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·基础研究·

常染色体显性遗传性先天性白内障的基因突变研究*

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摘要 目的:从收集的两个来自中国的常染色体显性遗传性的先天性核性白内障家系中,确定与其白内障致病相关的基因遗传突变位点,以明确致病原因。**方法:**首先通过记录详细的家系成员患病史、白内障手术史和其他临床资料,通过眼科常用的视力、眼压、裂隙灯检查以及眼底检查,排除家系成员的其他眼科疾病。并在取得家系成员的知情同意下,从家系成员的外周血白细胞中提取基因组 DNA,最后通过对已知的先天性白内障候选基因进行测序,以筛选出致病的突变位点。并通过软件分析突变位点的高保守性。**结果:**通过眼科常用的裂隙灯仪器检查,两个家系的先天性白内障临床表型均被确定为核性白内障类型。通过对先天性白内障就候选基因直接测序,发现了在晶状体蛋白γD 基因(CRYGD)中,核苷酸位置 c.193 处,发现了一个 G>A 的突变。该突变与两个家系中所有患病的个体共分离,未患病的成员和 120 名无关对照成员中未观察到该突变。共保守分析表明,一个高度保守的区域序列位于 CRYGD 的第 65 位密码子（P.65）。**结论:** 在两个常染色体显性遗传性先天性核性白内障的中国家系中发现了 CRYGD 基因的一个新突变 D65N,这是第一次在 CRYGD 基因的第 193 位核苷酸处,发现突变 G→A。导致了第 65 位密码子的天冬氨酸(D)突变为天冬酰胺(N),这些结果提供了强有力的证据,证明了晶状体蛋白γD 基因(CRYGD)是先天性白内障的致病基因,并与核性的先天性白内障临床表型高度相关。

关键词:常染色体显性遗传;先天性白内障;基因突变

中图分类号:R-33;R776.1 **文献标识码:**A **文章编号:**1673-6273(2023)10-1801-08

Study on Gene Mutation of Autosomal Dominant Congenital Cataract*

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ABSTRACT Objective: To identify the genetic mutation sites related to the pathogenesis of cataract from two families with autosomal dominant congenital nuclear cataract from China. **Methods:** First of all, the family members' disease history, cataract surgery history and other clinical data were recorded in detail, and other ophthalmic diseases of the family members were excluded through common ophthalmic examinations such as vision, intraocular pressure, slit lamp and fundus examination. With the informed consent of the family members, the genomic DNA was extracted from the peripheral blood leukocytes of the family members, and finally the known candidate genes for congenital cataract were sequenced to screen out the pathogenic mutation sites. The high conservatism of mutation sites was analyzed by software. **Results:** The clinical phenotype of congenital cataract in the two families was determined as nuclear cataract by the slit lamp instrument commonly used in ophthalmology. Through direct sequencing of candidate genes for congenital cataract, it was found that crystallin γ D gene (CRYGD), a mutation of G>A was found at the nucleotide position c.193. The mutation was isolated from all diseased individuals in the two families. The mutation was not observed in the non-diseased members and 120 unrelated control members. Co-conservative analysis showed that a highly conserved region sequence was located at codon 65 (P.65) of CRYGD. **Conclusion:** A new mutation D65N of CRYGD gene was found in two Chinese families with autosomal dominant congenital nuclear cataract. This is the first time that the mutation G → A was found at the 193th nucleotide of CRYGD gene. This results in the mutation of aspartic acid (D) at codon 65 to asparagine (N). These results provide strong evidence that crystallin γ D gene (CRYGD) is the pathogenic gene of congenital cataract, and is highly correlated with the clinical phenotype of nuclear congenital cataract.

Key words: Autosomal dominant inheritance; Congenital cataract; Gene mutation

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前言

先天性白内障是世界上儿童失明的主要原因之一。发病率为 0.6/10000-6/10000[1]。白内障可以单独发生，也可以与大量不同的代谢相关疾病或遗传综合征相关。发病机制复杂，约 1/3 与遗传有关。大多数先天性白内障是单基因疾病。有三种遗传模式。常染色体显性遗传是最常见的先天性白内障遗传模式[2]。但常染色体隐性或性染色体 X 连锁遗传的方式也有报道[3]。先天性白内障的临床表现不同，分类更困难。根据晶状体的混浊位置，同时为了反映潜在的基因型，可将其分为：核型、板层型、皮质型、极性型、缝合型、粉状型、蓝绿色型、珊瑚型、全晶状体型和其他次要亚型[4]。

到目前为止，已鉴定出 19 个基因与遗传性白内障相关[5]。包括五组：(1)晶体蛋白基因(CRYAA、CRYAB、CRYBA1/A3、CRYBA、CRYBB1、CRYBB2、CRYBB3、CRYGC、CRYGD、CRYGS)，约一半来自该基因的突变，编码晶状体蛋白。(2) MIP、GJA3 和 GJA8，编码膜转运蛋白。(3) BFSP1，BSFP2，编码细胞骨架蛋白。(4) PITX3、HSF4 和 MAF，编码转录因子。(5) Lim2，编码阿伦内膜蛋白[5]。

我们在两个中国家系中应用了对已知的功能性的候选先天性白内障致病基因进行检测。一个 CRYGD 基因中 G→A 的突变(c193.G→A)，被确定为该家系中先天性白内障的致病原因。这是第一例与 CRYGD 基因 D65N 突变相关的先天性核性白内障表型；它证明了先天性白内障突变基因的可能作用机制。

1 资料与方法

1.1 临床资料

(1)家系 A：一个有先天性白内障病史的四代中国家系，来自安徽省，共 15 名成员，包括 7 名患病的个体，8 名未患病的个体(图 1)，白内障的临床表型是核型。

(2) 家系 B：一个五代先天性白内障家系，来自中国河南省，包括 26 个成员，10 个患病个体，16 个未患病个体，见图 2，表型为核型和皮质混浊。

这两个家系都是从中国北京首都医科大学附属北京安贞医院收集的。研究方案遵循赫尔辛基宣言的原则。这项研究获得了首都医科大学伦理委员会的批准。所有家系参与者都获得了知情同意。通过采访家系成员，记录了详细的家系病史。所有参与的成员都接受了眼科检查，包括视力、裂隙灯检查、眼压测量、超声检查和瞳孔扩张的眼底检查。进行了眼前节照相，以记录患者白内障的表型。北京安贞医院眼科门诊部还收集了 120 名无先天性白内障遗传家族史的正常对照受试者。他们作为白内障家系的对照研究对象接受了完整的眼科检查，除轻度近视和老年性白内障外，没有其他眼部疾病。

1.2 基因组 DNA 制备

采集 200 μL 外周血，来自参与研究的家系成员。使用 QIAamp 血液试剂盒，从血液中提取基因组 DNA。

1.3 突变分析

我们对功能性候选基因进行了测序，包括 CRYAA(GenBank NM_000394)、CRYAB(GenBank NM_001885)、CRYBA1(GenBank NM_005208)、CRYBB1 (GenBank NM _001887)、CRYB2(GenBank N M00496)、CRYGC(GenBank M _020989)、CRYGD(GenBank N-M06891)、CRYCS(GenBank N-0017541)、GJA3(GenBank-NM021954)、GJA8(GenBank N_005267)、MIP(GenBank N M02064.3)、HSF4(GenBank NM_001040667.2)和 BFSP2(GenBank NM_003571)。我们通过聚合酶链反应(PCR)扩增了基因的每个外显子和内含子 - 外显子连接，并使用先前发表的引物序列，见表 1[6]。每个反应混合物(25 μL)包含 20 ng 基因组 DNA、1× PCR 缓冲液、1.5 mM $MgCl_2$、0.2 mM dNTPs、0.5 μM 正向和反向引物以及 2.5U Taq DNA 聚合酶(Qiagen)。PCR 程序用于 DNA 扩增：95℃，3 分钟；随后在 95℃下进行 35 次循环 30 秒，在 57℃-63℃下循环 30 秒(退火温度取决于不同的引物)；72℃，持续 45 秒；最后在 72℃下延长 7 分钟。先证者和一名未患病成员的 PCR 产物使用 ABI3730 自动测序仪(PE Biosystems，Foster City，CA)进行测序。测序结果使用 Chromas 2.33 进行分析，并与 NCBI 数据库中的参考序列进行比较。然后，我们从两个家系成员的样本和 120 个同种族的对照中筛选出 CRYGD 的突变，以确认突变位点。

1.4 基因保守度分析

用 CLC Protein Workbench 12.0 软件分析了 CRYGD 基因野生型氨基酸序列。

2 结果

2.1 临床表现

(1)家系 A：在这个家系中，我们发现了一个明确诊断为 ADCC 的四代中国家系。该家系中所有患病的个体都患有中心性核混浊白内障，见图 3-A，B。先证者是一名 10 岁的男孩(IV:3)，自出生以来视力下降。他在 4 岁时被诊断为双眼先天性白内障。他的视力为 0.2/0.3。患病成员(IV:2)是先证者的哥哥，22 岁，11 年前患有左眼疾病，他的眼部临床症状相对轻微。另一名患病成员 IV:1 是先证者的堂兄弟，在 7 岁时接受了白内障摘除手术。家系成员无其他眼部或全身异常的家系史。(2) 家系 B：一个明确诊断为 ADCC 的五代中国家系，涉及核和外周皮质混浊，见图 3-C。根据病史和医疗记录，所有患病的个体在 2 岁之前被诊断为先天性白内障。10 名患者中均未接受过白内障手术，其中 4 人已死亡。先证者是一名 30 岁女性(IV:2)，直到视力严重下降才于医院就诊，视力为 0.2/0.2，这个家系的第五代(V:1，V:2，V:3)为刚出生的幼儿，未纳入诊疗。家系成员无其他眼部或全身疾病的家系史。

2.2 突变分析

通过对候选基因编码区的直接基因测序，我们确定了一个 G→A 的突变位置：在两个家系的所有患病个体中，CRYGD 第 2 外显子的 193 位，见图 4。然而，我们没有在任何未患病的家系成员或 120 名无关对照中发现这种突变。除了少数非致病性单核苷酸多态性(SNPs)外，我们没有在这两个家系中发现任何其他突变。

2.3 保守序列分析

通过多重序列比对，突变发生的位置位于多重物种的高度保守区域内，见图 5。

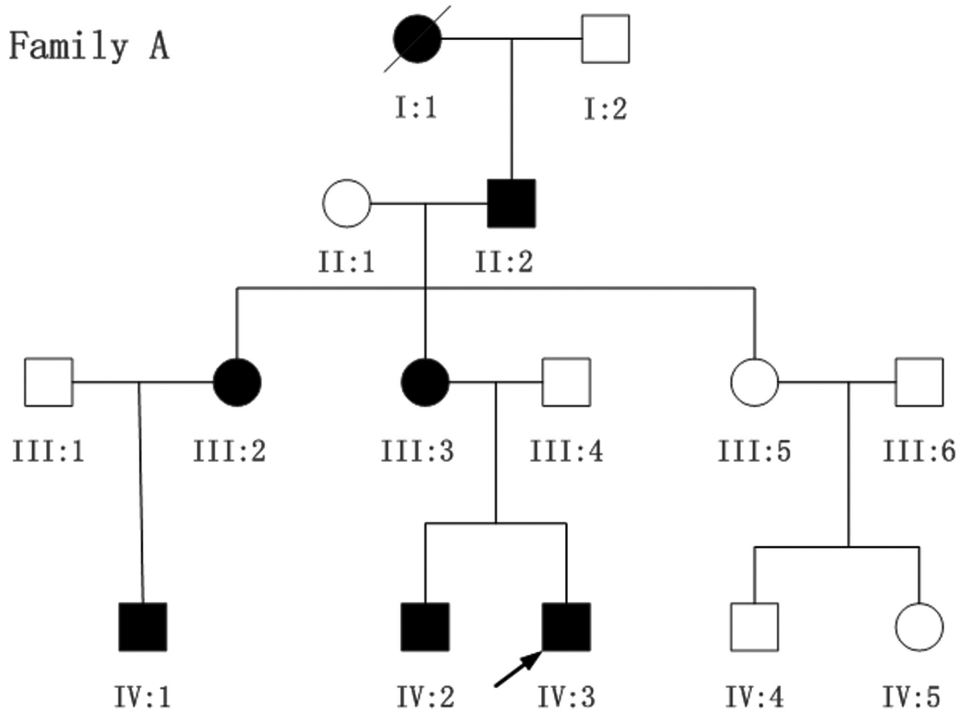

图 1 家系 A 的图谱。方形和圆形分别表示男性和女性。黑色符号表示患病成员。箭头表示先证者。

Fig.1 Pedigree of the Familiy A in the research. Squares and circles indicates males and females respectively. Blackened symbols denote affected status. The arrow indicates the proband.

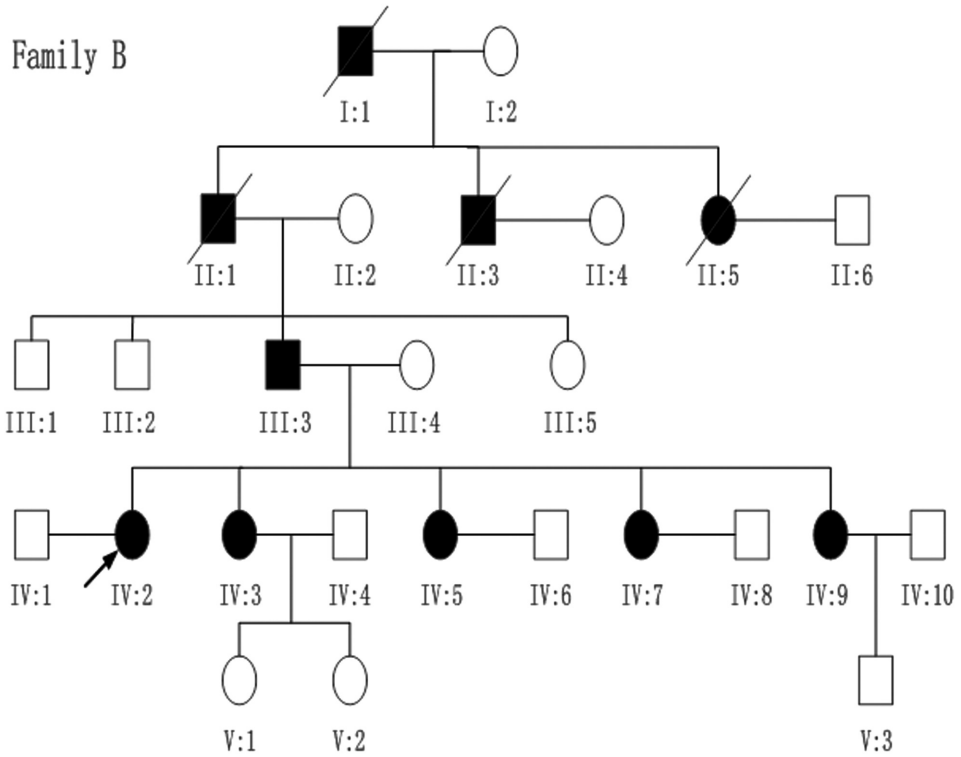

图 2 家系 B 的图谱。方形和圆形分别表示男性和女性。黑色符号表示患病成员。箭头表示先证者。

Fig.2 Pedigree of the Familiy B in the research. Squares and circles indicates males and females respectively. Blackened symbols denote affected status. The arrow indicates the proband.

3 讨论

通过对候选基因的突变分析,我们在两个中国家系中发现了一个新的突变 CRYGD(P.D65N),该突变与所有患病个体的疾病表型共存,但在任何未患病的家系成员或 120 名正常对照受试者中均不存在。

CRYGD 是编码 174 个氨基酸的蛋白质，位于染色体 2q33.3 上。CRYGD 是一种重要的结构蛋白,具有两个结构域 β 结构,折叠成四个非常相似的希腊钥匙基序,其高浓度和高保守的构象对称性与晶状体的高折射率有关,这能使晶状体保持

表 1 引物序列

Table 1 Primers for PCR

Name	Forward (5'-3')	Reverse (5'-3')
CRYAA-1	AGCAGCCTTCTTCATGAGC	CAAGACCAGAGTCCATCG
CRYAA-2	GGCAGGTGACCGAAGCATC	GAAGGCATGGTGCAGGTG
CRYAA-3	GCAGCTTCTCTGGCATGG	GGGAAGCAAAGGAAGACAGA
CRYAB-1	AACCCCTGACATCACCATTC	AAGGACTCTCCCGTCCTAGC
CRYAB-2	CCATCCCATTCCCTTACCTT	GCCTCCAAAGCTGATAGCAC
CRYAB-3	TCTCTCTGCCTCTTTCCTCA	CCTTGGAGCCCTCTAAATCA
CRYBA1-1	GGCAGAGGGAGAGCAGAGTG	CACTAGGCAGGAGAACTGGG
CRYBA1-2	AGTGAGCAGCAGAGCCAGAA	GGTCAGTCACTGCCTTATGG
CRYBA1-3	AAGCACAGAGTCAGACTGAA	CCCCTGTCTGAAGGGACCTG
CRYBA1-4	GTACAGCTCTACTGGGATTG	ACTGATGATAAATAGCATGAA
CRYBA1-5	GAATGATAGCCATAGCACTAG	TACCGATACGTATGAAATCTG
CRYBA1-6	CATCTCATACCATTGTGTTGAG	GCAAGGTCTCATGCTTGAGG
CRYBB1-1	CCCTGGCTGGGGTTGTTGA	TGCCTATCTGCCTGTCTGTTTC
CRYBB1-2	TAGCGGGGTAATGGAGGGTG	AGGATAAGAGTCTGGGGAGG
CRYBB1-3	CCTGCACTGCTGGCTTTTATTT	TCTCCAGAGCCCAGAACCATG
CRYBB1-4	CCAACTCCAAGGAAACAGGC	CCTCCCTACCCACCATCATCTC
CRYBB1-5	TAGACAGCAGTGGTCCCTGG	AGCACTGGGAGACTGTGGAA
CRYBB1-6	CCTAGAAAAGGAAACCGAGG	AGCGAGGAAGTCACATCCCA
CRYBB2-1	GTTTGGGGCCAGAGGGGAGT	TGGGCTGGGGAGGGACTTTC
CRYBB2-2	CCTTCAGCATCCTTTGGGTTC	GCAGTTCTAAAAGCTTCATCA
CRYBB2-3	GTAGCCAGGATTCTGCCATAG	GTGCCCTCTGGAGCATTTCAT
CRYBB2-4	GGCCCCCTCACCCATACTCA	CTTCCCTCCTGCCTCAACCTA
CRYBB2-5	CTTACCCTTGGGAAGTGGCAA	TCAAAGACCCACAGCAGACA
CRYGC-1	TGCATAAAATCCCCTTACCG	CCTCCCTGTAACCCACATTG
CRYGC-2	TGGTTGGACAAATTCTGGAAG	CCCACCCCATTCACTTCTTA
CRYGD-1	CAGCAGCCCTCCTGCTAT	GGGTCCTGACTTGAGGATGT
CRYGD-2	GCTTTTCTTCTCTTTTTATTTC	AAGAAAGACACAAGCAAATC
CRYGS-2	GAAACCATCAATAGCGTCTAA	TGAAAAGCGGGTAGGCTAAA
CRYGS-3	AATTAAGCCACCCAGCTCCT	GGGAGTACACAGTCCCCAGA
CRYGS-4	GACCTGCTGGTGATTTCCAT	CACTGTGGCGAGCACTGTAT
GJA3-1	CGGTGTTCATGAGCATTTTC	CTCTTCAGCTGCTCCTCCTC
GJA3-2	GAGGAGGAGCAGCTGAAGAG	AGCGGTGTGCGCATAGTAG
GJA3-3	TCGGGTTCCCACCCTACTAT	TATCTGCTGGTGGGAAGTGC
GJA8-1	CCGCGTTAGCAAAAACAGAT	CCTCCATGCGGACGTAGT
GJA8-2	GCAGATCATCTTCGTCTCCA	GGCCACAGACAACATGAACA
GJA8-3	CCACGGAGAAAACCATCTTC	GAGCGTAGGAAGGCAGTGTC
GJA8-4	TCGAGGAGAAGATCAGCACA	GGCTGCTGGCTTTGCTTAG
MIP-1	GTGAAGGGGTTAAGAGGC	GGAGTCAGGGCAATAGAG
MIP-2,3	CGGGGAAGTCTTGAGGAG	CACGCAGAAGGAAAGCAG
MIP-4	CCACTAAGG TGGCTGGAA	CTCATGCCCCAAAACTCA
HSF4-1	CATCCCATCCAGCCAGCCTTT	GGGCATGGGTGTTCACTGACG
HSF4-2	CCTCGACCCATATCCCCGTAA	GCAGGAGCAAGGCAGGCAGT
HSF4-3	GCGGGAATGAGCAAAGAGGA	GCCAAGGCAGGAGAGAGGAA
HSF4-4	TCCCCAGCCTCGCCATTCT	CCCGGTGAAGGAGTTTCCAG
HSF4-5	GCTGGGGCCTGAGGGAG	GGCTTCCATCTTCTCTTCCTTT

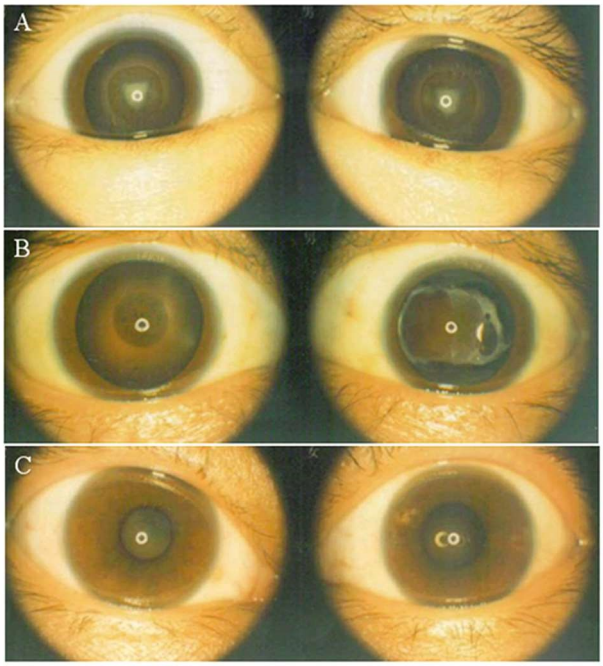

图 3 来自两个家系的不同个体的裂隙灯照片。家系 A(A 和 B)的裂隙灯照片。A：来自 A 家系的先证者(IV:3)，涉及双眼核混浊。B：先证者的哥哥(IV:2)的照片，右眼显示核混浊，左眼的晶状体已被摘除。C：来自 B 家系的先证者显示核混浊和周围皮质混浊。

Fig.3 Slit lamp photographs of different individuals from two families. Slit lamp photographs of Familiy A (A andB). A: the proband from family A, involving the nucleus opacity in both eyes. B: the photograph of the proband's elder brothor(IV2), right eye shows nuclear opacity, the len in left eye has been extracted. C: The proband from family B shows that the opacity is a nuclear and peripheral cortex opacities.

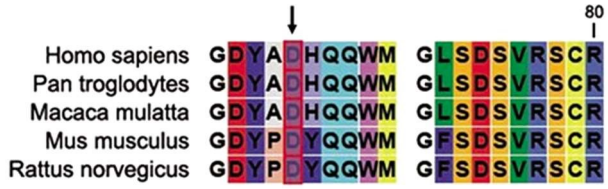

图 5 来自不同物种的 CRYGD 基因的多序列比对。显示了来自不同物种的 CRYGD 的部分氨基酸序列的多重比对。比对数据表明，在不同物种的 CRYGD 基因中，第 65 位(箭头所示)的天冬氨酸高度保守。

Fig.5 Multiple-sequence alignment in CRYGD from different species. A multiple alignment of partial amino acid sequences of CRYGD from different species is shown. The alignment data indicate that asparticacid at position 65 (indicated by an arrow) is highly conserved in different species in CRYGD.

透明。多重序列比对的结果表明 Asp65 是一个高度保守的残基，见图 5。

晶状体蛋白分为三个主要家族：α-、β- 和 γ- 晶体蛋白，构成大多数物种中 80%-90%的可溶性蛋白质[7]，维持晶状体的透明度和折射率。在人类发育过程中，晶状体中央纤维细胞失去细胞核，这些晶体蛋白被制造出来，然后在整个生命中被保留下来，使它们成为极其稳定的蛋白质。人类 γ- 晶体蛋白基因簇包括六个基因：CRYGA、CRYGB、CRYGC、CRYGD、CRYGE、CRYGF，还有 CRYGG [8] 在所有哺乳动物中，而 CRYGC 和 CRYGD 仅在人类中编码大多数晶状体 γ- 晶体蛋白 [9,10]，且

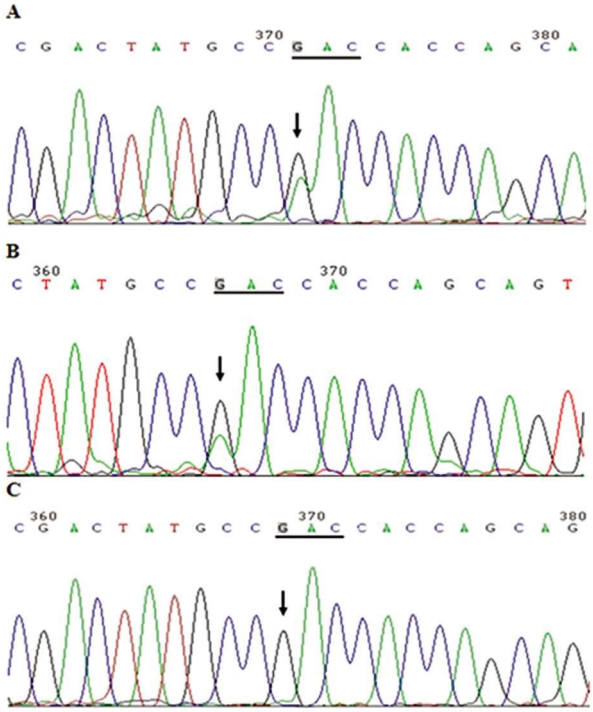

图 4 CRYGD 的 DNA 序列谱图。A：显示了 CRYGD 中 D65N 突变的 DNA 序列谱图。我们在家系 A 的所有患者中检测到它。在 193 位(G>A)观察到一个单一的突变，即 G/A 双峰(由箭头指示)。B：我们在家系 B 中受患病成员的相同位置检测到一个相同的突变(由箭头表示)。C：未受影响的家系成员和另外 120 名正常人，没有突变存在。

Fig.4 DNA sequence chromatograms of CRYGD. A: DNA sequence chromatograms of the D65N mutation in CRYGD are shown.we detected it in all patients of the Family A. A single transition is observed at position 193 (G>A) as a G/A double peak(indicated by an arrow). B: We detected a same mutation at the same position with affected members in Family B (indicated by an arrow). C: Sequence of unaffected individuals and another 120 normal people, there was no mutation existed.

CRYGD 是一种最重要的 γ- 晶体蛋白，在胚胎人类晶状体的纤维细胞中高浓度表达，随后形成晶状体核纤维 [11-15]。因此，CRYGD 中的突变可能影响核纤维的正常发育，导致核型白内障。因此，根据本研究中发现的基因突变以及临床表型，位于外显子 2 的突变 C.G193A 被预测会导致密码子 65（P.D65N)处 Asp 对 Asn 的保守取代。

核性白内障是指晶状体的胚胎和 / 或胎儿细胞核内的混浊。迄今为止，已鉴定出 8 种核性白内障基因(CRYBA1、CRYAA、CRYBB2、CRYBB3、CRYGC、CRYGD、CX46 和 CX50)，其中 CRYBA1，CRYAA 和 CRYGD 仅与核性白内障表型相关，而与粉状型白内障无关[16]，而基因 CX46、CX50、CRYBB2、CRYBB3 和 CRYGC，它们仅是粉状型白内障的候选基因。据报道，在两岁以下个体的晶状体中，γ- 晶体蛋白的比例为 35% CRYGS、45%CRYGC 和 20%CRYGD[17]。

截至目前，已报告 CRYGD 中约有 20 个突变(表 2)，其中 11 个突变与核型先天性白内障有关(表 3)，比例约为 50%。因此，CRYGD 与核型白内障有很大的相关性。已经对其中一些核表型进行了功能分析。(1999 年，Stephan 等人)[38]揭示了突变 R14C 形成二硫键连接的低聚物，这显著提高了蛋白质溶液的相分离温度，从而使 R14C 逐渐沉淀。(2001 年，Pande 等人)[39]

表 2 目前为止发现的与 CRYGD 基因相关的突变位点总结

Table 2 Summary of identified mutations in CRYGD

Mutation	Amino acid	Phenotype	Origin of family	Reference
c.176G>A	R58H	aculeiform	Switzerland, Macedonia, Mexican	[18]
c.181G>C	G61C	coralliform	Chinese	[19],[20]
c.43C>A	R15S,	coralliform	Chinese	[21]
c.43C>T	R15C,	Punctate cataract, juvenile progressive/	Caucasian	[22]
c.229C>A	R77S	anterior polar coronary	India	[23]
c.70C>A	P23T	cerulean and coralliform	Saudi	[24]
c.70C>T	P23S	polymorphic	Russia	[25]
c.320A > C	E107A	nuclear	Mexico	[26]
c.127T>C	Trp43Arg	nuclear	Chinese	[16]
c.109C>A	R36S	nuclear nucleus and perinuclear cortex	Chinese Czech Republic Caucasian	[27],[28]
c.34C>T	R14C	coralliform/nuclear	Chinese	[29]
c.401A>G	Y134C	nuclear	Brazilian	[30]
c.106G>C	Ala36Pro	nuclear	Chinese	[31]
c.110G>C	R36P	nuclear	Chinese	[32]
c.418C>T	R140X	nuclear	India	[33]
c.168C>G	Y56X	nuclear	Brazilian	[34]
c.470G>A	W156X	nuclear	India	[35]
c.494delG	p.Gly165fs	nuclear	Chinese	[36]
c.403C>A	Y134X	no data	Danish	[37]

表 3 与核性白内障相关的 CRYGD 基因突变位点总结

Table 3 Summary of CRYGD mutation for nuclear cataract

Mutation	Amino acid	Phenotype	Origin of family	Reference
c.320A > C	E107A	nuclear	Mexico	[26]
c.127T>C	Trp43Arg	nuclear	Chinese	[16]
c.109C>A	R36S	nuclear nucleus and perinuclear cortex	Chinese Czech Republic Caucasian	[27],[28]
c.34C>T	R14C	coralliform/nuclear	Chinese	[29]
c.401A>G	Y134C	nuclear	Brazilian	[30]
c.106G>C	Ala36Pro	nuclear	Chinese	[31]
c.110G>C	R36P	nuclear	Chinese	[32]
c.418C>T	R140X	nuclear	India	[33]
c.168C>G	Y56X	nuclear	Brazilian	[34]
c.470G>A	W156X	nuclear	India	[35]
c.494delG	p.Gly165fs	nuclear	Chinese	[36]
c.403C>A	Y134X	no data	Danish	[37]

p.Arg36Ser 的功能测定表明，这种突变不会改变蛋白质的折叠，但会改变 CRYGD 的表面特征，降低了其溶解度并提高了晶体成核速率和沉淀，在至少一种情况下，晶状体会形成混浊。（2010 年，Venkata Pulla Rao Vendra 等人）[40] 检测到，E107A（CRYGD 中的一种点突变）不会影响蛋白质的构象和稳定性，但当引入细胞系时，会导致溶解度大幅降低，并在体外和原位产生光散射聚集颗粒。（2007 年，Zhang LY 等人）[36]对 CRYGD 中的 c.494delG 进行了研究，这是发现的第一个导致核先天性白内障的 CRYGD 缺失突变。假设具有丧失溶解性和定位于核包膜的突变蛋白会损害晶状体纤维细胞分化中的核变形和降

解，导致晶状体发育过程中的不透明形成。(2010 年,Binbin Wang 等人)[16]表明,p.Trp43Arg 突变导致了显著的三级结构变化。突变蛋白比野生型蛋白稳定性差得多,并且在受到诸如热和紫外线照射等环境胁迫时更容易形成聚集。

在我们的研究中,我们检测到 CRYGD 密码子(p.D65N)的一个新突变,这是两个中国家系中先天性核性白内障的发病原因和基础。这种突变是首次报道。对于不同的临床表型,可以推测,修饰因子或上位性因素,例如基因启动子位点的差异,可能会调节晶状体中 CRYGD 的表达。残基 65 天门冬氨酸高度保守,是一种高度极性的无电荷残基,在 p.D65N CRYGD 突变体中,它被极性、负电荷残基天冬酰胺取代。它会导致结构不稳定并破坏蛋白质的折叠。

总之,我们在两个中国的常染色体显性遗传性先天性白内障家系中发现了一种新的 CRYGD 基因的杂合子突变 D65N。我们的结果进一步证实了 CRYGD 在维持晶状体光学清晰度方面的重要性。需要进一步研究来阐明这种新发现的突变与白内障发病机制相关的病理生理后果。该突变支持 CRYGD 基因在人类先天性白内障形成中的作用,并为先天性白内障的遗传异质性提供了更多证据。

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