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Genetic Analysis of a Family with a Novel Type I Fibrillinopathy

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Abstract

Background: This study describes a novel polymorphism in the Fibrillin gene (FBN1) and the associated unique Type I Fibrillinopathy phonotypic variant found in a single family. Clinical data were taken at a single academic institution while blood samples were sent for commercially available sequencing.

Methods: The proband of the study was referred to the authors with ectopia lentis (EL). A careful family history revealed several other family members with zonular instability detected at the time of cataract surgery. A thorough workup for known causes of EL uncovered a novel polymorphism in the FBN1 gene. A pedigree was devised and, medical records and genetic testing was obtained on eight additional family members. Retrospective analysis of clinical information and family history data were combined with prospective genetic analysis of the available cohort family members.

Results: The novel misprint mutation c.730T>C in the FBN1 gene was detected in all three family members with confirmed EL at the time of cataract surgery. In addition, this misprint was detected in 3 of 6 offspring of known carriers who had not yet undergone cataract surgery.

Conclusions: In our analysis of this single family we describe a novel Type I Fibrillinopathy. This phenotypic presentation is unique in that the zonular insufficiency in this family does not manifest until the time of cataract surgery. The presence of this disease entity provides a possible explanation for idiopathic zonular weakness encountered in what is expected to be routine ocular surgery.

Keywords: Genetics; FBN1; Ectopia lentis; Marfan syndrome

Introduction

Fibrillin is a 350 kDa glycoprotein that is a major component of extracellular microfibrils [1]. Fibrillin is encoded on the gene, FBN1, found on chromosome 15q21 [2]. In 1995, Wheatley et al. demonstrated that fibrillin is widely distributed throughout ocular connective tissues including the lens capsule and zonular fibers [3]. Mutations in FBN1 are known to cause Marfan syndrome, an autosomal dominant, multi-system connective tissue disorder [4]. Diagnosis of Marfan syndrome is made using the revised Ghent nosology [5]. In the revised Ghent nosology, Ectopia Lentis is one of the major clinical features of Marfan syndrome that can be used to establish a definitive diagnosis. However, the presence of isolated Ectopia Lentis (EL) with a known mutation in FBN1 is insufficient to establish this diagnosis. These patients, representing about 5% of all adults with known FBN1 mutations, instead are classified as having a Type 1 Fibrillinopathy [6].

At the present time, over 600 novel FBN1 mutations have been reported and registered for Marfan syndrome and related Fibrillinopathies [7]. We report a novel polymorphism in the FBN1 gene (c.730T>C) found in a single family with a somewhat unique phenotypic variant of Type 1 Fibrillinopathy.

Methods

The proband of this study was identified following a referral from an outside institution for surgical management of EL. A careful family history was taken which was remarkable for multiple family members with evidence of zonular instability, most often not detected until the time of cataract surgery. The patient was sent for evaluation by the department of genetics at William Beaumont Hospital. A thorough workup for known causes of EL uncovered a novel polymoprhism in the FBN1 gene. A pedigree was constructed with the help of the patient and a very thorough analysis of the family history (Figure 1). After approval by the Human Investigations Committee at William Beaumont Hospital, medical records and prospective genetic testing was obtained on eight additional family members.

Genotyping was performed using the commercially available DNA diagnostics Lab at Tulane University Health Science Center [8]. Following a careful informed consent process, venous blood samples were taken from six family members. These blood samples were placed on ice and sent via overnight mail to the DNA diagnostics Laboratory. One additional family member obtained genetic testing independently through the same diagnostics laboratory in conjunction with her primary ophthalmologist. Per their established protocol, the laboratory performed a 2-step assay; first amplifying DNA sequences from all 65 exons and exon flanking regions for the FBN1 gene for human fibrillin-1 using 66 specific primer pairs for the polymerase chain reaction (PCR). This was followed by nucleotide sequencing of all PCR products. Individuals participating in genetic testing were all thoroughly questioned regarding history of eye disease as well as other systemic medical issues. They were encouraged to share the results of their genetic testing with their primary care physicians as well as private ophthalmologists.

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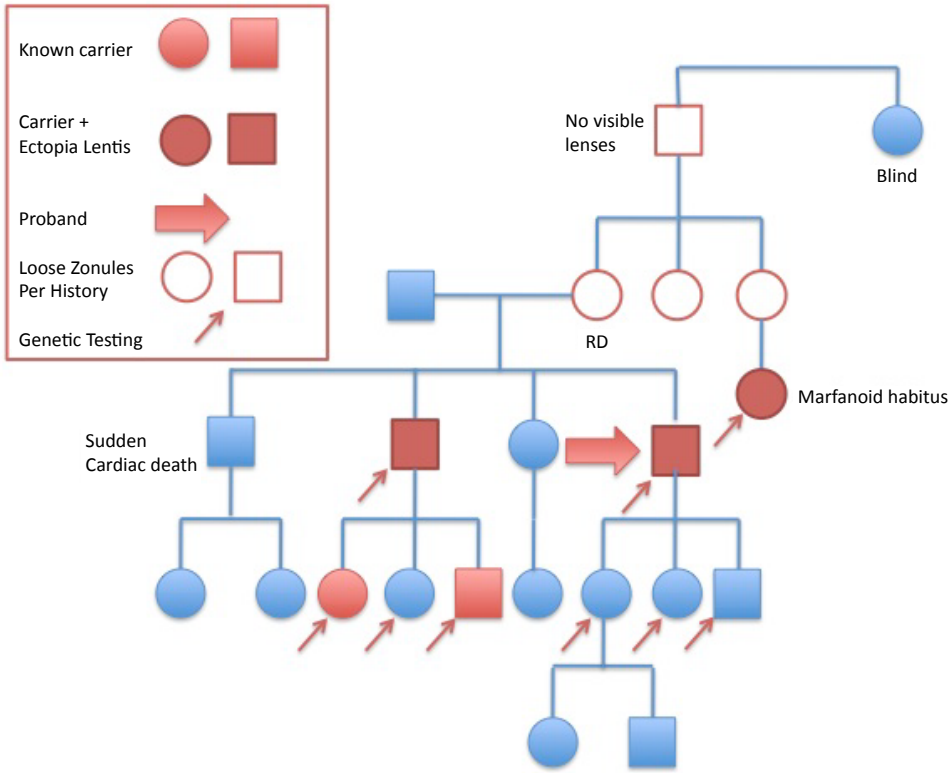

Figure 1: Pedigree of the cohort family.

Results

The misprint mutation c.730T>C was detected on exon 6 of FNB1 in five of the eight family members who obtained genetic testing. This mutation was present in all three family members who were tested and had a positive clinical history of EL at the time of cataract surgery. It was also identified in two younger family members who were yet to develop cataracts. No evidence of zonular insufficiency has been identified in these individuals. The identified mutation results in a change from cysteine to arginine at amino acid position 244. A careful family history performed by the department of genetics at William Beaumont Hospital. This was remarkable for the several conditions known to be associated with Marfan syndrome/Fibrillinopathy (Figure 1). The proband's maternal grandfather had "no visible lenses," as well as glaucoma and his maternal grandmonther was blind from unknown causes. His mother as well as her two sisters had zonular weakness detected at the time of cataract surgery. His mother additionally suffered a detached retina. The proband's eldest passed away from sudden cardiac death but it is unknown if this was or was not aortic dissection. Notably, the only first cousin is the only family member to have a Marfanoid habitus as well as zonular deficiency and tested positive for the familial mutation. None of the younger generation are Marfanoid on appearance of have been diagnosed with any conditions known to be associated with Marfan syndrome.

Discussion

In our genotypic and phenotypic analysis of this single family, we describe a novel misprint mutation in FBN1. This misprint mutation involves the loss of a cysteine residue from the peptide structure of the fibrillin glycoprotein. The resulting phenotypic manifestation of EL would be predicted by Faivre et al. who in 2007 analyzed 1013 probands with Marfan-related phenotypes. They showed that a higher probability of EL was found in patients with a missense mutation substituting or producing a cysteine, when compared with other missense mutations [9]. Disulfide binding between cysteine residues in fibrillin-1 is an extremely common and highly preserved motif within the structure of the glycoprotein [10]. It has been suggested and reasonably inferred that cysteine localization and disulfide bonding play a crucial role in the function of fibrillin as a structural element of the suspensory ligaments of the lens [9].

Because none of the family members in this study fulfill the Ghent criteria for Marfan syndrome, the diagnosis associated with this genetic presentation is Type 1 Fibrillinopathy. This phenotypic presentation is somewhat unique in that the vast majority of family members do not have any clinical evidence of zonular insufficiency until the time of cataract surgery. This has predictably led to several cataract extraction operations fraught with complications performed on different family members prior to identification of the underlying pathology. This unique phenotypic twist has not previously been reported in the literature. The presence of this manifestation of Type 1 Fibrillinopathy provides a possible explanation for cases of idiopathic zonular weakness/insufficiency encountered in what is expected to be routine ocular surgery.

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