New Compound Heterozygous CYP4V2 Mutations in Bietti Crystalline Corneoretinal Dystrophy

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Short report

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Abstract

Background: Bietti crystalline corneoretinal dystrophy (BCD) is an autosomal recessive retinal dystrophy which is caused by the mutations of *CYP4V2*.Here we identified new *CYP4V2*compound heterozygous mutations in BCD.

Methods:381 pathogenic genes related to retinal diseases were screened by targeted sequence capture array techniques and confirmed by Sanger sequencing.

Results: Two female siblings with BCD carry two compound heterozygous mutations in *CYP4V2*. One was missense mutation c.1198C>T (p.R400C) and the other was frameshift mutation c.802-8_810delinsGC (p.V268_E329del).Optical coherence tomography (OCT) showed that the ellipsoid zone was absent in the macular regions and electroretinogram (ERG) revealed poor cone and rod responses.

Conclusions: Newcompound heterozygous mutations in *CYP4V2* are related to the BCD.Our study expands our knowledge of heterogenic phenotypes and genotypes through genetic diagnosis of the BCD patients.

Background

Bietti crystalline corneoretinal dystrophy (BCD) is an autosomal recessive retinal dystrophy which is characterized by numerous tiny glistening yellow-white crystals at posterior pole of the retina. Some cases also have similar crystals at the corneoscleral limbus. Clinically, this disease can be divided into three stages: Stage 1: RPE atrophy with uniform fine white crystalline deposits at the macular area. Stage 2: RPE atrophy extends beyond the posterior pole and the atrophy of choriocapillaris in the posterior pole. Stage 3: RPE-choriocapillaris complex atrophy throughout the fundus. Crystalline deposits at the corneal limbus are probably prominent at the advanced stage of atrophy of the RPE-choriocapillaris complex.[1] Although BCD has been reported worldwide, it seems more frequent in East Asia, especially in China and Japan. The prevalence of BCD in China was 1 per 24 000 for the total population, but in Europe, BCD only accounted for 3% of all nonsyndromic retinitis pigmentosa.[2] BCD is caused by the mutations of *CYP4V2*, which encodes a 525 amino acid protein and plays an important role in fatty acid and steroid metabolism.[3] Over 100 cases of mutations in *CYP4V2* gene have been reported.[4]

Here we aim to perform genetic screening for BCD based on targeted next generation sequencing. A large-scale mutation screening of 381 known retinal degenerative-related genes was performed and identified two compound heterozygous mutations in the *CYP4V2* gene.

Methods

A case of 35-year-old lady came to our clinic for myopia laser correction without any other ocular complains or any general diseases. However, we found crystalline lesions in the posterior pole of both eyes during fundus examination. After obtaining medical and ophthalmic histories, we gave the patient

and her family a complete ophthalmological examination including central visual acuity with EDTRS charts, slit lamp biomicroscopy of the anterior segment, fundus exam, fundus photography, visual field, Optical coherence tomography (OCT), Fluorescence angiography (FFA), standard ERG and multifocal ERG (mfERG). The approval of the Ethics Committee of Shenzhen Eye Hospital and the informed consent from the patients were obtained. We extracted genomic DNA from peripheral blood by standard protocols and collected the protein coding regions of targeted genes by targeted sequence capture array technique. This technique could capture 381 pathogenic genes related to retinal diseases, which included *CYP4V2* gene associated with BCD. Polymerase chain reaction(PCR) and Sanger sequencing were used to confirm the screening results.

Results And Discussion

The best corrected visual acuity (BCVA) of the proband was 0.9 (nearly 20/20) in both eyes. The intraocular pressure was normal. The sclera, conjunctiva, cornea and lens were normal. The physiological blind spot was enlarged by visual field tests. Optical coherence tomography (OCT) showed that the ellipsoid zone was absent in the macular regions (Fig. 1). Fundus fluorescein angiography (FFA) showed that the surrounding granules in the posterior pole were stained with fluorescence and the omental vessels were thin. Photopic and scotopic electroretinogram (ERG) revealed that the amplitudes of a- and b-waves were severely decreased, indicating poor cone and rod responses (Fig. 1). We found that her elder sister had the same sign. For her elder sister, we also found that the retinal phenotypes were almost identical (Fig. 1). We found two compound heterozygous mutations in CYP4V2 of the proband. One was missense mutation c.1198C > T (p.R400C) and the other was frameshift mutation c.802-8_810delinsGC (p.V268_E329del). Similarly, her sister also carried the same mutations (Fig. 2). The missense mutation c.1198C > T (p.R400C) resulted in a change from arginine to cysteine at amino acid codon 400. The other frameshift mutation c.802-8_810delinsGC (p.V268_E329del) leads to the deletion of all 62 amino acids in exon 7. Missense mutation c.1198C > T(p.R400C) has been reported twice before, which was compound heterozygous mutation with R400H in one case and a homozygous point mutation in the other case.[5, 6] Frameshift mutation c.802-8_810delinsGC (p.V268_E329del) is common in BCD patients in East Asia.[7] Although most patients with BCD develop decreased vision, nyctalopia, and paracentral scotomata, few patients complain no symptoms. In our case, the patients have no subjective symptoms, which may be due to the specific genetic defects (new compound heterozygous mutations). In addition, most patients of BCD usually present in the 2nd or 3rd decade of life and clinical features do not seem to correlate well with the age of debut. We can't exclude the possibility that the disease is still in its early stages. Patients are often asymptomatic during the earliest stage of BCD, which increase difficulty in diagnosis. Some reports suggested that phenotype associated with genetic disease is determined by genotype and environment commonly and different diseases depend on the degree of influence of these two factors.[8] Studies of genotype and phenotype analysis based on large sample are necessary to explore the pathogenesis of BCD and the determinant of disease progression.

Conclusions

In this study we found new compound heterozygous mutations in *CYP4V2* in BCD, which were a new pathogenic cause. Our study expands our knowledge of heterogenic phenotypes and genotypes through genetic diagnosis of the BCD patients.

Abbreviations

BCD
Bietti crystalline corneoretinal dystrophy
BCVA
Best corrected visual acuity
ERG
Electroretinogram
mfERG
Multifocal electroretinogram
OCT
Optical coherence tomography

Declarations

Availability of data and materials

The data during the study are available from the corresponding author on reasonable request.

Contributions

TW, QC, HL, JW analysed the data and revised the paper. XY designed and directed the study and XY, TW wrote the manuscript. All authors read and approved the final version of the manuscript.

Ethics declarations

Ethics approval and consent to participate

This stuy were approved by the Ethics Committee of Shenzhen Eye Hospital.The study was performed according to the Helsinki Declaration of 1975, as revised in 1996. The informed consent from the patients were obtained.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

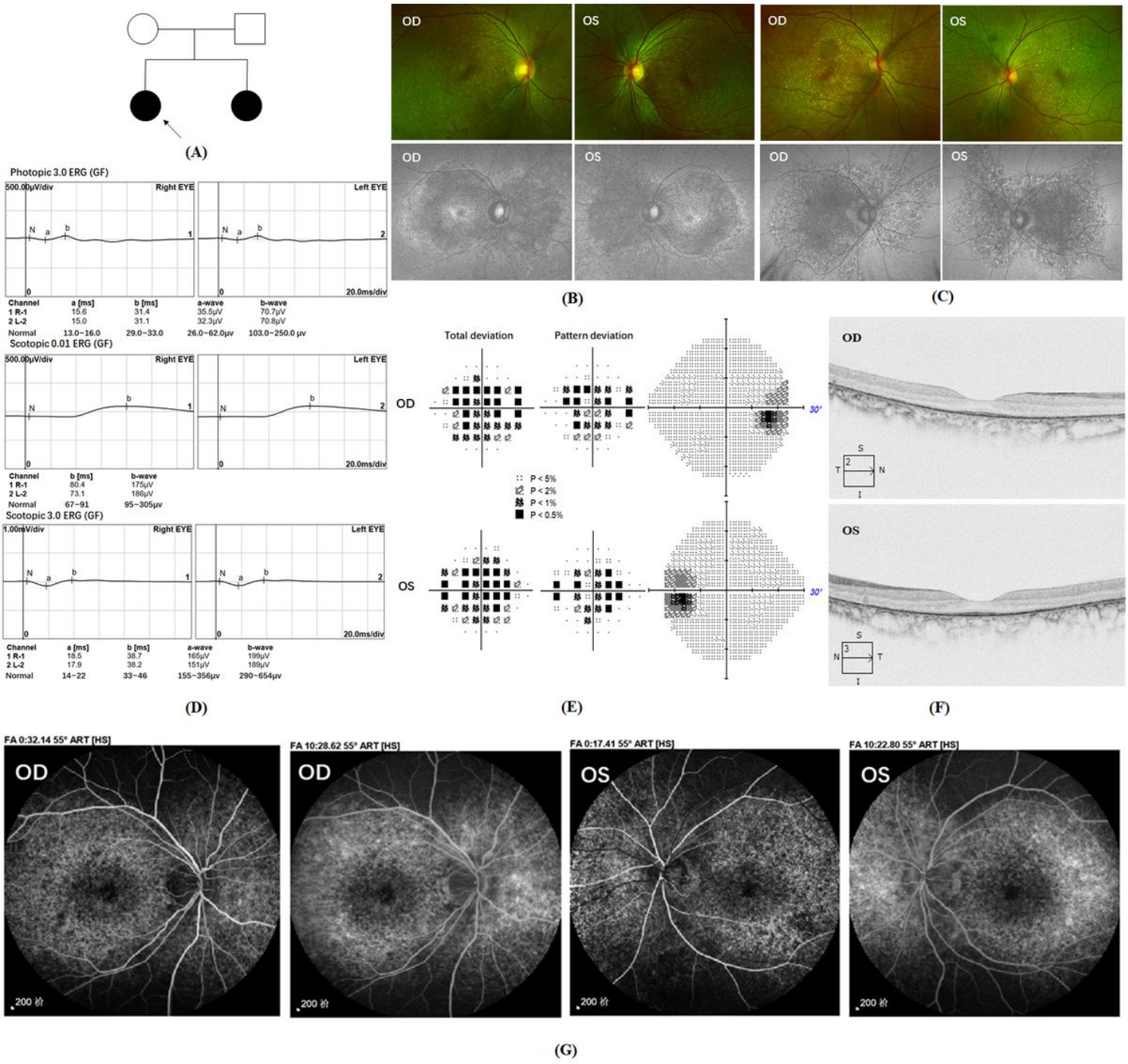

Figure 1

A family with Bietti crystalline corneoretinal dystrophy. A.Pedigree of the family with Bietti crystalline corneoretinal dystrophy; B. The proband patient: scanning laser ophtalmoscope showed crystalline points in the posterior pole of both eyes and fundus autofluorescence imaging showed a butterfly-shaped hypofluorescence with rim increased autofluorescence in both eyes;C. The sister of the proband: the retinal phenotype is identifical to the proband. D. The amplitudes of the a- and b-waves were significantly reduced in the photopic (which reflects cone response) and scotopic ERG (which reflects rod response). E.Visional field tests showed that the blind spot of both eyes was enlarged. F. OCT indicated that ellipsoid

zonewas absentin both eyes; G. Fluorescence angiography showed that crystalline lesions were stained with fluorescence in the posterior pole and the omental vessels were thin in both eyes.

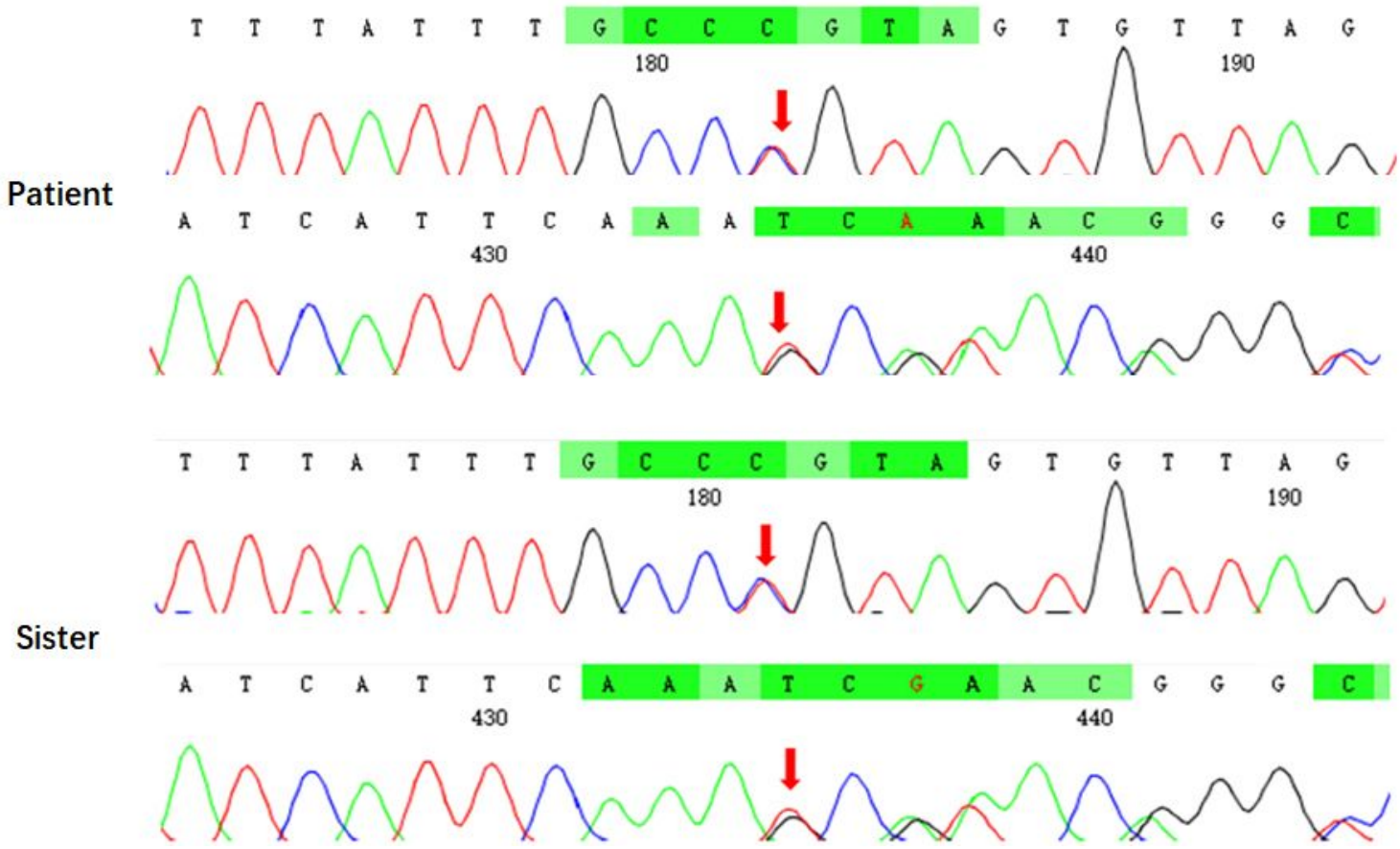

Figure 2

Mutations in CYP4V2 gene in the proband and her sister.Sequence shows the heterozygous missense mutation c.1198C>T(p.R400C) and frameshift mutation c.802-8_810delinsGC(p.V268_E329del) found in both patients.