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Analysis of PDE6G mutations in a patient with retinitis pigmentosa

Xiaona Liu[1†], Peiyan Shi[1†] and Jinling Ge[1*]

Abstract

Background Mutations in PDE6A and PDE6B are known to cause autosomal recessive RP in humans, On the other hand, mutations in PDE6G are rare but can lead to severe early-onset RP.

Case presentation An 8-year-old Chinese boy was referred to our hospital for poor vision issues. Refraction with cycloplegia showed high hyperopia with astigmatism both eyes. Funduscopic examination revealed typical bone spicule-type pigment deposits in the periphery and midperiphery. The patient was given glasses and a whole exome sequencing containing mitochondrial genes was performed. The results of genetic testing showed that there was a heterozygous frameshift mutation and a segment deletion in the proband's PDE6G gene. Analysis of the parental genes showed that frameshift mutation was inherited from the proband's mother and segment deletion from his father.

Conclusions In this paper, we give a firsthand report that the complex heterozygous mutations of PDE6G gene can causes autosomal recessiveRP (arRP), which expands the understanding of the pathogenic genes of RP.

Keywords PDE6G, Retinitis pigmentosa, Mutations

Background

Retinitis pigmentosa (RP) is the most common form of hereditary retinal degeneration, with a worldwide prevalence of 1 in 4000 [1]. There are many pathogenic genes in retinitis pigmentosa, but there are still many unrecognized mutated genes [2]. This paper reported a case of PDE6G complex heterozygous gene mutation which has never been reported before.

Case presentation

An 8-year-old Chinese boy was referred to our hospital for poor vision issues on January 30, 2023. There were no other vision issues. The right eye uncorrected visual acuity was 0.4 and best-corrected visual acuity was 0.8 by +5.50DS+1.50DC×90, the left eye uncorrected visual acuity was 0.4 and best-corrected visual acuity was 0.8 by +6.0DS+1.50DC×12. Anterior segment exam was unremarkable. Funduscopic examination revealed typical bone spicule-type pigment deposits in the periphery and midperiphery, the optic disk and blood vessels were normal, foveal reflex wasabsent. Fundus autofluorescence showed diffuse hypofluorescence in both eyes (Fig. 1). No systemic concerns were noted. There was no family history of retinal degeneration. Further testing revealed markedly constricted visual fields and electroretinograms showed markedly reduced rod-cone responses (Fig. 2). The patient was given glasses and a whole exome

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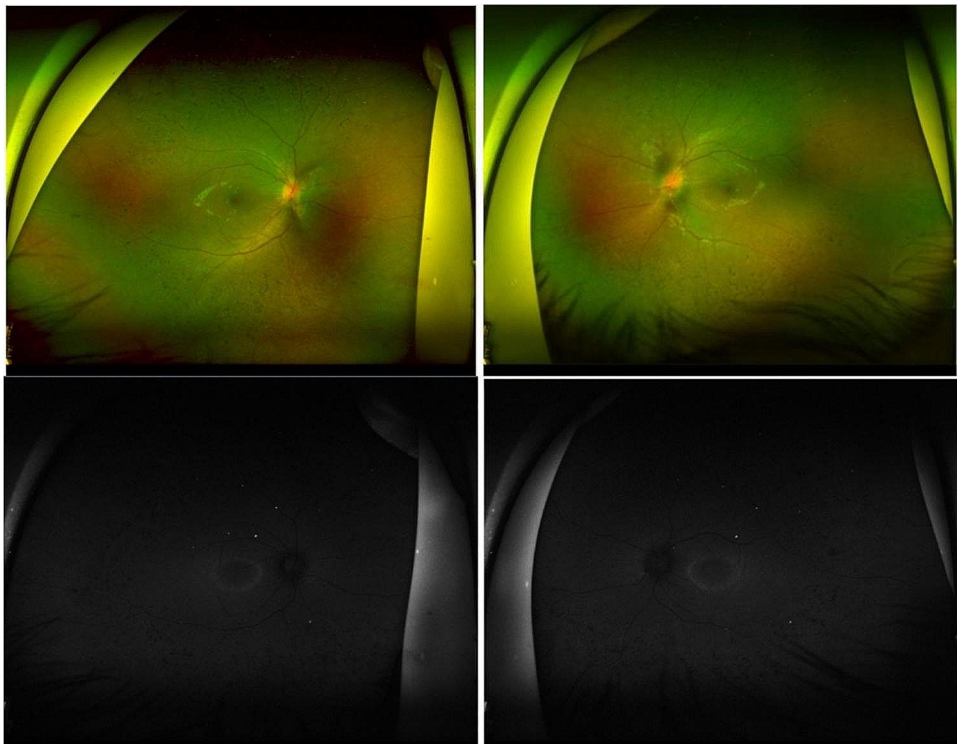

Fig. 1 Ultra-widefield imaging demonstrated peripheral bone spicule-type pigment deposits, absence of foveal reflex in both eyes. Fundus autofluorescence showed bull's eye lesion

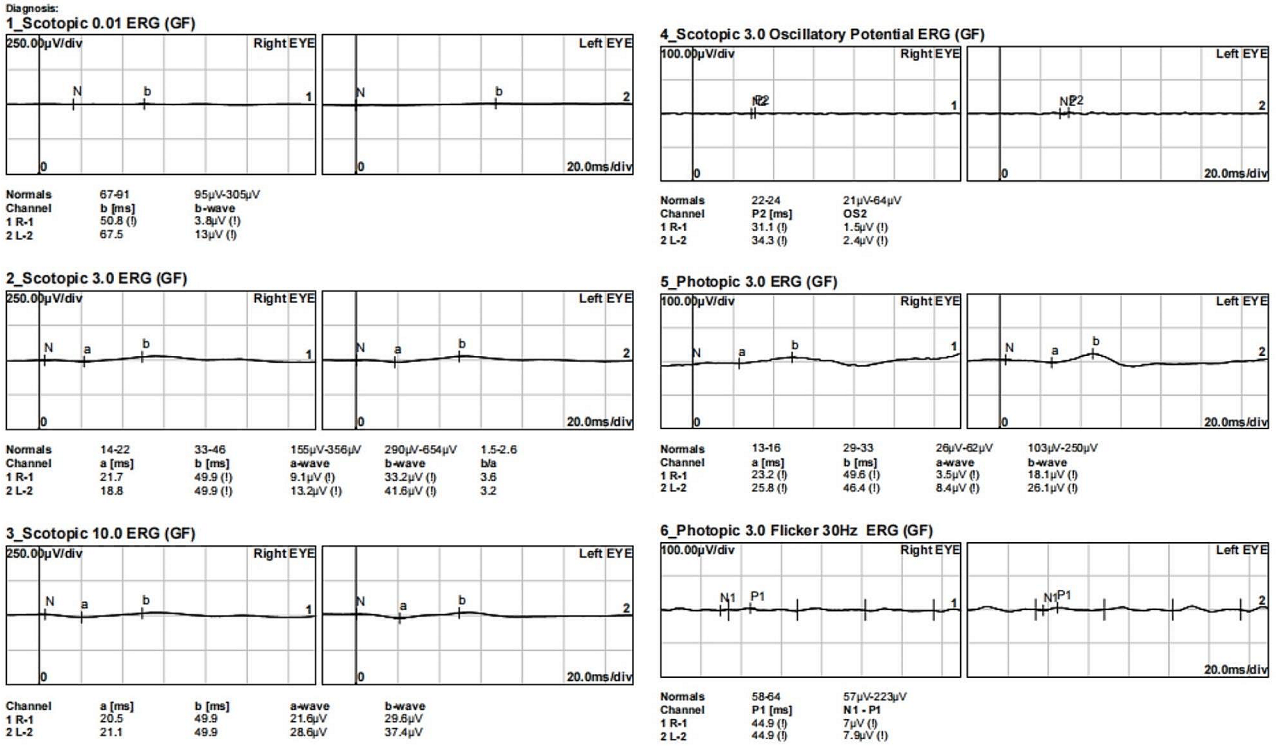

Fig. 2 Rod-cone degeneration noted on electroretinogram. It is undetectable responses for rod or cones

sequencing containing mitochondrial genes was performed. The results of genetic testing showed that there was a heterozygous frame shift mutation in the proband's PDE6G gene, i.e. c.95del: p.Q32Rfs*62, and a deletion of about 6.72Kbp in the proband's 17q25.317q25.3 segment (Fig. 3). Parental segregation analysis showed a frameshift mutation and a segment deletion, in which frameshift mutation was inherited from the proband's mother and segment deletion from his father.

Discussion and conclusions

The most common inherited eye disease is retinitis pigmentosa (RP) [3], which is genetically heterogeneous retinopathy caused by photoreceptor cell death and retinal pigment epithelial atrophy that eventually results in blindness in both eyes [4–6]. At present, more than 90 non-syndromic RP-related genes have been identified [7], and their pathogenicity patterns are complex, which involve autosomal dominant (AD, 15–25%), autosomal recessive (AR, 5–20%), Xlinked (XL, 5–15%), simplex or sporadic (40–50%), digenic and mitochondrial inheritance (very rare) [8, 9]. In general, patients with X-linked RP exhibit more severe disease phenotypes than those with arRP, whereas patients with adRP have the best prognoses with preserved central vision [4].

The PDE6G gene is located at 17q25.3 and harbors four exons, encoding the gamma subunit of cGMP phosphodiesterase (cGMP-PDE). cGMP-PDE, rod-specific phosphodiesterase 6 (PDE6), composed of alpha and beta catalytic subunits and 2 identical inhibitory gamma subunits, is one of the key enzymes that regulates the level of cGMP in vertebrate photoreceptor cells [9–11]. Mutations in PDE6A and PDE6B are common [12], on the other hand, mutations in PDE6G are rare yet can lead to severe early-onset RP. Other than a prior case reported by Dvir L that showed a homozygous single base change (c.187+1G>T) located in the conserved intron 3 donor splice site of PDE6G from an extended consanguineous Muslim Arab Israeli family [9], there are no other case reports of arRP caused by PDE6G gene variation (previously) reported. Affected individuals had markedly constricted visual fields. Both scotopic and photopic electroretinograms were severely reduced. Fundoscopy showed typical bone spicule-type pigment deposits spread mainly at the midperiphery. Macular involvement was indicated by the lack of foveal reflex. However, our case did not show pallor of the optic disk and typical cystoid macular edema as described by Ldivir et al.

In this case, the whole exome and adjacent splicing region of PDE6G were analyzed, and it was found that the subject carried a heterozygous frameshift mutation: c.95del: p.Q32Rfs*62, and the deletion of the 95th T base of cDNA, resulting in the 32nd codon changing from encoding glutamine (CAG) to encoding arginine (CGC), and then migrating to produce a stop codon in advance. The copy number variation analysis of the whole exome and the adjacent splicing region of PDE6G showed that there was about 6.72Kbp missing in the PDE6G gene. It was found that the T base deletion variation came from the mother and the fragment deletion variation came from the father, which eventually led to the complex heterozygous variation of PDE6G. Deletion of the 95th T base of PDE6G gene was recorded in ClinVar, but it has not been found in human genetic variants; Three cases containing PDE6G copy number variants were recorded in the DECIPHER database, but these cases (DECIPHER ID: 361103, Duplication; 395989, Deletion; 396086, Deletion) are fragment heterozygous mutations and do not exhibit the phenotype of retinal pigmentosa. However, chr17: 81,656,692–81,663,209 detected in this caseinvolves exon 1 of PDE6G gene, a known pathogenic gene included in OMIM, and this deletion mutation has not been reported in the literature. Mutations in PDE6G gene can lead to autosomal recessive retinitis pigmentosa type 57 (OMIM#613582). The main clinical manifestations include cystic macular edema, optic disc pallor, retinitis pigmentosa, retinal vascularization, etc. The disease has a severe early onset eye disease, which is consistent with the present case. Some studies have found that damage to photoreceptor cells caused a marked reduction in scotopic and photopic electroretinograms as early as 4 years of age [9].

In this paper, we report that the complex heterozygous variation of PDE6G gene can cause arRP, which expands the understanding of the pathogenic genes of RP. There are no prior cases reported with this genetic presentation. Whole exome sequencing can fully understand the genetic characteristics of patients, improve the accuracy

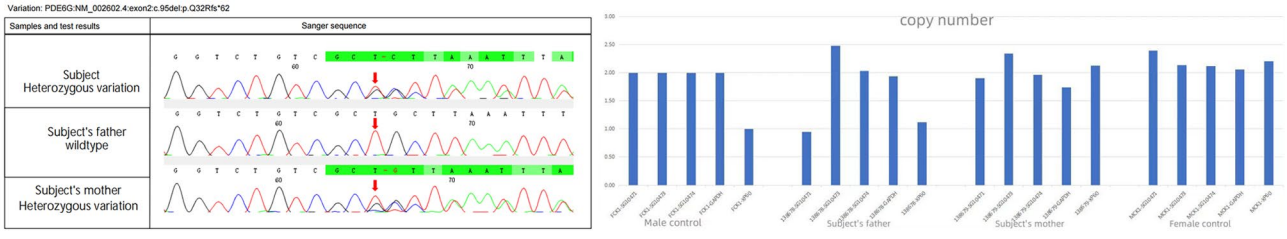

Fig. 3 A simple pedigree with genetic variants identified in the probing and segregated in the parents

of diagnosis of RP, and further explore the mechanism of disease occurrence and explore the correlation between genotype and phenotype.

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Author contributions
Xiaona Liu and Peiyan Shi are the major contributor in writing the manuscript. Jinling Ge analyzed and interpreted the result regarding the disease. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate
Not applicable.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare no competing interests.

Consent to Publish
Not applicable.

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