

Identification of a Fibrillin-1 Gene Mutation in a Monozygotic Twin Presenting with Bilateral Juvenile-onset Ectopia Lentis

Dear Editor,

Ectopia lentis (EL) refers to displacement of a lens from its normal location, often when the fibrillin-rich microfibrils of the ciliary zonule are stretched. Marfan syndrome (MFS) is the most common systemic disease associated with EL [1]. MFS is an autosomal dominant connective tissue disorder with major involvement of ocular, skeletal, and cardiovascular systems [1]. The diagnosis of MFS is made on the basis of clinical and genetic criteria that are referred to as the Ghent criteria [1]. Mutations in the fibrillin-1 (*FBNI*) gene located on chromosome 15q12 are known to be causative for MFS [1-3]. The *FBNI* mutations are associated with an increased risk of aortic dilatation and dissection, regardless of the clinical presentation [3]. We report a case of monozygotic twin boys presenting initially with juvenile-onset bilateral EL with disease-causing missense mutation in the *FBNI* gene.

Five-year-old monozygotic twin boys were referred for evaluation of low vision in both eyes. They were born at 37 weeks gestation and weighed about 2.5 kg. They were the second birth of non-consanguineous parents. There was no previous family history of ocular, systemic, or chromosomal disorders. The first-born boy had best-corrected visual acuity (BCVA) of 20 / 50 in the right eye with a refraction of +2.00 Dsph = -4.50 Dcyl \times 170°A and 20 / 120 in the left eye with a refraction of +1.00 Dsph = -7.75 Dcyl \times 180°A. On slit lamp examination, the lenses of the right and left eyes were upwardly and superonasally dislocated, respectively, with the left eye having more severe displacement (Fig. 1A). The second boy's BCVA was 20 / 60 in the right eye with a refraction of +1.50 Dsph = -5.75 Dcyl \times 10°A and 20 / 50 in the left eye with a refraction of +2.00 Dsph = -4.00 Dcyl \times 10°A. The lenses were displaced superotemporally and upwardly in his right and left eyes, respectively (Fig. 1B). No other features of MFS were identified on initial examination. After obtaining informed consent from their parents, direct DNA sequencing of the

FBNI gene was performed. Direct sequencing of all exons of the *FBNI* revealed a heterozygous missense mutation (c.7583G>T) in exon 62 which results in a change from cysteine to phenylalanine (Cys2528Phe) (Fig. 1C and 1D). This mutation was first reported in a French female patient with MFS but has not been previously reported in Korea [4]. It is predicted to be damaging as shown in Sorting Intolerant from Tolerant analysis (SIFT, <http://sift.jcvi.org>). This mutation was absent in their parents (Fig. 1C). Based on the molecular result, cardiac evaluation was recommended, and echocardiography was performed which revealed aortic root dilatation in both patients. They were prescribed a beta-blocker to prevent further enlargement

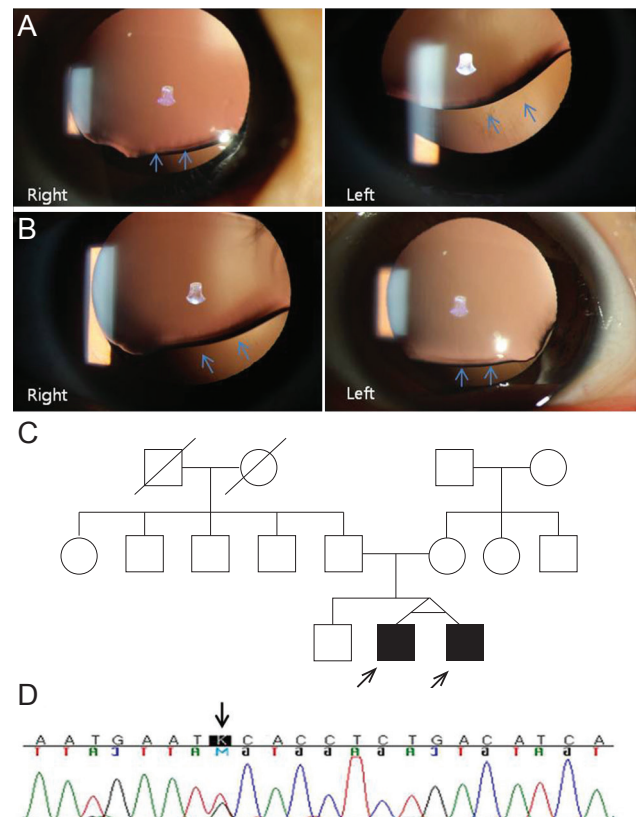


Fig. 1. (A) Images of patient 1. The lenses were displaced upwardly and superonasally in his right and left eyes, respectively. (B) Images of patient 2. The lenses were displaced superotemporally and upwardly in his right and left eyes, respectively. (C) Family pedigree and mutational analysis. Squares and circles indicate males and females, respectively; the darkened symbols represent the affected. Deceased members are indicated by symbols with diagonal lines. The patient above the arrow is the proband. All family members except the twins were examined and determined to be normal. (D) Electropherogram depicting the sequence encompassing the heterozygous G to T transition mutation at nucleotide 7583 (c.7583G>T) in exon 62 of *FBNI* in the twins.

of the aortic root. The amblyopia was successfully treated with spectacle correction of high astigmatism. After 1 year, the first-born boy had BCVA of 20 / 25 in the right eye and 20 / 60 in the left eye. The second boy's BCVA was 20 / 40 in the right eye and 20 / 32 in the left eye.

FBNI encodes fibrillin-1, a cysteine-rich secreted glycoprotein that is a vital component of the extracellular matrix and the major structural element in the suspensory ligaments of the lens [1-3]. *FBNI* mutations have been associated with a broad spectrum of phenotypes ranging from single connective tissue manifestations such as isolated EL, to lethal neonatal MFS [1-3]. It is interesting that a heterozygous missense mutation of c.7583G>T (Cys2528Phe) in exon 62, confirmed in our 5-year-old twin boys, was associated with juvenile-onset ocular and cardiovascular manifestations. Mutations in exons 59-65 were reported to be associated with major involvement of the cardiovascular system [5]. Our finding demonstrates the necessity of molecular analysis for *FBNI* gene mutation in patients presenting with isolated EL. Molecular diagnosis enables proper and early identification of affected patients who need adequate follow-up and treatment for prevention of the life-threatening complications of MFS.

Upwardly dislocated lenses, found in all of our cases, must be differentiated from lens coloboma, which represents incomplete lens formation due to failure of the fetal fissure to close completely. In our cases, the lens changes were not accompanied by other ocular colobomatous changes of the eyelid, iris, choroid, or optic disc. Anterior optical coherence tomography may be useful to visualize anterior segment structures. In this case, successful improvement of visual acuity with appropriate spectacles alone shows that appropriate optical correction should be tried first in children with EL. Careful and repeated measurements of phakic or aphakic refraction are necessary to achieve the best possible vision. Surgical procedures should be considered for the prevention of irreversible amblyopia when the dislocated lens edge bisects the pupillary axis or spectacle correction is impossible.

In conclusion, we described monozygotic twin boys presenting initially with juvenile-onset bilateral EL with

disease-causing de-novo missense mutation in the *FBNI* gene. In patients with isolated EL, molecular analysis for *FBNI* gene should be performed for prompt diagnosis and early identification of cardiovascular complications. Furthermore, this study aids in expanding the genotype-phenotype association with respect to *FBNI* mutation in MFS.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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