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·论著·

1个先天性晶状体脱位家系的基因突变位点

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[摘　要]　**目的：**分析1个先天性晶状体脱位家系原晶状体原纤维蛋白1(fibrillin-1，FBN1)基因突变的情况。**方法：**对1个单纯性晶状体脱位家系中的25位家族成员(包括5名患者)进行眼睛及全身临床检查。从外周静脉血抽提DNA进行PCR扩增反应，并对FBN1全部65个外显子进行测序分析。**结果：**在5位患者的核苷酸序列中均发现FBN1基因c.1759胸腺嘧啶突变为胞嘧啶。这个点突变导致FBN1蛋白第587号的半胱氨酸被精氨酸代替。**结论：**c.1759胸腺嘧啶突变是导致患者晶状体脱位的FBN1基因突变位点，该结论进一步丰富了马凡综合征(Marfan syndrome，MFS)基因突变库，并有助于该家系中相关亲属的遗传咨询。

[关键词]　先天性晶状体脱位；FBN1基因；悬韧带

A gene mutation locus in a family with inherited ectopia lentis

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Abstract　**Objective:** To identify the genetic defects of a family with inherited ectopia lentis. **Methods:** Among 25 family members, 5 patients underwent general physical and full ophthalmic examinations. Genomic DNA was extracted from leukocytes of venous blood of every family member. Polymerase chain reaction (PCR) amplification and Sanger's sequencing of all exons of fibrillin-1 (FBN1) gene were analyzed. **Results:** A C>T mutation was identified at FBN1 nucleotide position c.1759. This mutation led to substitution of Cysteine for Arginine at condon 587. No FBN1 gene defects were found in any unaffected family member. **Conclusion:** We identified a mutation in FBN1. Our result expanded the mutation spectrum of FBN1 and also provided genetic counseling for the family relatives.

Keywords　inherited ectopia lentis; fibrillin-1 gene; zonular fiber

先天性晶状体脱位(ectopia lentis，EL)是一种因晶状体悬韧带发育异常而导致晶状体异位的疾病[1]。EL可单独发生，也可是马凡综合征(Marfan syndrome，MFS)的一个表现[2-4]。

在EL致病基因的研究[5-10]中，晶状体原纤维蛋白1(fibrillin-1，FBN1)基因突变被多次证实。

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FBN1基因位于15号染色体长臂21，长235 kb。FBN1基因编码的原纤维蛋白-1是10~12 nm微纤维的主要成分，而晶状体悬韧带主要由这种纤维结构构成[11-12]。FBN1蛋白主要包括3个重复模体：第1个是半胱氨酸残基富集的EGF样结构域，第2个是含有8个半胱氨酸残基的TGF-β1样结构域，第3个模体是由前2个结构域混合组成。FBN1基因突变导致的疾病可分为短指-晶状体脱位综合征(Marchesani syndrome，MASS)、单纯性晶状体脱位、单纯性骨骼改变的MFS和胸主动脉瘤[13]。FBN1基因突变在多个外显子中均有报道，而涉及到半胱氨酸改变时，常伴有晶状体半脱位表现[4]。

本研究收集到1个单纯性晶状体脱位家系，经突变基因测序分析发现患者均携带FBN1基因c.1759 T>C突变，现报告如下。

1 对象与方法

1.1 对象

本研究收集到1个包括4代人的先天性晶状体脱位家系。该家系共有27位成员，其中有5位表现出双眼晶状体脱位。家庭成员均接受了眼部和全身检查。本研究严格遵守赫尔辛基宣言，家系成员均知情同意。

1.2 DNA 测序

采用Genomic DNA purification kit(美国Promega公司)提取全血基因组DNA。Primer 5.0软件设计FBN1基因全部65个外显子，引物由上海生工生物公司合成。通过PCR反应分别扩增FBN1基因的每个外显子。扩增的PCR产物通过ABI PRISM3.0 Genetic analyzer(上海生工生物公司)测序。使用DNAstar软件分析测序结果。

2 结果

2.1 临床结果

该家系共发现5位EL患者(图1)。另据家系成员描述，I:2从小视力差，但多年前已去世，没有相关临床检查记录。5位患者均表现为双眼晶状体脱位(图2A)，心血管系统及骨骼系统没有相关症状表现(表1)。其余家系成员中未见晶状体脱位(图2B)。

2.2 基因测序结果

基因测序分析结果显示：EL患者FBN1基因15号外显子上均发生点突变。cDNA第1759碱基发生杂合性突变：c.1759 T>C，导致第5个EGF样结构域中半胱氨酸残基变成精氨酸残基(图2C)。而家系中正常个体并未检测到类似的改变(图2D)。

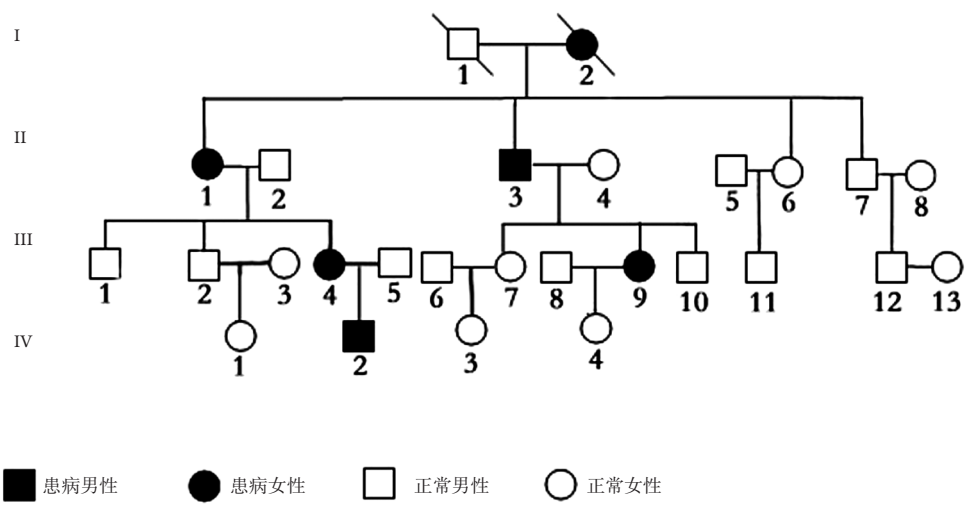

图1 家系图

Figure 1 Pedigree of the family

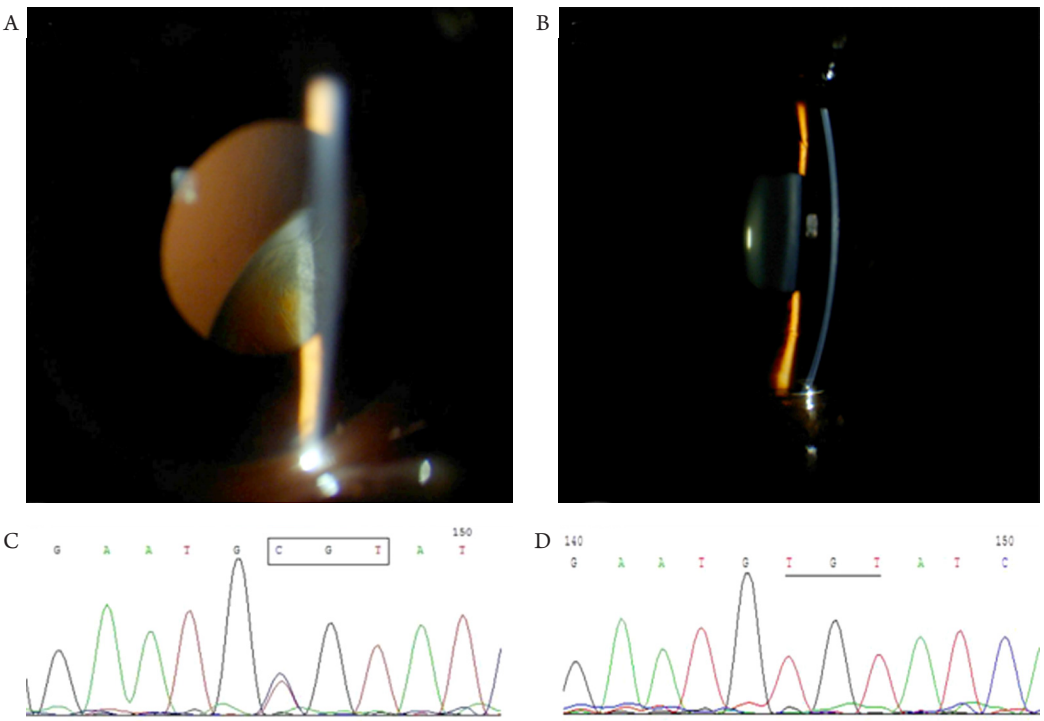

图2 晶状体脱位表现及测序结果

Figure 2 Slit-lamp examination and sequencing results

(A)患者II:1：眼前节裂隙灯检查示晶状体向鼻下方移位；(B)未受累家属II:6；(C)患者II:1基因测序可见杂峰；(D)正常家属II:6的基因测序结果。

(A) Slit-lamp result of patient II:1 shows the lens dislocation; (B) Slit-lamp examination result of an unaffected family member II:6; (C) DNA sequence result shows a heterozygous T>C transversion in patient II:1; (D) Normal sequence result of unaffected family member II:6.

表1 家系患者临床检查结果

Table 1 Baseline data of the patients in the family

参数	患者				
	II:1	II:3	III:4	III:9	IV:2
年龄/岁	69	66	54	44	23
性别	女	男	女	女	男
晶状体脱位	+	+	+	+	+
近视	+	+	+	+	+
角膜病变	–	–	–	–	–
斜视	–	–	–	–	–
青光眼	–	–	–	–	–
视网膜脱离	–	–	–	–	–
身高/cm	158	170	157	168	163
臂展/cm	157	172	157	169	165
臂展/身高(正常<1.5)	0.99	1.01	1	1.01	1.01
心血管系统	–	–	–	–	–
骨骼系统	–	–	–	–	–

3 讨论

本研究检查了1个先天性晶状体脱位家系并发现有5位患者携带了FBN1基因点突变c.1759，这个点突变导致了587号半胱氨酸残基被精氨酸残基代替。保守的半胱氨酸残基被替代后，可能会导致第5个EGF样结构域错误折叠。

自从1991年第1次发现FBN1基因突出与MFS有关，至今已有超过1 300个FBN1基因突变被报道[10,14]。基因型改变与表型改变逐渐建立起对应联系，2010年修订的Ghent疾病分类学标准[15]明确了晶状体脱位在MFS诊断中的重要性，以及致病基因FBN1突变检测在诊断中的作用。本研究回顾了关于FBN1基因半胱氨酸残基发生改变后的基因型-表型关系。当半胱氨酸发生改变后，发生晶状体脱位的概率显著增加[16]；而突变没有涉及半胱氨酸残基时，发生晶状体脱位的概率显著降低[17]。提示半胱氨酸残基的改变和晶状体脱位紧密相关。

原纤维蛋白聚合形成10~12 nm的微纤维，后者再进一步形成弹性纤维，是晶状体悬韧带的主要成分[18-19]。弹性纤维在机体中许多有弹力的组织中发挥重要作用，如大动脉管壁、肺组织、皮肤等。在进行裂隙灯检查时，可发现悬韧带一端连接在晶体上，而另一端游离在房水中。由此推测该基因位点突变主要导致悬韧带微纤维蛋白与睫状体连接异常，进而导致晶状体脱位，但并不影响心血管及骨骼系统。

本研究中5名患者携带一致的FBN1基因突变，临床表现一致。致病基因明确，为家系成员的早期诊断、预后预测及遗传咨询提供了有力的分子依据。

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