• Letter to the Editor •

An *HK1* pathogenic variant associated with an atypical retinal dystrophy phenotype: a case report and insights from literature

Yong-Yue Su, Kai-Rui Qiu, Feng Wen, Xiao-Lai Zhou

State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangdong Provincial Key Laboratory of Ophthalmology and Visual Science, Guangdong Provincial Clinical Research Center for Ocular Diseases, Guangzhou 510060, Guangdong Province, China

Correspondence to: Xiao-Lai Zhou and Feng Wen. State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangdong Provincial Key Laboratory of Ophthalmology and Visual Science, Guangdong Provincial Clinical Research Center for Ocular Diseases, Guangzhou 510060, Guangdong Province, China. zhouxiaolai@gzzoc.com; wenfeng208@foxmail.com

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Dear Editor,

Hexokinase 1 (HK1) catalyzes the phosphorylation of glucose to glucose-6-phosphate, the first rate-limiting step in glucose metabolism[1-2]. HK1 exhibits strong expression in various retinal layers, including the photoreceptor inner segment, inner and outer plexiform layers, inner nuclear layer, and ganglion cell layer[3-4]. Pathogenic variants in the *HK1* gene have been implicated in inherited retinal dystrophies, most commonly autosomal dominant retinitis pigmentosa (RP)[5-9]. Recent studies have also reported *HK1* pathogenic variants in pigmented paravenous retinochoroidal atrophy (PPRCA) and cone-rod dystrophy (CRD)[9-12]. The full spectrum of retinal dystrophies linked to *HK1* pathogenic variants is not yet completely understood.

CRD typically manifests with color vision disturbance, light intolerance, night blindness, and reduced central visual acuity, followed by progressive peripheral vision loss due to cone and rod photoreceptor dysfunction[13]. Pathogenic variants in at least 34 genes cause CRD, though *HK1*-related CRD remains rare[14].

We describe a 37-year-old Chinese patient with CRD carrying the c.883C>T pathogenic variant in the *HK1* gene, which has not been previously reported in association with retinal dystrophy. This report expands understanding of *HK1* gene pathogenic variants in inherited retinal dystrophies and highlights the importance of genetic screening in CRD diagnosis.

CASE PRESENTATION

Ethical Approval This study was carried out following the institutional guidelines and ethical standards of the Declaration of Helsinki and was approved by the Institutional Review Board of Zhongshan Ophthalmic Center (Approval Number: 2022KYPJ211-3). Written informed consent was obtained from the study participant.

The patient, a 37-year-old male, presented to our hospital eleven years after the initial onset of blurred vision in both eyes, which he initially attributed to worsening myopia. Over time, as the blurring persisted and worsened, it became clear that corrective glasses were inadequate to address his declining vision. He denied any neurological symptoms, systemic disorders, history of surgery, trauma, or similar ocular conditions in his family.

Upon examination, his best-corrected visual acuity (BCVA) was 20/400 in both eyes (right eye: -7.00 D sphere, -1.25 D cylinder at 30 degrees; left eye: -7.25 D sphere, -2.25 D cylinder at 155 degrees). Intraocular pressures were 14.3 mm Hg in the right eye and 15.7 mm Hg in the left, with axial lengths measured at 26.37 mm (right eye) and 26.99 mm (left eye). Pupillary response to light was prompt, symmetrical, and without evidence of a relative afferent pupillary defect. Slit-lamp examination revealed a normal anterior segment.

Multimodal imaging confirmed progressive retinal degeneration, particularly involving the photoreceptor layers (Figure 1). Fundus photography, performed at the patient's first visit to our hospital (11y after symptom onset), revealed a darker macular center with no evidence of bone spicule pigmentation.

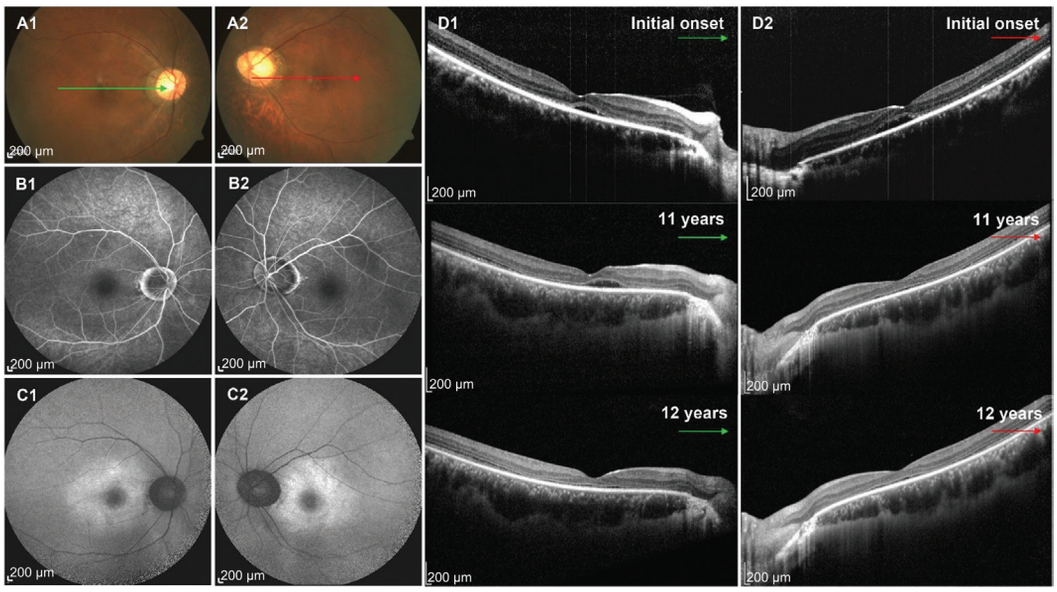

Figure 1 Multimodal imaging of the patient with *HK1* pathogenic variant Fundus photography (A1, A2), FFA (B1, B2), and AF (C1, C2) images were obtained at the patient's first visit to our hospital, which occurred 11y after the initial onset. Fundus photography reveals a darker appearance at the macular center, with no bone spicule pigmentation observed. FFA demonstrates a circular window defect at the posterior pole, indicating retinal thinning or atrophy, while AF imaging shows hyperautofluorescence in a circular pattern in the macular region, suggesting alterations in the photoreceptors or RPE. OCT images (D1, D2), obtained at symptom onset and 11 and 12y later, reveal progressive blurring and disruption of the photoreceptor layers in the macula, with persistent neurosensory detachment. Scale bars=200 μm. HK1: Hexokinase 1; FFA: Fundus fluorescein angiography; AF: Autofluorescence; RPE: Retinal pigment epithelium; OCT: Optical coherence tomography.

Fundus fluorescein angiography (FFA) demonstrated a circular window defect at the posterior pole, suggesting retinal thinning or atrophy. Autofluorescence (AF) imaging showed hyperautofluorescence in a circular pattern within the macular region, indicating alterations in the photoreceptors or retinal pigment epithelium (RPE).

Optical coherence tomography (OCT) findings further confirmed the involvement of the outer retinal structures. At the initial onset, OCT performed at a local clinic revealed neurosensory detachment with blurred and interrupted light bands in the photoreceptor layers of the macular region. Twelve years later, OCT imaging at our hospital demonstrated increased disorganization of the outer retinal structures and persistent neurosensory detachment, highlighting the progressive nature of the disease.

Electrophysiological testing provided additional evidence of photoreceptor dysfunction (Figure 2). At the initial onset, electroretinography (ERG) showed mild abnormalities. By the time of the patient's visit to our hospital (11y after symptom onset), ERG revealed prolonged latency and reduced amplitude in both scotopic (rod) and photopic (cone) responses, indicating substantial impairment of both rod and cone photoreceptors. Multifocal ERG at the same time point demonstrated a reduced central amplitude, reflecting loss of macular function. Visual field testing revealed a diffuse reduction in light sensitivity, with the central field being the most affected.

Whole exome sequencing identified a heterozygous pathogenic variant in the *HK1* gene, with a cytosine-to-thymine substitution at nucleotide position 883 (c.883C>T), leading to a change from arginine to a termination codon at amino acid position 295 (p.Arg295Ter; Figure 3A). Consistent with this truncating nature, *in silico* analysis using MutationTaster predicted that the variant alters protein features and triggers nonsense-mediated mRNA decay (NMD). To experimentally validate these computational predictions, we isolated and cultured patient-derived urine epithelial cells to assess the variant's impact on HK1 expression. Western blot analysis revealed a significant reduction (~50%) in HK1 protein levels in the patient's urine epithelial cells compared to normal controls, with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) used as a loading control (Figure 3B). Furthermore, quantitative real-time PCR (qPCR) demonstrated decreased *HK1* mRNA expression at both 5' and 3' regions of the pathogenic variant site, indicating likely NMD (Figure 3C).

These findings suggest that the *HK1* pathogenic variant may primarily affect the photoreceptor layers, with progressive deterioration in both structural integrity and functional capacity over time. Based on these findings, the patient was diagnosed with inherited retinal degeneration with a phenotype consistent with CRD.

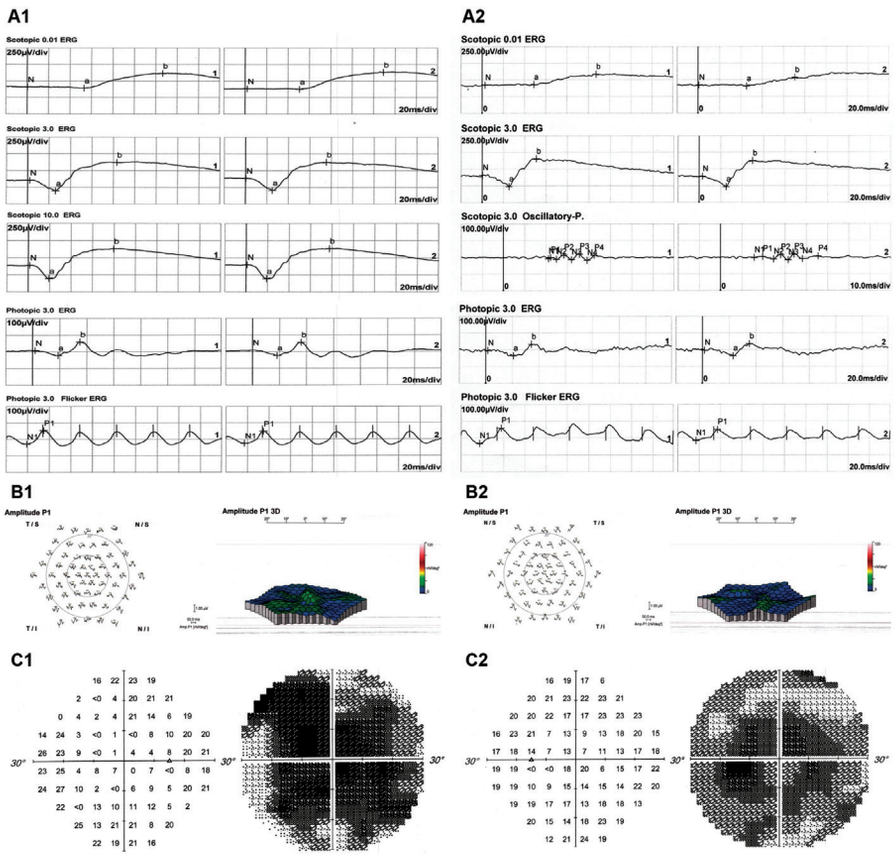

Figure 2 ERG, multifocal ERG, and visual field findings of the patient with *HK1* mutation ERG reveals a significant progression, with prolonged latency and decreased amplitude in both scotopic (rod) and photopic (cone) responses, from the initial onset (A1) to 11y later (A2). Multifocal ERG (B1, B2) performed 11y later demonstrates a central reduction in amplitude, reflecting deteriorating macular function. Visual field tests (C1, C2) performed eleven years later show a diffuse decrease in light sensitivity, with the central area being most affected, suggesting advancing degeneration of photoreceptors or the RPE. HK1: Hexokinase 1; ERG: Electroretinography; RPE: Retinal pigment epithelium.

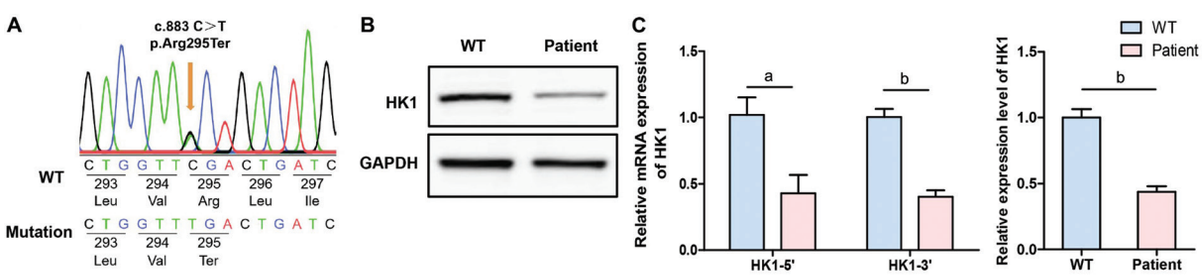

Figure 3 Genetic and protein analysis A: Sequence chromatogram confirming a heterozygous c.883C>T pathogenic variant in the *HK1* gene, resulting in a premature stop codon (p.Arg295Ter); B: Western blot analysis of urine-derived epithelial cells shows markedly reduced HK1 protein levels in the patient compared with WT control, with GAPDH as a loading control, indicating that the pathogenic variant decreases HK1 protein expression; C: qPCR analysis of *HK1* mRNA levels in urine epithelial cells, demonstrating reduced expression at both 5' and 3' regions relative to the c.883C>T pathogenic variant site when compared with controls. Data were normalized to GAPDH and are presented as mean±SD. [a]*P*<0.05, [b]*P*<0.01. HK1: Hexokinase 1; WT: Wild-type; GAPDH: Glyceraldehyde-3-phosphate dehydrogenase; qPCR: Quantitative real-time polymerase chain reaction; SD: Standard deviation.

DISCUSSION

We present a male patient with progressive blurred vision whose clinical and imaging characteristics were consistent with CRD. Notably, genetic testing revealed a heterozygous pathogenic variant in the *HK1* gene (NM_033500.2:c.883C>T, p.Arg295Ter), which is the first report linking this variant to retinal dystrophy, thereby expanding the known spectrum of *HK1*-associated phenotypes.

Previous studies have most frequently reported that pathogenic variants in the *HK1* gene result in autosomal dominant RP, characterized by night blindness, decreased central vision, and peripheral vision loss, often due to the E847K (c. 2539G>A) pathogenic variant[5-9,12]. In addition to RP, rare phenotypes associated with *HK1* pathogenic variants have

been documented; for example, Shah *et al*[10] and Sato *et al*[11] reported cases of PPRCA. Furthermore, Okur *et al*[12] described S445L (c.1334C>T) in *HK1* leading to a complex phenotype involving RP, CRD, and optic atrophy, accompanied by cystic brain lesions and neurological abnormalities. Yuan *et al*[9] found that the E851K variant (c.2551G>A) in *HK1* can also cause dominant macular dystrophy and CRD, primarily affecting cone photoreceptors rather than rods. The clinical phenotypes of inherited retinal dystrophies caused by pathogenic variants in the *HK1* gene are summarized in Table 1.

In this study, our patient presented with CRD and was found to harbor a heterozygous Arg295Ter (c.883C>T) pathogenic variant in the *HK1* gene, a variant that introduces a premature termination codon and has not been previously reported. HK1, an important enzyme in the glycolysis pathway that catalyzes the first step in glucose metabolism[1-2]. Given its essential role in glycolysis, this pathogenic variant was predicted to induce NMD, leading to reduced transcript levels. Consistent with this, qPCR analysis demonstrated decreased *HK1* mRNA expression at both upstream and downstream regions of the pathogenic variant site, supporting the involvement of NMD in the pathogenesis. Notably, this nonsense pathogenic variant differs from previously described missense pathogenic variants, which may account for the distinct CRD phenotype observed in our patient. The patient exhibited progressive vision loss without significant night blindness. ERG revealed impaired cone and rod cell function, and OCT showed retinal thinning and loss of the photoreceptor layer. Additionally, OCT displayed neurosensory detachment, also described as "foveal cavitation", which may be indicative of photoreceptor dysfunction[15]. Unlike the case reported by Okur *et al*[12], the CRD in our patient was not accompanied by optic atrophy or neurological symptoms. Differentiating this case from RP is crucial. Furthermore, although the patient had photoreceptor loss, this was not characteristic of RP, which typically starts with peripheral abnormalities and presents with bone spicule pigmentation. A limitation of this report is the absence of a family segregation analysis due to the unavailability of the patient's relatives. Nonetheless, our *in vitro* data provide robust evidence of NMD and reduced HK1 protein expression, strongly supporting the variant's pathogenicity. Future functional validation in retinal models may further clarify the direct causal link between this systemic metabolic defect and the specific ocular phenotype.

In conclusion, our study used whole exome sequencing to identify a heterozygous *HK1* c.883C>T (p.Arg295Ter) pathogenic variant associated with CRD in a Chinese patient with a comprehensive ophthalmic evaluation. The *HK1* pathogenic variant contributed novel insights into the spectrum of *HK1*-associated retinal dystrophies.

Table 1 Summary of previously reported cases of *HK1*-associated retinal dystrophy

Reference	Family No.	No. of affected individuals	Clinical symptoms	Ocular phenotype	Inheritance	Variant	Ethnicity
Kubota *et al*[5]	F1	3	Gradual decrease of vision and increase of night blindness	RP	AD	c.2539 G>A, p.E847K	Japanese
Sato *et al*[6]	F1	4	Night blindness	RP	AD	c.2539G>A, p.E847K	Japanese
Okur *et al*[12]	F1	NA	Peripheral vision loss and gaze abnormality	RP	NA	c.1241G>A p.G414E	NA
	F2	NA	Photophobia, slight exotropia, bilateral strabismus	RP, CRD, optic atrophy	NA	c.1334C>T p.S445L	NA
	F3	NA	NA	RP, optic atrophy	NA	c.1334C>T p.S445L	NA
Yuan *et al*[9]	F1	3	Central scotoma	RP, CRD, macular dystrophy	AD	c.2551G>A, p.E851K	Chinese
	F2	1	Constricted visual field	RP	AD	c.2551G>A, p.E851K	Caucasian
	F3	1	NA	RP	AD	c.2551G>A, p.E851K	Caucasian
	F4	4	NA	RP	AD	c.2551G>A, p.E851K	Caucasian
Wang *et al*[7]	F1	18	Photophobia, color vision changes, and decreased central vision	RP	AD	c.2539G>A, p.E847K	Caucasian
Sullivan *et al*[8]	F1	21	NA	RP	AD	c.2539G>A, p.E847K	Americans or Europeans
Sato *et al*[11]	F1	1	Metamorphopsia	PPRCA	NA	c.2539G>A,p.E847K	Japanese
	F2	4	NA	PPRCA	AD	c.2539G>A,p.E847K	Japanese
Shah *et al*[10]	F1	NA	Bilateral blurry and decreased vision	PPRCA	AD	c.2551G>A, p.E851K	Caucasian

HK1: Hexokinase 1; RP: Retinitis pigmentosa; CRD: Cone-rod dystrophy; PPRCA: Pigmented paravenous retinochoroidal atrophy; AD: Autosomal dominant; NA: Not available.

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Conflicts of Interest: Su YY, None; **Qiu KR,** None; **Wen F,** None; **Zhou XL,** None.

REFERENCES

1 De Jesus A, Keyhani-Nejad F, Pusec CM, *et al*. Hexokinase 1 cellular localization regulates the metabolic fate of glucose. *Mol Cell* 2022;82(7):1261-1277.e9.

2 Wang HM, Vant JW, Zhang A, *et al*. Organization of a functional glycolytic metabolon on mitochondria for metabolic efficiency. *Nat Metab* 2024;6(9):1712-1735.

3 Babu VS, Mallipatna A, Deepak SA, *et al*. Integrated analysis of cancer tissue and vitreous humor from retinoblastoma eyes reveals unique tumor-specific metabolic and cellular pathways in advanced and non-advanced tumors. *Cells* 2022;11(10):1668.

4 Samra YA, Zaidi Y, Rajpurohit P, *et al*. Warburg effect as a novel mechanism for homocysteine-induced features of age-related macular degeneration. *Int J Mol Sci* 2023;24(2):1071.

5 Kubota D, Matsumoto K, Hayashi M, *et al*. High-resolution photoreceptor imaging analysis of patients with autosomal dominant retinitis pigmentosa (adRP) caused by *HK1* mutation. *Ophthalmic Genet* 2020;41(6):629-638.

6 Sato S, Morimoto T, Hotta K, *et al*. Eleven-year follow-up of a Japanese retinitis pigmentosa patient with an HK1 gene mutation. *Ophthalmic Genet* 2019;40(5):466-469.

7 Wang F, Wang YD, Zhang B, *et al*. A missense mutation in *HK1* leads to autosomal dominant retinitis pigmentosa. *Invest Ophthalmol Vis Sci* 2014;55(11):7159.

8 Sullivan LS, Koboldt DC, Bowne SJ, *et al*. A dominant mutation in hexokinase 1 (*HK1*) causes retinitis pigmentosa. *Invest Ophthalmol Vis Sci* 2014;55(11):7147.

9 Yuan ZS, Li BY, Xu MC, *et al*. The phenotypic variability of HK1-associated retinal dystrophy. *Sci Rep* 2017;7(1):7051.

10 Shah SM, Schimmenti LA, Chiang J, *et al*. Association of pigmented paravenous retinochoroidal atrophy with a pathogenic variant in the HK1 gene. *Retin Cases Brief Rep* 2022;16(6):770-774.

11 Sato S, Morimoto T, Fujikado T, *et al*. Two Japanese families with pigmented paravenous retinochoroidal atrophy and HK1 mutation: a case report. *Case Rep Ophthalmol* 2024;15(1):8-14.

12 Okur V, Cho MT, van Wijk R, *et al*. *De novo* variants in HK1 associated with neurodevelopmental abnormalities and visual impairment. *Eur J Hum Genet* 2019;27(7):1081-1089.

13 Georgiou M, Robson AG, Fujinami K, *et al*. Phenotyping and genotyping inherited retinal diseases: Molecular genetics, clinical and imaging features, and therapeutics of macular dystrophies, cone and cone-rod dystrophies, rod-cone dystrophies, Leber congenital amaurosis, and cone dysfunction syndromes. *Prog Retin Eye Res* 2024;100:101244.

14 Falsini B, Placidi G, De Siena E, *et al*. Genetic characteristics of 234 Italian patients with macular and cone/cone-rod dystrophy. *Sci Rep* 2022;12(1):3774.

15 Leng T, Marmor MF, Kellner U, *et al*. Foveal cavitation as an optical coherence tomography finding in central cone dysfunction. *Retina* 2012;32(7):1411-1419.