Weill-Marchesani-like syndrome caused by an *FBN1* mutation with low-penetration

Guo-Yuan Yang, Xi Huang, Bing-Jie Chen, Zhu-Ping Xu

Department of Ophthalmology, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China.

Weill-Marchesani syndrome (WMS) is a rare connective tissue disorder characterized by brachydactyly, short stature, joint stiffness, cardiovascular abnormalities, and eye anomalies including microspherophakia, cataracts, ectopia lentis, myopia, and secondary glaucoma. Patients with incomplete WMS signs are diagnosed with Weill-Marchesani-like syndrome (WMS-like). To date, both autosomal dominant (AD) and autosomal recessive (AR) inheritance modes have been reported for WMS. Genetic heterogeneity in WMS suggests a connection between these genes. AR and AD WMS cannot be distinguished clearly by clinical findings alone.[1] Furthermore, inter-familial as well as intra-familial clinical variability due to different fibrillin-1 gene (*FBN1*) mutations also exists.[2,3] The clinical heterogeneity and incomplete penetrance of *FBN1* gene mutations can usually present a diagnostic dilemma for WMS. Here, we report the genetic analysis and clinical observations of a Chinese family affected with AD WMS-like due to a heterozygous mutation in *FBN1* using whole-exome sequencing. This study was approved by the Research Ethics Committee of the Hospital Authority of West China Hospital, Sichuan University, and adhered to the tenets of the Declaration of Helsinki and the association for research in vision and ophthalmology statement on human subjects. Written informed consent was obtained from the family for publication of this study and any accompanying images.

One pedigree [Figure 1A] with three generations suspected of having WMS-like was recruited. Detailed medical and family histories were obtained. Clinical evaluations of each family member were performed on all members. Whole exome sequencing (WES) was performed on II-1 to identify the genetic cause in the family. Cosegregation of the mutation was determined with Sanger sequencing on other family members.

The proband was a 68-year-old man (I-1). His visual acuity was 20/500 in the right eye (OD) and 20/200 in the left eye (OS). The real refractive status of this man was not obtained because his lenses were downward displaced [Figure 1B]. However, he had normal axial length (23.21 mm in OD and 23.23 mm in OS) and corneal refractive power. Increased intraocular pressure was found in OD (30 mmHg), while the value was normal in OS (17.9 mmHg). Though upward dislocation of the lens made it impossible to measure its thickness, no spherophakia was found by slit lamp microscopy when the pupil was dilated. He had a short stature (163 cm) with typical brachydactyly [Figure 1C]. No joint stiffness or cardiac abnormalities were found. Based on the combined characteristic of ectopia lentis, brachydactyly, and short stature, he was diagnosed with WMS-like. His daughter (II-1), who was 47-year-old, also was affected. Slit lamp microscopy after pupil dilation found she had upward lens luxation and coloboma in the lower part of the lens [Figure 1D]. Her enlarged axial length (28.71 mm in OD and 25.96 mm in OS) was the cause of her high myopia. Her intraocular pressure was normal (15 mmHg in OD and 13 mmHg in OS). Brachydactyly and a short stature (150 cm) were also very obvious.

This woman (II-1) had three children. No abnormality was found in the elder children (III-1 and III-2). Their heights were 171 and 158 cm, respectively. The third child (III-3) was a 17-year-old boy. Examination revealed mild and partial opacity on the posterior part of the lens [Figure 1E]. However, both slit lamp microscopy and ultrasound biomicroscopy found no lens luxation. His lens thickness was 3.31 and 3.30 mm for the right and left eye, respectively. The axial length was 24.04 mm for OD and 24.56 mm for OS. The real refractive status of this man was not obtained because his lenses were downward displaced [Figure 1B].

Correspondence to: Prof. Zhu-Ping Xu, Department of Ophthalmology, West China Hospital, Sichuan University, No. 37 Guo Xue Alley, Chengdu, Sichuan 610041, China

E-Mail: xuzp@hotmail.com

Copyright © 2021 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2021;134(11) Received: 15-09-2020 Edited by: Li-Shao Guo
WES analysis on II-1 found heterozygous mutations found that an intronic mutation (c.1327+1G>A) in FBN1 gene was suspected as the causative agent. None of the other WMS and WMS-like syndrome genes (ADAMTS10, LTBP2, and ADAMTS17) was mutated in II-1. The other two affected members, I-1 and III-3, shared the same heterozygous mutation in this site with II-1. The three unaffected family members (II-2, III-1, and III-2) were homozygous for the wild-type allele (GG). Thus, the heterozygous mutation in FBN1 was identified as the cause of this WMS family. The genotypic results of all the family members are presented in Figure 1F. As shown in the University of California, Santa Cruz (UCSC) gene database, the intronic mutation (c.1327+1G>A) in FBN1 (transcript ID NM_000138.5) is predicted to abolish a splice donor site. According to the online Mutation Taster analysis (http://www.mutationtaster.org/), the mutation taster score for this mutation is 1, which means this sequence is highly conserved.

FBN1 encodes fibrillin-1, which is a large glycoprotein (320,000). It forms “microfibrils” with uniform diameters (10–12 nm) that are ubiquitously distributed in all connective tissues. Therefore, mutations of the FBN1 gene could cause structural or functional abnormalities in connective tissue.

In this pedigree, an intronic mutation (c.1327+1G>A) in FBN1 was identified as the causative mutation. This mutation is within 5-bp of a splicing junction, which can cause incorrect exon and intron recognition and result in an aberrant transcript of the mutated gene. This mutation was once reported in a white British individual with isolated ectopia lentis by Chandra et al in 2012. The patient in that study only showed isolated downward lens subluxation with no musculoskeletal or cardiovascular findings. In our research, pedigree member I-1 also showed downward lens subluxation. However, a short stature (163 cm) and brachydactyly were also present in this patient. Clinical heterogeneity was very obvious in this family. The daughter (II-1) of the proband, who carried the same mutation as her father, showed coloboma of both lenses rather than downward subluxation. On the other hand, the daughter had much greater axial length (28.71 mm in OD and 25.96 mm in OS) than her father (23.21 mm in OD and 23.23 mm in OS). However, none of these clinical characteristics

Figure 1: (A) Pedigree diagram of the family. (Solid black pattern means affected member.) (B) Downward dislocation of the lens in I-1. (C) Brachydactyly in I-1. (D) Upward lens luxation and coloboma in the lower part of the lens in II-1. (E) Mild opacity on the posterior part of the lens in III-1 (arrow shows the opacity). (F) Sequencing results of each member in this family. (I-1, II-1, and III-3 showed heterozygote mutant of C>T. II-2, III-1, and III-2 showed wide type of CC).
passed onto III-3. Though III-3 inherited this mutation (c.1327+1G>A) in FBN1, he was barely affected except for mild congenital cataracts. His mild phenotypic presentation and good corrected visual acuity may occlude the true diagnosis. As he is only 17 years now, late onset of the phenotype may present in the future.

In summary, we found a WMS-like pedigree caused by an FBN1 mutation (c.1327+1G>A), which was previously reported to be associated with isolated ectopia lentis. But our study increased the scope of the clinical heterogeneity of this FBN1 mutation and revealed the importance of intronic sequence analysis.

**Acknowledgements**

The authors are thankful to this family for their participation in this study.

**Conflicts of interest**

None.

**References**