillae and upper abdomen, along with keloidal scarring at some sites of surgical incisions (fig. 3i), and widening of other surgical scars. He has bilateral pes planus, contractures of the toes (fig. 3j) and a mild scoliosis with right rib prominence. His measurements are shown in table 1.

Patient IV-6 is the son of III-4. He had bilateral undescended testes, first detected at 6 months of age. Measurements are shown in table 1. As an infant his craniofacial exam was unremarkable (fig. 3k, l). As a child, he had bilateral ptosis, with downsloping palpebral fissures, malar flattening, large ears, and a prominent nasal bridge (fig. 3e, f). He had a long, deep philtrum and a high palate (fig. 3g). His ears were bilaterally cupped with thickened helices. He had a high, narrow palate but no maloccluded teeth. He had a mild annular disc bulge at L4–L5, and leftward protrusion of the L5–S1 disc. X-rays of IV-5 revealed an S-shaped thoracolumbar scoliosis (fig. 4a, b). Her thoracic spine curved right convex 16° between T7–T12 and lumbar spine curved left convex 20° at T12–L3. Spondylolisthesis of L5 upon S1 was noted, with anterior displacement of the L5 vertebral body (fig. 4b). Mild fusions of the posterior elements of C2 and C3 were also seen (fig. 4c). A CT angiogram of III-4 demonstrated minimal tortuosity of the left internal carotid artery (fig. 4d) and also found a posterior aneurysmal outpouching of the infrarenal abdominal aorta, measuring 20 × 12 mm (fig. 4e). Incidental note was made of the pectus excavatum (fig. 4f). Lumbosacral MRI confirmed dural ectasia in III-4 (fig. 4g) and in III-1 (fig. 4h). III-4 had mild posterior scalloping of vertebral bodies T12, L4 and L5, slender pedicles in L1 and L2, bilateral perineural cysts associated with the S2 and S3 nerves, and bony remodeling and expansion of the sacral canal.

There was a midline annular tear of the T12–L1 disc without protrusion, focal disc protrusions at L1–L2, L2–L3, L4–L5, and L5–S1, and displacement of the right S1 nerve root by the L5–S1 disc. III-1 had ectasia at L5 and S1, associated with an intrasacral meningocele at S2–S3, a mild annular disc bulge at L4–L5, and leftward protrusion of the L5–S1 disc.

To date, the classical finding of aortic ectasia has been diagnosed among 5 family members: IV-5, III-4, III-1, IV-6 and IV-2. Patient IV-5 has developed progressive moderate aortic root ectasia with dilation of the sinuses of Valsalva but no aortic aneurysm (fig. 4i). Her mitral valve is slightly redundant with mild prolapse. Her triscupid valve is more redundant and prolapses to a greater extent. A muscular mass was also identified in the left ventricular septum at 14 months of age; it has not increased in size on subsequent assessments and does not obstruct flow. Echocardiogram of patient III-4 at age 35 years found that her aortic annulus measured 2.1 cm, the aortic sinus mea-
sured 3.9 cm, the ascending aorta 2.8 cm, and the descending aorta 2.6 cm in its mid-portion and 2.2 cm at the level of the diaphragmatic hiatus. Her mitral valve was slightly displaced, but not prolapsed, with physiological regurgitation. Patient III-1 was found to have dilation of the aortic sinus to 5.0 cm at age 34 years. Trace regurgitation of the mitral valve was also seen at that time. At age 38 years and 8 months, his aortic root and ascending aorta had become severely dilated, measuring 4.5 cm at the root and 5.7 cm at the ascending aorta. Cardiac MRI found an aneurysm of the proximal ascending aorta involving the sinuses of Valsalva and measuring 6.0 × 6.7 × 5.2 cm. His mitral valve was mildly calcified, but not prolapsed. He underwent urgent repair with a Bentall procedure at that time.

In Patient IV-6, the brother of IV-5, mild enlargement of the ascending aorta (to 1.3 cm) was detected by echocardiography at 4 months of age, for which he was prescribed atenolol. In the most recent echocardiogram, performed at 2 years 5 months of age (fig. 4j), the aortic root measured 2.4 cm at the sinus of Valsalva (>97th centile, +3 SD). Loss of the sinotubular junction demarcation line was also seen.

The echocardiogram in Patient IV-2 found normal sinus rhythm with a transitional incomplete right branch bundle block. The sinus of Valsalva was mildly dilated at 2.8 cm², with a Z-score of +3.6 based on body surface area (fig. 4k). He had no mitral valve prolapse. Family member IV-1 (the elder son of III-1) had no physical features of Marfan syndrome and had a normal echocardiogram at 14 years and 1 month of age (fig. 4l, also see online suppl. material, www.karger.com/doi/10.1159/000347163).

**Fig. 4.** Diagnostic imaging studies of affected family members. 

- **a** PA view of the thoracolumbar spine of IV-5 at 6 years and 5 months shows an S-shaped thoracolumbar scoliosis with a right convex curvature measuring 16° between T7 and T12. The left convex curvature measures 20° between T12 and L3. Spondylolisthesis of L5 upon S1 is shown in the lateral view (b) with the L5 vertebral body displaced anteriorly one-half the width of the S1 vertebral body. 
- **c** Lateral X-ray of the cervical spine of IV-5 at age 6 years shows an S-shaped curve with fusion of the posterior elements of C2 and C3. 
- **d** CT angiogram of III-4 at age 35 years demonstrates minimal tortuosity of the left internal carotid artery inferior to the entrance into the cranium at the carotid canal. 
- **e** CT angiogram of III-4 also identifies a posterior aerenural outpouching of the infrarenal abdominal aorta, measuring 20 × 12 mm. 
- **f** Note was made on CT of the inferior pectus excavatum in III-4. The superior portion of the sternum shows mild pectus carinatum as well. 
- **g** T2-weighted MRI sagittal Fast Relaxation Fast Spin Echo (FRFSE) sequence section of the lumbar spine of III-4 at 36 years of age. 
- **h** and of III-1 at 38 years of age, demonstrating dural ectasia. 

- **i–l** Echocardiograms for IV-5 at 7 years and 2 months (i), IV-6 at 2 years and 5 months (j), IV-2 at 7 years and 1 month (k) and IV-1 at 14 years and 1 month of age (l) are shown.

**Sanger Sequencing of the FBN1 Gene**

Mutation testing of the FBN1 gene was performed by the John Welsh Cardiovascular Diagnostic Laboratory at Baylor College of Medicine. A c.7409G>A variant, which is predicted to encode a p.Cys2470Tyr missense mutation in FBN1, was identified in III-1, III-4, IV-2, IV-5, and IV-6. IV-5 was also found to have the following common variants thought not to be pathogenic: a homozygous c.1415G>A (p.C472Y) variant, a homozygous IVS56+17C>G variant, a homozygous IVS60–113C>A variant, and a heterozygous c.7410C>T (p.Cys2470) variant. The c.7409G>A variant was confirmed to be absent from II-3, III-3, and IV-1 (see fig. 1).

**Discussion**

This family demonstrates 3 generations with multiple affected individuals in which skeletal and cardiovascular features consistent with Marfan syndrome are present. Though neither an autopsy report nor DNA were available on II-1, we surmise that he was also affected. A C-terminal c.7409G>A (p.Cys2470Tyr) missense mutation in exon 59 of the FBN1 gene has been detected in this family, which cosegregates with the clinical features of the disorder. In patient IV-5, the IVS60–113C>A, IVS56+ 17C>G, c.1415G>A (p.C472Y) and c.7410C>T (p.Cys2470) variants were also detected in the FBN1 gene, but these are believed to be single-nucleotide polymorphisms of no functional significance. Patient IV-5 also presented with an apparently de novo 46,XX,del(5) (q33.1q33.3).

A p.Cys2470Tyr missense mutation has previously been reported for a single patient with Marfan syndrome [Attanasio et al., 2008]. Similar to the family described in this case report, this patient had skeletal, cardiovascular and mild dermatological findings consistent with Marfan syndrome. The skeletal features included a reduced upper:lower segment ratio, pectus excavatum requiring surgery, pes planus, and scoliosis exceeding 20° of curvature. The sole cardiovascular finding reported was dilatation of the ascending aortic arch. The dermatological finding was striae atrophicae.

Genotype-phenotype correlations for rare DNA variants in FBN1 have been presented in other studies, in an attempt to distinguish rare, highly penetrant variants from rare variants of no functional significance [Faire et al., 2007, 2009]. Rare variants of clinical significance also provide insight into the importance of specific domains for the tissue-specific functions of the protein as a whole.
Mutations in the first 15 exons of *FBN1* are infrequent but tend to be associated with ectopia lentis [Turner et al., 2009]. Missense mutations in exons 2–17 are associated with severe eye pathology [Jin et al., 2007; Evangelisti et al., 2010] or isolated ectopia lentis [Adès et al., 2004]. Certain mutations within exons 1–10 have been associated with significant cardiovascular pathology [Attanasio et al., 2008]. Neonatal Marfan syndrome and severe Marfan syndrome are associated with missense mutations in exons 24–40 [Pepe et al., 2001; Turner et al., 2009], which affect the 8-Cys motif and cbEGF domains 11–18 [Hirani et al., 2008]. Neonatal Marfan syndrome is most strongly associated with missense mutation in exons 24–27 and 31–32 [Palz et al., 2000]. In patients with classical Marfan syndrome associated with a mutation in this region, there is a high frequency of aortic dilatation requiring surgery, mitral valve abnormalities, ectopia lentis, scoliosis, and shortened survival [Faivre et al., 2007].

Conflicting reports exist regarding the severity of phenotypes associated with missense mutations in exons 59–65, affecting cEBF domains of the protein. Several studies report milder cardiovascular features [Palz et al., 2000; Comeglio et al., 2007], lack of aortic pathology, and a tendency to have fewer features of the Ghent criteria [Comeglio et al., 2007; Turner et al., 2009]. Consistent with findings in this report, other studies [Arbustini et al., 2005; Rand-Hendriksen et al., 2007; Turner et al., 2009] did not associate missense mutations in this region with milder cardiovascular features. Twenty percent of patients with mutations in this region demonstrated cardiovascular findings as children [Arbustini et al., 2005]. Attanasio et al. [2008] reported that 90% of novel mutations they detected were within exons 59–65, and 90% of patients had classical Marfan syndrome with severe cardiovascular involvement. According to Turner et al. [2009], a third of patients with mutations in this region had aortic dilatation requiring surgical intervention. An IVS58–2A>G mutation that results in skipping of this exon has been reported to cause primary dissection of the descending aorta [Palz et al., 2000]. A p.Tyr2849X missense mutation in exon 65 is associated with early risk of aortic dissection and sudden death [Gao et al., 2010a]. Rand-Hendriksen et al. [2007] report that among 5 mutations within exons 59–65, the dura mater was affected in all cases. In the same cohort, the ocular system was affected in 60% of cases, the cardiovascular system in 80% of cases and the skeletal system in 40% of cases [Rand-Hendriksen et al., 2007]. Adès et al. [2004] documented skeletal involvement, ectopia lentis and mitral prolapse in missense mutations within these exons.

The p.Cys2470Tyr mutation replaces a cysteine residue with a tyrosine residue. Many pathogenic *FBN1* missense mutations affect cysteine residues or residues directly adjacent to cysteine residues, and these may alter the c-EBF domain structure or calcium-binding domains of FBN1 protein [Pepe et al., 2001]. Cysteine missense mutations are associated with a higher probability of ascending aortic dilatation and mitral valve prolapse, and tend to be associated with major cardiovascular involvement [Turner et al., 2009]. Ectopia lentis may be more likely in mutations affecting cysteine residues [Attanasio et al., 2008] regardless of the location of the mutation [Turner et al., 2009; Gao et al., 2010b].

In the family presented in this report, all patients known to harbor the c.7409G>A (p.Cys2470Tyr) missense variant demonstrated aortic root dilatation. Several family members demonstrated congenital cardiac valve anomalies or mild prolapse of one or more cardiac valves. Two patients had aneurysms, 1 of which was a cause of death for patient II-1. Both adult subjects with the variant had dural ectasia, consistent with the findings of Turner et al. [2009] of dural ectasia in 83% of individuals with mutations in exons 59–65. Interestingly, there was no family history of ectopia lentis or other ophthalmological involvement. This is consistent with a trend among other reports in the literature of missense variants in this region that lack association with ectopia lentis [Turner et al., 2009], although a p.E2447K missense mutation in the same exon (59) has been reported to cause autosomal dominant ectopia lentis [Palz et al., 2000]. This family’s history confirms the association of dural ectasia and the lack of association of ophthalmological findings with some C-terminal exon missense mutations. Most importantly, it refutes the lack of cardiovascular pathology suggested to be associated with this region. Furthermore, the mild carotid tortuosity and the abdominal aortic aneurysm found in a young, healthy woman suggests that other cardiovascular imaging techniques apart from echocardiograms may be of use in assessment and follow-up of Marfan syndrome patients.

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