A 2-Year-Old Child with Bilateral Ectopia Lentis and a Novel *FBN1* Gene Variant Cys129Ser

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Abstract

Marfan syndrome and dominant ectopia lentis are part of type 1 fibrillinopathies that are caused by *FBN1* pathogenic variants. Making a diagnosis could be challenging due to the clinical overlap between these disorders. The revised Ghent criteria used for Marfan syndrome diagnosis helped in resolving some of the confusion, especially in younger children. We report on a case of bilateral ectopia lentis in a 2-year-old child with a normal echocardiogram. *FBN1* sequencing revealed a novel likely pathogenic variant described as c.385T > A (p.Cys129Ser). The patient's father also has a history of bilateral ectopia lentis and his genetic analysis detected the same *FBN1* variant as the proband.

Keywords

- Marfan syndrome
- ectopia lentis
- cys129ser

Introduction

Fibrillin 1 is a cysteine-rich glycoprotein that is a primary component of the 10 to 12 nm extracellular microfibrils, which are broadly distributed in elastic and nonelastic connective tissues.¹ Pathogenic variants in *FBN1* located on chromosome 15q12 have been found to cause Marfan syndrome as well as other connective tissue disorders including autosomal dominant ectopia lentis.² *FBN1* pathogenic variants that have been described include missense, nonsense, small deletions, and splice site mutations. The most common type of pathogenic variants are missense mutations affecting the highly conserved cysteine residues.^{3,4}

Marfan syndrome is an autosomal dominant disorder characterized by clinical manifestations mainly in the cardiovascular, ocular, and skeletal systems. The Ghent criteria used to diagnose Marfan syndrome have been revised to be more applicable for the younger population and to reduce the number of premature diagnosis.⁵ Fibrillin-1 microfibrils are a major component of the zonular fibers which hold the lens in its normal position.⁶ Marfan syndrome is the most common cause of inherited ectopia lentis which is considered a cardinal feature of the syndrome. Isolated ectopia

lentis, inherited as either dominant (*FBN1*) or recessive (*ADAMTSL4*), is the second most frequent cause of inherited ectopia lentis.⁷

Case Presentation

Our patient initially presented at 18 months of age with bilateral lens subluxation and high myopia. He underwent a slit lamp exam that revealed a superior subluxation in the right lens and superior/temporal subluxation in the left lens. Both lenses had highly myopic and irregular retinoscopy > – 20. Funduscopy examination showed pink and sharp disc borders and healthy rim bilaterally as well as normal foveal contour and pigmentation of the macula bilaterally. Vessels and periphery were also normal bilaterally on funduscopy. His physical examination was negative for other clinical manifestations suggestive of Marfan syndrome scoring 1 in the systemic calculator of the revised Ghent criteria. He subsequently underwent *FBN1* sequencing through commercial gene sequencing, which detected a novel likely pathogenic variant consistent with an *FBN1*-related disorder. This variant is denoted as c.385T > A (p.Cys129Ser). He has had multiple echocardiograms,

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the most recent of which at the age 2 years had a calculated Z-score of 1.03 that was considered to be at the upper limits of normal. The patient's father was also positive for the *FBN1* pathogenic variant found in his son. He is 71.5 inches tall and has a history of bilateral lens subluxation at the age 16 years, which required lens extraction. He has had an echocardiogram that was normal and had no skeletal features suggestive of Marfan syndrome (systemic score = 0). Both proband's elder sisters are negative for the c.385T > A *FBN1* variant and do not have ectopia lentis.

Method

The coding sequence of *FBN1* was amplified by polymerase chain reaction (PCR) and each PCR product (amplicon) then sequenced bidirectionally, using the Sanger sequencing methodology. Of the 62 amplicons in this test, 62 were successfully analyzed, 0 could not be successfully analyzed, and 0 have not yet been processed. NM_000138 was the mRNA transcript used.

Discussion

Marfan syndrome and familial ectopia lentis are part of the clinical spectrum of diseases called collectively "type 1 fibrillinopathies," which are caused by pathogenic variants in *FBN1*.⁸ A clinical overlap is present between these disorders as ectopia lentis is also the most common ocular finding in Marfan syndrome.⁹ Children affected by Marfan syndrome may have incomplete expression of their phenotypes, which can make the diagnosis more challenging.¹⁰ Several correlations have been found between various *FBN1* pathogenic variants and specific clinical manifestations. An association between ectopia lentis and missense mutations involving cysteine, regardless of its location within the protein, has been found to be statistically significant.⁸

The current revised Ghent criteria put more emphasis on the two cardinal features of Marfan syndrome: aortic root dilation and ectopia lentis. Accordingly, in the absence of aortic root dilation and family history of Marfan syndrome, ectopia lentis and *FBN1* pathogenic variants that have been previously associated with aortic disease are sufficient to make a diagnosis of Marfan syndrome.⁵ Previously, patients who presented with isolated ectopia lentis and a pathogenic variant in *FBN1*, were misdiagnosed as familial ectopia lentis, even though their pathogenic variants have been described before to cause Marfan syndrome.^{11,12}

Our patient had a systemic score of 1, seeing that high myopia (> -20 diopters) was the only feature positive on his physical examination. The father's systemic score was 0, as he was negative for all the clinical manifestations used in the calculation of systemic score based on the new Ghent nosology.⁵ Our proband's father, now 32 years old, underwent a genetic evaluation and a cardiovascular assessment that revealed the same *FBN1* pathogenic variant found in his son but no aortic root changes. His phenotype is isolated ectopia lentis without any other clinical manifestations known to be associated with Marfan syndrome. Since he is older than 20 years, a

diagnosis of ectopia lentis syndrome can safely be made at this point based on established criteria.⁵

Our proband has a novel variant in *FBN1* described as c.385TA (p.Cys129Ser), which was present in the heterozygous state. This variant is a missense mutation and has been scored as likely pathogenic variant, using common scoring algorithms used by commercial laboratories. Two additional missense mutations were detected in the *FBN1* gene of our proband (c.385T > A, c.2956G > A). Both of these have been described as benign and had no association with Marfan syndrome.¹³ The C192S variant is a nonconservative amino acid substitution, which is likely to impact secondary protein structure, as these residues differ in polarity, charge, and size. It affects a cysteine residue within an epidermal growth factor (EGF)-like domain of the *FBN1* gene, which may affect disulfide bonding. Using PolyPhen-2 and SIFT bioinformatics tools, the C192S variant was predicted to be probably damaging with a score of 0.993 and -8.068, respectively. The PolyPhen-2 and SIFT protocols predict the effect of a single amino acid substitution on the function of a human protein.^{14,15} Additionally, the p.Cys129Ser variant was predicted as most likely to interfere with function using Align-GVGD, which is a web-based program that predicts the effect of missense mutation based on the biophysical characteristics of amino acids and multiple protein sequence alignments.^{16,17}

A pathogenic variant denoted as p.C129Y, which affects the same cysteine residue as in our proband, has been described before in two cases.^{18,19} The p.C129Y variant was first identified in a neonate who presented with a severe phenotype of Marfan syndrome.¹⁹

Novel pathogenic variants are variants that have never been described before and therefore, cannot be evidently associated with specific phenotypes such as aortic root dilation. By definition, a novel *FBN1* pathogenic variant does not fit the new Ghent criteria, which state that the *FBN1* mutation should be previously associated with aortic disease.⁵

Our patient currently does not satisfy the revised Ghent criteria. However, a diagnosis of familial ectopia lentis is premature at this point. Given the not unlikely possibility of developing aortic root dilation, we recommended that our patient undergoes cardiovascular surveillance at frequent intervals to monitor the status of the ascending aorta, until such a time that either he is older than 20 years with no aortic root involvement or evidence in the medical literature shows that patients with this variant are not at risk of aortic *FBN1*-related manifestations.^{20,21}

In summary, we present a case of a child with ectopia lentis and a novel *FBN1* likely pathogenic variant. Once a genetic testing reveals an *FBN1* pathogenic variant, aortic disease monitoring is recommended due to the clinical overlap between Marfan-related conditions. The management challenge remains for individuals with phenotypes suggestive of isolated ectopia lentis; we are cautious in our approach and recommend Marfan screening guidelines until proven not necessary.

Conflict of Interest

None.

Authors' Contributions

A.N.M. organized and prepared the manuscript for first draft. P.S.A. is a medical geneticist who executed the project, designed and critically reviewed the manuscript.

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