Letter to the Editor

Homozygosity for a \textit{FBN1} missense mutation causes a severe Marfan syndrome phenotype

To the Editor:

Marfan syndrome (OMIM 154700) is a connective tissue disorder involving the cardiovascular, ocular, and skeletal systems caused by heterozygous mutations in \textit{FBN1}. It is autosomal dominant with clinical variability partially explained by allelic heterogeneity (1). Individuals with biallelic \textit{FBN1} mutations provide insight into molecular mechanisms and clinical care of Marfan syndrome. We report a woman with severe Marfan syndrome homozygous for a previously unreported \textit{FBN1} missense mutation.

The proband is a Mexican-American woman born from a consanguineous union ($F = 0.25$). She was thin with a pectus carinatum, scoliosis, arachnodactyly, dislocated lenses, mitral valve prolapse, aortic dilatation, dural ectasias, and anterior sacral meningocele. Brain imaging revealed low lying cerebellar tonsils and moderate hydrocephalus. Her scoliosis worsened, her ocular lenses were extracted, she developed urethral prolapse and neurogenic bladder, and an eye was enucleated for glaucoma. She had mild cognitive impairment.

At 18 years of age, her height was 155 cm (10th percentile), span to height ratio was 1.05, and she had a narrow, asymmetric face, dolichocephaly, hypertelorism with an interpupillary distance of 6.4 cm (97th percentile), down-slanting palpebral fissures, kyphoscoliosis, narrow palate, positive wrist and thumb signs, arachnodactyly with middle finger length of 8.4 cm (97th percentile), and mild joint contractures (Fig. 1). Clinical sequencing of \textit{FBN1} revealed homozygosity for a single base pair substitution, c.7726C>T, predicting p.Arg2576Cys (transcript NM_000138.4).

She became pregnant at 20 years of age. Her aortic root was 4.3 cm at 14 weeks gestation. At 30 weeks she developed chest pain and dyspnea. Computerized tomography scan revealed new aortic insufficiency and dilatation. Cesarean section and aortic root repair of a type A dissection were performed.

Her son was small for gestational age but healthy. He had dolichocephaly, down-slanting palpebral fissures, midface hypoplasia, high narrow palate, and mild right knee contracture. Ophthalmology exam and echocardiogram were normal. Mutation testing has not been performed, but heterozygosity has been assumed.

The proband’s mother lacks examination findings of Marfan syndrome and had a normal optometry examination. Mutation analysis confirmed her to be heterozygous for c.7726C>T. The proband’s father had a cardiac event attributed to drug abuse although aortic dissection cannot be excluded. He reportedly had no other features of Marfan syndrome, but was unavailable for the examination.

Patients from five families have been reported with confirmed homozygosity or compound heterozygosity for \textit{FBN1} mutations (Table 1) (2–5). In each case, the individual with two \textit{FBN1} mutations exhibited more severe manifestations than their heterozygous family members. In addition, heterozygous parents in several families lacked or had only mild Marfan syndrome manifestations.

The proband’s mutation has not been reported in the medical literature but was seen in another patient tested at the same clinical laboratory. It is predicted to be disease causing by Mutation Taster ($p = 0.999$) and probably damaging by POLYPHEN-2.

Fig. 1. The proband at 18 years of age, demonstrating hypertelorism, down-slanting palpebral fissures, long and slender extremities (a), kyphoscoliosis (b), facial asymmetry and narrow palate (c), and arachnodactyly (d).
The fibrillin-1 protein is composed of repeating epidermal growth factor (EGF)-like modules that contain conserved cysteine residues forming disulfide bonds important for secondary structure. Our patient’s mutation substitutes a seventh cysteine into an EGF-like module and meets criteria for a causal mutation in fibrillin-1 (1). However, the mutation has apparently not resulted in Marfan syndrome in the proband’s parents. There is support for a ‘threshold’ effect in animal models of Marfan syndrome and hypomorphic alleles may not disturb protein function sufficiently to exert phenotypic effects (6).

Our patient exhibited several findings that were not considered typical for Marfan syndrome including: mild cognitive impairment, hypertelorism and moderate hydrocephalus. These features may be the result of homozygosity for other uncharacterized alleles in our patient because of the parental consanguinity.

In summary, we have reported the clinical and molecular findings in a patient with severe Marfan syndrome due to a previously unreported, homozygous missense mutation in the FBN1 gene. This case demonstrates the importance of establishing a molecular diagnosis, particularly in patients with a severe phenotype.

Acknowledgements

We are very grateful to the family for allowing us to prepare this report.

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Army, nor the US Government.

Table 1. Summary of patients with homozygous or compound heterozygous mutations in FBN1

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<th>SS</th>
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References


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Ao, enlarged aortic diameter or aortic dissection; EL, ectopia lentis; M, individual manifesting Marfan syndrome as defined by the reporting authors; SS, systemic score as defined in the revised Ghent criteria [Loeys et al. (1)]; U, unknown.

Patients 5 and 6 are siblings.

Patients 7 and 8 are siblings.

(http://genetics.bwh.harvard.edu/pph2/). The arginine residue is conserved down to the pufferfish, Fugu rubripes. It was not present in the Exome Variant Server (http://evs.gs.washington.edu/EVS/) or the database of FBN1 mutations (http://umd.be/FBN1/), but was recorded as rs147195031 in the Database of Single Nucleotide Polymorphisms (dbSNP; http://www.ncbi.nlm.nih.gov/projects/SNP/), with an estimated heterozygosity score of 0 ± 0.015.