Scientific letters

Marfan Syndrome Caused by Somatic Mosaicism in an *FBN1* Splicing Mutation

Síndrome de Marfan causado por mosaicismo somático de una mutación en splicing *en* FBN1

To the Editor,

Marfan syndrome (MIM 154700) is an autosomal dominant disease affecting the skeleton, eyes, and cardiovascular system. Its estimated prevalence is 2 to 3 per 10 000 individuals. According to the revised Ghent nosology, diagnosis can be established by the presence of a pathogenic mutation in the fibrilin-1 gene (*FBN1*) in association with aortic root dilatation.[1] Of the more than 1800 mutations identified, most are specific to a single family, and 25% are de novo mutations; high intrafamiliar and interfamiliar variation has prevented the establishment of a correlation between genotype and phenotype.[1] A possible cause of the varied phenotypic expression is parental mosaicism, which should be borne in mind in genetic counseling after diagnosis of de novo cases. However, there have been few reports of families with Marfan syndrome associated with mosaicism in *FBN1*.[2–5]

Here, we describe a new mosaic splicing mutation in *FBN1*. The proband is a 34-year-old man with no siblings. He was diagnosed with Marfan syndrome on the basis of ectopia lentis and aortic root dilatation and has a systemic score of 4 (myopia > 3 diopters, positive thumb sign, chest deformity, and treated scoliosis). Family history includes ischemic heart disease in the father, treated by revascularization, and type B aortic dissection in the mother, treated by percutaneous placement of an endovascular prosthesis (Figure).

Following informed consent, the proband underwent a genetic analysis by mass sequencing of 30 genes related to aortic disease. The study identified a previously unknown heterozygous mutation in intron 22 of *FBN1* (c.2677+5G>C; NM_000138.4). In silico analysis (with SSF, MaxEnt, NNSplice, and HFF) showed that the mutation disrupts the natural splicing donor site, indicating possible disease association. This variant has not been reported

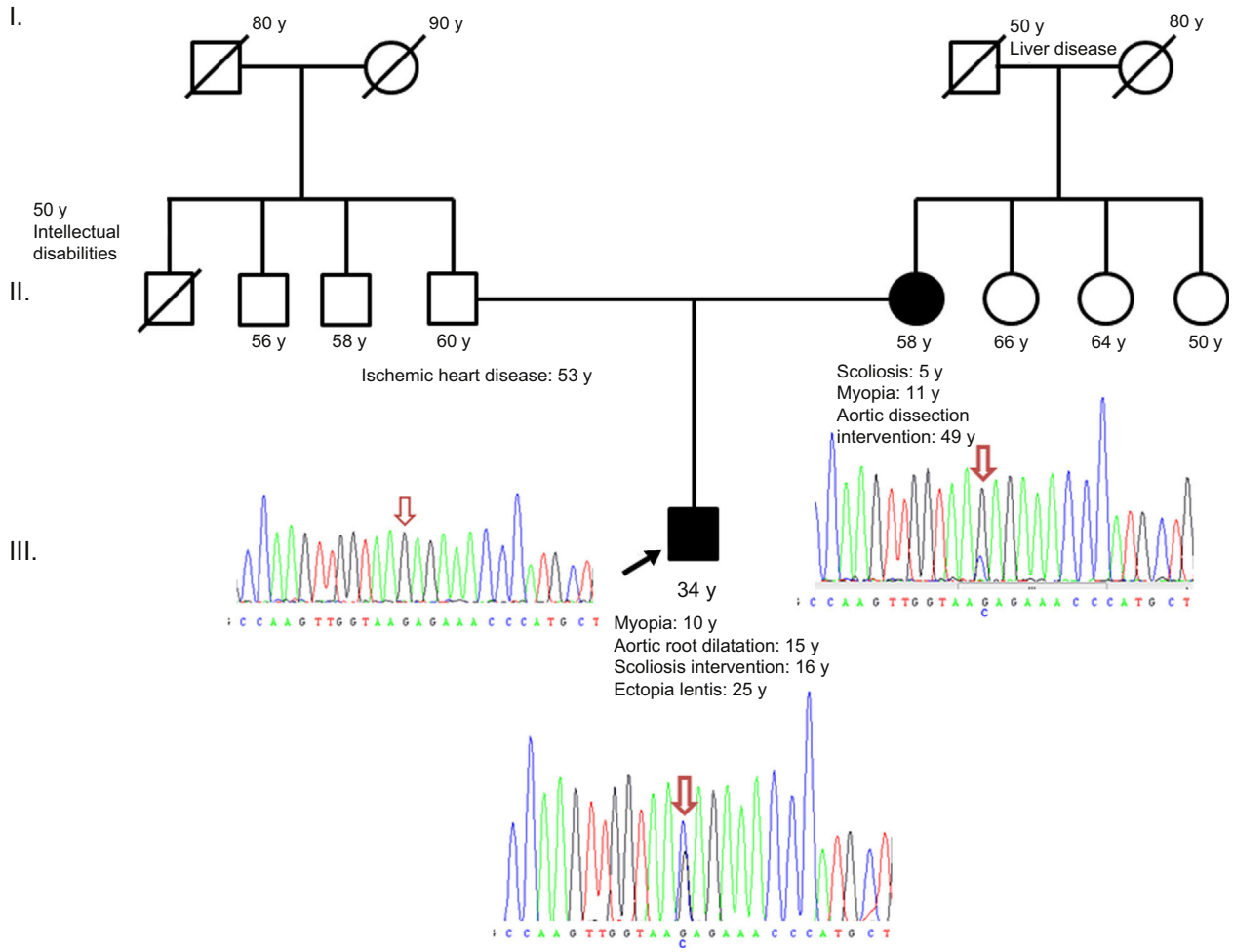

Figure. Family tree and electropherograms of the *FBN1* region containing the c.2677 + 5G>C mutation (arrow). The mutated allele (cytosine, blue) is present in a lower proportion in the mother than in the proband, suggesting mosaicism.

before in the general population (dbSNP, Exome Variant Server); however, a mutation involving a different nucleotide change at the same position has been reported in a Marfan syndrome patient, suggesting that this position is important for correct RNA processing.[6] The genetic analysis also identified 2 mutations of unknown pathogenicity, in *TGFBR1* (c.409G>A; p.Val137Ile) and in *LMNA* (c.1158-6C>T, NM_170707.3).

A familial study confirmed that the mother meets the diagnostic criteria for Marfan syndrome (aortic dissection and family history) with a systemic score of 3 (scoliosis, myopia > 3 diopters, and *pectus excavatum*). She has 3 sisters with no disease phenotype, and both elderly parents died several years ago, apparently from noncardiovascular causes, although no data are available.

The familial cosegregation analysis began with the mother and was directed at *FBN1* and at *TGFBR1*, included because of its association with familial aortic syndromes. The study showed that the mother does not carry the *TGFBR1* mutation but is mosaic for the *FBN1* mutation (Figure). The presence of this somatic mosaicism indicates that the mutation arose *de novo* during the mother's embryonic development, and the analysis was therefore not continued in her sisters. Following recommended procedures for confirmation of suspected mosaicism, we extended the genetic analysis to another tissue (bucal mucosa) and confirmed the results with a second independent primer pair. These tests yielded a similar percentage of cells containing the mutant allele, indicating that the mutation event occurred in the early stages of embryogenesis.

The literature on mosaicism in Marfan syndrome reveals that parent carriers have less severe phenotypes than probands or express no manifest phenotype, independently of sex.[2–5] However, in the family studied here, the mother has a prominent vascular phenotype, despite carrying the mutation in mosaicism. This discrepancy could in principle reflect differences in the type of genetic alteration; however, this hypothesis is not supported by the published data, which show that a weaker phenotype in the mosaic parent is found with all types of mutation, whether causing amino acid substitution or protein truncation.[2–5] We therefore recommend close clinical follow-up of patients with a mosaic mutation, even if it is present in a low percentage of cells.

The intrafamiliar variation encountered here might be explained by a protective effect of the *TGFBR1* variant found in the son. Another possible explanation is the age difference, since aortic dilatation in Marfan syndrome is progressive and therefore likely to worsen with age. Moreover, pregnancy is an additional risk factor for aortic dilatation in patients with underlying aortic disease.[1]

In summary, we present an example of somatic mosaicism in *FBN1* that illustrates the importance of considering this possibility in genetic counseling programs. This would permit a more focused strategy than would be possible otherwise. This case also shows that somatic mosaicism is not always associated with a less severe progression of Marfan syndrome.

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The Longitudinal Childhood Obesity Study (ELOIN): Design, Participation and Characteristics of the Baseline Sample

Estudio Longitudinal de Obesidad Infantil (ELOIN): diseño, participación y características de la muestra

To the Editor,

Controlling childhood obesity is a global health priority.[1] Obesity is associated with comorbidity in childhood and, if it persists, leads to a higher risk for diseases in adulthood.[2] According to the Spanish National Health Survey, the prevalence of obesity in the 2- to 17-year-old population age group increased from 8.4% in 1993 to 10.5% in 2011.[3] The factors most widely studied by researchers to explain the high incidence of childhood obesity are energy balance, food intake, physical activity, and sedentary behavior.[4]

The Longitudinal Childhood Obesity Study (ELOIN) is a prospective, population cohort study that started in 2012 and aims to describe variations in overweight and obesity, determine the association of overweight and obesity with sociodemographic and lifestyle factors, and estimate their impact on health. This dynamic cohort and the baseline sample are composed of children aged 4 years. Follow-up measurements are being recorded at ages 6, 9, 12, and 14 years. The target population is children born between 15 January 2008 and 30 November 2009, living in the Madrid Autonomous Community, and under the care of one of the 31 pediatricians in the Madrid Sentinel Primary Care Physician Network. The study design has already been described in the literature.[5] We collected data for the baseline sample in 2 consecutive steps: at a physical examination performed by the