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A *FBN1* mutation association with different phenotypes of Marfan syndrome in a Chinese family

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ABSTRACT

Background: Previous studies demonstrated that patients with different *FBN1* mutations often present more considerable phenotypic variation compared to different members of the related family carrying a same mutation. The purpose of our study was to identify pathogenic mutation and provide more information about genotype–phenotypic correlations in a large Chinese family with Marfan syndrome.
Methods: 15 related family members from a Chinese 4-generation pedigree with Marfan syndrome underwent physical, ophthalmologic, radiological and cardiovascular examinations. The propositus has De Bakey III aortic dissection and didn't fulfill the revised Ghent criteria for Marfan syndrome. Nine family members have ectopia lentis and their echocardiogram was normal. Five other family members have no evidence of Marfan syndrome. Genomic DNA was isolated from blood leukocytes. The exome sequencing was employed on the propositus, then the Sanger sequencing was conducted for mutation verification in other 14 participants of this family.
Results: The causative mutation in *FBN1* discovered in the propositus was a known heterozygous missense mutation, c.1633T>G (p.R545C), in exon 14 (NM 000138). This same mutation was also identified in all 9 ectopia lentis patients and one unaffected 8-year-old girl. However, the same mutation was not discovered in other 4 unaffected family members.
Conclusions: Our data enhance the information of genotype–phenotype correlation owing to *FBN1* mutations. To our current knowledge, we firstly reported that the same *FBN1* mutation, c. 1633C>T (Arg545Cys), was detected simultaneously in three different cardinal phenotypes (ectopia lentis, aortic dissection and unaffected) within one family. The unaffected girl with *FBN1* mutation may presumably represent a rare case of nonpenetrance.

1. Introduction

Marfan syndrome (MFS) is an autosomal dominant genetic disorder of connective tissue, mainly related to cardiovascular, skeletal and ocular systems, followed by lung, skin and central nervous system, the incidence rate is about 1/5000–1/10000 and 25% to 30% of MFS patients were sporadic cases [1]. Fibrillin-1 (*FBN1*) gene plays important roles in the pathogenesis of MFS.

FBN1, consisting of 65 exons, encodes a secreted 350-kDa glycoprotein that play a role as a structural component of calcium-binding microfibrils [2]. *FBN1* contains 47 epidermal growth factor (EGF)-like domain modules (among them 43 cbEGF-like modules, and 4 non-cbEGF-like modules) [3]. Since 1991 the first mutation of *FBN1* associated with MFS was confirmed [4], more than 1200 mutations have been detected and most mutations located in cbEGF-like domains [5].

Mutations in *FBN1* have been identified in a series of fibrillinopathies, including MFS [4], isolated ectopia lentis (EL) [6,7], geleophysic andacrophysic dysplasia [8], MASS (mitral valve, aorta, skeleton, and skin) syndrome [9], Weill–Marchesani syndrome, Shprintzen–Goldberg syndrome, and familial ascending aortic aneurysm and aortic dissection [10–12].

To date, the specific genotype–phenotype correlations have not been established between identified mutations of *FBN1* and MFS. The accurate diagnosis of MFS is difficult because of the age-related features of some clinical symptoms as well as variable phenotype of MFS [13]. Given the very complex genotype–phenotype correlation of *FBN1* mutation between families and even within the same family, more research is needed to refine the relevance.

Previous studies demonstrated that patients with different *FBN1* mutations often present more considerable phenotypic variation

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compared to different members of the related family carrying a same mutation. In our study, we detected a mutation of *FBN1* in 15 related family members from a 4-generation pedigree associated with quite different clinical features.

2. Materials and methods

2.1. Patients and clinical data

A 4-generation pedigree (Fig. 1) with Marfan syndrome was recruited from the First Affiliated Hospital of Zhengzhou University (Zhengzhou, Henan, China). All the patients of our study were diagnosed in the eye center of the First Affiliated Hospital of Zhengzhou University. This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Zhengzhou University. Family history, medical and personal history of each participant were cautiously reviewed. All participants included in the study underwent physical, ophthalmologic, radiological and cardiovascular examinations. All the MFS patients were diagnosed according to revised Ghent criteria.

Clinical data and peripheral blood were collected from 15 related family members (nine patients with predominant EL and their echocardiogram were normal: II:7, III:1, III:2, III:4, III:6, III:9, and IV:1, IV:2, IV:5, the propositus with De Bakey III aortic dissection, flatfoot and didn't fulfill the revised Ghent criteria for Marfan syndrome: II:4, five unaffected family members have no evidence of Marfan syndrome: II:5, III:3, III:5, III:7, and IV:3, IV:4).

2.2. Molecular analysis

To identify the pathogenic mutation for the phenotypes presented in this family, the exome sequencing was performed as custom service (Genergy Biotech, Shanghai, China) on proband. Sanger sequencing was conducted for verification of candidate mutation in all participants of this family.

Briefly, genomic DNA was isolated from blood leukocytes with QIAamp DNA Blood Kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. The 20 μL PCR mixtures included 10 ng genomic DNA, 10 pmol of each primer, 0.2 mM dNTP, 2.5 mM $MgCl_2$ and 0.25 U Taq DNA polymerase. All of the reagents were purchased from Takara (Takara, Tokyo, Japan). The sequences of the PCR primer for Sanger sequencing is *FBN1* F5′-CAGACTTCGGATTTAAGGAGTCTTAT-3′; *FBN1* R5′-ATGGCAAGCTCTCCTAGCAT-3′. All reactions had an initial denaturation step of 3 min at 94 °C, followed by 35 cycles of 94 °C for 30 s denaturation, 57 °C for 30 s annealing and 72 °C for 1 min, and a final elongation step at 72 °C for 10 min on a Gene Amp PCR system 9700 (Applied Biosystems, Foster City, CA). The length of the PCR product was 597 bp, exon 14 was located in the middle of the PCR product. The sequences were analyzed by using an ABI PRISM model 3100 DNA Sequencer (PE Applied Biosystems, Perkin-Elmer). Nucleotide numbers are found on the mRNA isoform NM_000138 (Correlagen Diagnostics, Inc., Waltham, MA).

3. Results

3.1. Clinical findings of the pedigree

Nine of the 26 members in this 4-generation family were diagnosed as having MFS. Except for partial flat foot, no skeletal system abnormalities, such as long limbs and arachnodactyly were observed in all patients (Table 1). Except the propositus, other nine patients showed bilateral lenses dislocation as a predominant clinical manifestation (Fig. 2). Only one patient in this study displayed retinal detachment after orthopedic surgery. In addition, cardiovascular system abnormalities were absent in the nine EL patients by echocardiogram (Fig. 3). However, the propositus displayed thoracic aortic dissection by Computed Tomography (CT), hypertension, without EL.

3.2. Mutation analysis

After candidate genes were screened, a known heterozygous missense mutation, c.1633T>G (p.R545C), in exon 14 of *FBN1* (NM 000138) was observed in the proband and subsequently confirmed in all 9 EL patients and one unaffected 8-year-old girl (Fig. 4). This mutation was not detected in other 4 family members with no diagnostic features of MFS. The mutation is co-segregated with the disorder in the family and is closely associated with phenotypes of the Chinese family. The quite different phenotype of the mutation is a striking feature in this family and there is evidence for genetic modifiers affecting the *FBN1* mutant phenotype.

4. Discussion

Marfan syndrome is characterized by a complex clinical manifestations of multiple organ systems, usually involving the ocular, skeletal, and cardiovascular systems. The EL and aortic aneurysm are issues of particular concern to clinical doctors [14]. For MFS, the most life-threatening manifestation are cardiovascular complications, including aortic root aneurysm and aortic dissection [15]. About 80% of MFS patients were diagnosed with Ectopia lentis [6]. Even in the same family, MFS patients' phenotypes are very diverse and complex. In our study, there are three quite different phenotypes within p.R545C carriers in the family, including nine patients of ectopia lentis, one patient of aortic dissection and one unaffected.

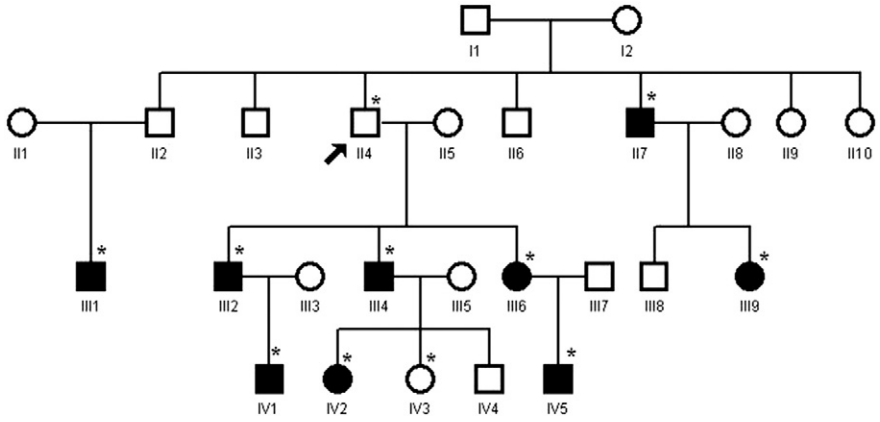

Fig. 1. Pedigree of the Chinese family with MFS. Squares indicate males and circles indicate females. The filled symbols represent the patients. Arrow indicates the propositus. * show heterozygous mutation present.