Familial Ectopia Lentis: Looking Beyond Marfan’s Syndrome

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ABSTRACT
Ectopia lentis has a myriad of causes, with Marfan’s syndrome and homocystinuria being well-known causes. Here, we report two siblings with ectopia lentis and tall stature presenting with a diagnostic challenge.

CASE DESCRIPTION
The proband, a 20-year-old lady born of a consanguineous marriage, presented with complaints of tall stature and significant myopia from 5 years of age. Clinical examination revealed dysmorphic facies in the form of a beaked nose with an elongated face with malar flattening (Fig. 1). Her height was 184 cm, arm span to height ratio of >1.05, and upper segment to lower segment ratio of 0.85. She had a high arch palate with malalignment of teeth. Her best corrected visual acuity was six out of nine in both eyes, with ocular examination showing bilateral superonasal lens dislocation (Fig. 2) with myopic fundi (Fig. 3).

Her younger brother (15 years of age) was also tall (178 cm) and had similar facies with superotemporal lens dislocation and a normal fundus examination. Both parents were of normal height with no ocular abnormalities (Table 1). Initially, they were referred to as suspected Marfan’s syndrome/homocystinuria. However, a normal echocardiogram and normal serum homocysteine levels ruled out the other diagnoses. A genetic evaluation was performed as the siblings were born out of a consanguineous marriage, suspecting an autosomal recessive inheritance.

Whole exome sequencing showed homozygous missense variation in exon 25 of the ASPH gene [chr8:g.61503432C>T, (RefSeq NM_004318.3)] leading to substitution of arginine by glutamine at codon 735 (p.Arg735Gln, R735Q) in both the siblings. This condition is called Traboulsi syndrome and is characterized by lens subluxation, spontaneous filtering blebs, and marfanoid habitus. This variant has been previously reported as pathogenic.

Introduction
Traboulsi syndrome is a rare autosomal recessive disorder caused by a mutation in the aspartate β-hydroxylase (ASPH) gene. It is also known as facial dysmorphism–lens dislocation–anterior segment abnormalities and spontaneous filtering blebs syndrome.¹ Here, we report two siblings with similar clinical features, in whom exome sequencing identified a mutation in the ASPH gene, which has been reported as pathogenic previously.²

Fig. 1: Photograph (front and side profile) showing the dysmorphic facial features of the proband with elongated facies, beaked nose, retrognathia, and malar hypoplasia

Figs 2A and B: (A) Slit lamp examination shows superonasal subluxation of the lens in the right eye; (B) Left eye in the proband

**DISCUSSION**

The most common causes of ectopia lentis with marfanoid habitus are Marfan’s syndrome and homocystinuria. However, the absence of cardiac abnormalities and intellectual disability leads to a diagnostic dilemma in such cases. In our cases, a whole exome sequencing revealed the diagnosis of Traboulsi syndrome, which is a rare autosomal recessive disorder characterized by spontaneous lens subluxation, shallow anterior chamber, and facial dysmorphism in the form of the beaked nose, elongated face, maxillary hypoplasia, and overcrowding of teeth.1 Although rare, skeletal and cardiac abnormalities have been reported.4–6 This syndrome was originally described in a consanguineous Druze family in Lebanon in 1995, and the pathogenic mutation was identified in 2014.1,2 Since then, only 21 genetically proven cases of this syndrome have been reported to date, including five patients from India.5–8

This syndrome occurs due to biallelic variants in the ASPH gene in chromosome 8q12. This gene is found to be highly expressed during the development of the lens. The gene encodes an enzyme called asparyl/asparaginyl β-hydroxylase, which hydroxylates aspartic acid and asparagine residues on epidermal growth factor domain-containing proteins. Arginine residue at the 735th position in the catalytic domain is critical for the function of the ASPH enzyme. Hence, the substitution of arginine by tryptophan (R735W) or glutamine (R735Q) may lead to a loss of ASPH enzyme activity.1 The R735Q variant has been previously reported by Siggs et al.2 However, their patient did not have any skeletal abnormality.

The presence of this clinical phenotype can be explained by studies that found fibrillin-1 (FBN1) and latent transforming growth factor β-binding protein-2 to be ASPH substrates. Mutation in the FBN1 gene leads to Marfan’s syndrome, which is a genetic cause of ectopia lentis. However, asparagine hydroxylation of FBN1 protein is observed only during the development of the embryo, and so its functional significance of hydroxylation is yet to be ascertained.9 Although the role of FBN1 in Traboulsi syndrome is unknown, it may be proposed that the overlapped phenotypes may indicate a molecular link between ASPH and FBN1.

**CONCLUSION**

We would like to conclude that Traboulsi syndrome must be considered as a differential diagnosis for familial ectopia lentis with Marfanoid habitus.

**REFERENCES**