

CASE REPORT

Thymine > cytosine missense mutation at nucleotide 3538 in fibrillin-1 gene in Marfan syndrome: A case report of an aggressive phenotype

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**Abstract**

Aim: To report the case of a patient with Marfan syndrome that presented with an heterozygous change from thymine (T) to cytosine (C) at nucleotide 3538, resulting in a missense change from cysteine to arginine at codon 1180 in exon 28 (3538 T>C; cys1180arg) of the FBN1 gene, causing a severe phenotype of the disease with early-onset bilateral lens subluxation with nasal displacement of the lens and absent zonules.

Background: Ectopia lentis (EL) is a major criterion to diagnose MFS, a connective tissue disorder caused by a mutation in the FBN1 gene.

Case Description: An 11-year-old boy with a history of MFS causing severe aortic root dilatation with increasing dimension and no evidence of dissection. Refraction revealed bilateral myopia with astigmatism and deprivation amblyopia in the left eye. Slit-lamp examination evidenced iridodonesis with flat iris in both eyes, and nasal displacement of the lens that was mild in the right eye and moderate in the left eye with absent temporal zonular ligaments.

Conclusion: MFS typically presents with EL with superotemporal displacement of the lens secondary to zonular laxity. Our patient has bilateral lens subluxation with nasal displacement of the lens and absent zonules, due to a missense change from cysteine to arginine at codon 1180 in exon 28 (3538 T>C; cys1180arg) of the FBN1 gene, resulting in a severe phenotype of the disease.

Clinical Significance: This mutation can be the cause of an aggressive phenotype with complete zonular weakness at a young age.

Introduction

Marfan syndrome (MFS, MIM #154700) is an autosomal dominant connective tissue disorder caused by a mutation in the fibrillin-1 (FBN1) gene on chromosome 15q21.1.^[1] It has a prevalence of 1/5000–20,000, affecting both sexes equally, with no ethnic or racial group predilection.^[2–4] Clinical criteria have been used to diagnose MFS (Ghent nosology), as a set of major and minor manifestations in numerous tissues and systems (skeletal, ocular, cardiovascular, pulmonary,

dura, skin, and integument).^[5] Ectopia lentis (EL) occurs in 50–80% of patients.^[1,3,5,6] It is usually bilateral, symmetric, and characteristically, the displacement of the lens occurs superotemporally and is secondary to zonular laxity.^[2,3] The zonular microfibrils (ZM), whose primary constituent is the glycoprotein FBN1 (MIM #134797), are structurally and functionally abnormal: They are loosely arranged and disorganized.^[1] Cysteine substitutions in the cysteine-rich epidermal growth factor-like (EGF-like) domain of FBN1, and

mutations located in exons 24–32 of the FBN1 gene, correlate with severity of disease.^[1,4,7]

Case Report

An 11-year-old boy was referred for subluxated crystalline lens. The patient had a known history of MFS diagnosed clinically at the age of 2½ years and confirmed by DNA testing at 4 years of age. He possesses a mutation in the FBN1 gene, involving a heterozygous change of thymine (T) to cytosine (C) at nucleotide 3538, resulting in a missense change from cysteine to arginine at codon 1180 in exon 28 (3538 T>C; cys1180arg). His past medical history was significant for severe aortic root dilatation (ARD) requiring maximal medical therapy, mild thoracolumbar scoliosis, and pes planus. Past ocular history involved EL, high myopia corrected with glasses since age 2, and allergic conjunctivitis. Family history was negative for MFS.

On ocular examination, his best-corrected visual acuity measured 20/20 - right eye (OD) and 20/50 in the left eye (OS). Refraction was $-5.50 + 3.00 \times 90^\circ$ OD and $-10.50 + 5.00 \times 90^\circ$ OS. Pupils, confrontation visual fields, and intraocular pressure were normal OU. Ocular motility examination was unremarkable. Slit-lamp examination revealed bilateral iridodonesis, asymmetric nasal displacement of the crystalline lenses worse OS, and complete absence of the temporal zonular ligaments (ZL) [Figure 1]. Fundoscopic examination was unremarkable bilaterally.

Discussion

EL is one of the major criteria in the diagnosis of MFS.^[1,3,5] Typically, the displacement of the lens occurs superotemporally and is secondary to ZL due to abnormal FBN1, the main glycoprotein of ZM.^[3,6,8] In MFS, the FBN microfibrils (FM) are structurally and functionally abnormal: They are loosely arranged and disorganized within the zonular fibers (ZF) and are significantly more susceptible to proteolytic degradation by proteases.^[1] Maumenee reported that in 170 eyes of patients with MFS, superior displacement of the lens was seen in 77% of the eyes.^[9] Nasal displacement (nasal, superonasal, or inferonasal) was seen in 15.2% compared to 36.5%, in which the direction was temporal (temporal, superotemporal, or inferotemporal).^[9] In 3.5%, the lens was exclusively nasally displaced, as observed in our patient. Rarefaction of the zonules was present in patients with severe dislocation of the lens, and matting of the ZF on the lens surface with marked irregularity of the zonular pattern was observed in two patients <10 years (downward and upward dislocation).^[9] However, none of the patients had absent ZL like our patient. The correlation between genotype and the severity of the systemic manifestations and the direction of dislocated lenses was not analyzed.

Beene *et al.* have studied FBN1 abnormalities in the lens and zonules in MFS.^[10] They found a variable distribution and structure of FM in the three FBN -rich lens capsule zones, with disruption and fragmentation of the FM in the lens capsule.^[10] The qualitative, quantitative, and structural abnormalities of

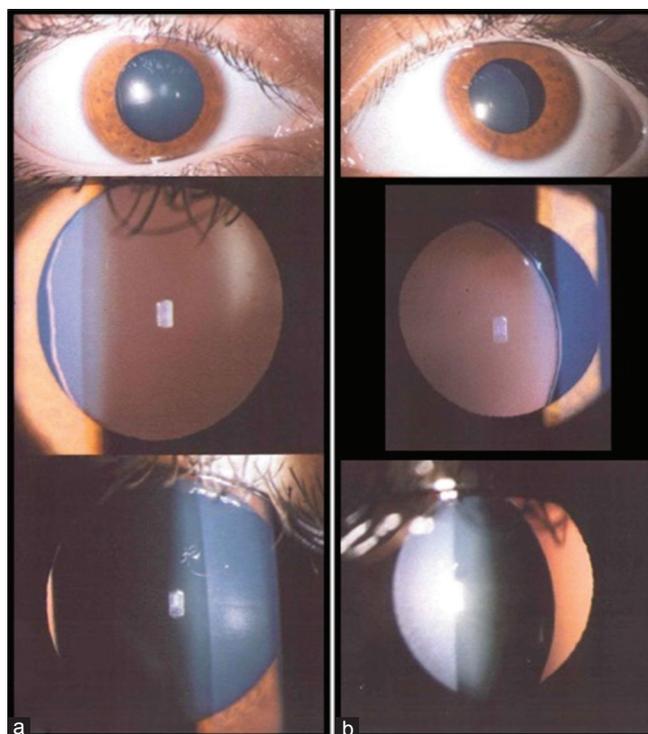


Figure 1: Slit-lamp photograph of the right (a) and left (b) eye. Note the bilateral asymmetric nasal displacement of the crystalline lenses worse in the left eye, with complete absence of the temporal zonular ligaments

FBN deposition in the lens capsule and FBN expression are consistent with a role in the mutations.^[10] In addition, they have observed in a murine model of MFS and in the process of microfibril assembly *in vitro* that rodent zonules are composed of both FBN1 and FBN2, with architecturally intact zonules composed of FBN2 in the FBN1-deficient eyes.^[10] In the case of our patient, there could be an abnormal adherence and integration of the ZM to the lens, causing secondary absence of temporal ZL. Likewise, the absence of ZL may indicate that the mutation in this patient is very aggressive, leading to impaired FBN1 microfibril assembly without compensation.

FBN1 gene is a 237-kb gene consisting of 65 exons located at 15q21.1, which codifies for FBN1.^[6] FBN1 consists of 47 EGF-like domains, 43 of which are calcium binding (cbEGF) and two are cysteine-rich EGF-like domains.^[6] It has been reported that cysteine substitutions in EGF-like domains of FBN1 result in more aggressive phenotypes of MFS.^[1,4,8] In addition, the location of the mutation correlates to the phenotypic severity: FBN1 mutations in exons 59–65 are associated with a mild phenotype characterized by a lack of ARD, and mutations in exons 24–32 correlate with severe disease, characterized by early-onset MFS and a severe cardiovascular phenotype.^[1,4,7] Furthermore, patients with missense mutations involving a cysteine had a higher probability of ascending aortic dilatation ($P = 0.0022$), and a missense mutation in exons 24–32 correlates with EL diagnosed before 25 years ($P = 0.0009$).^[4] Our patient had a heterozygous change from T to C at nucleotide 3538, resulting in a missense change from cysteine to arginine in FBN1 at codon 1180 in exon 28 of the FBN1 gene; this may explain the severity of the disease seen in him, characterized by an aggressive phenotype, with severe cardiovascular disease and early-onset bilateral nasal dislocation of the lens with absent zonules. According to the Universal Mutation Database (<http://www.umd.be>), 3077 pathogenic mutations in FBN1 have been described. Our patient's mutation has been documented in only two other cases, originating from France, but only one has clinical data, which does not include the severity of the cardiovascular disease or the characterization of EL.

Conclusion

Our patient presented with an aggressive phenotype of the disease including severe progressive ARD and nasal displacement of the lens with absent ZL. This mutation can be the cause of

an atypical and more aggressive presentation of the disease at a young age.

Clinical Significance

This mutation can be the cause of an aggressive phenotype with complete zonular weakness at a young age.

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