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Case Report

Two Japanese Families with Pigmented Paravenous Retinochoroidal Atrophy and HK1 Mutation: A Case Report

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Keywords

Hexokinase 1 · Pigmented paravenous retinochoroidal atrophy · Retinitis pigmentosa · Ultra-widefield fundus imaging · Whole-exome sequencing

Abstract

Hexokinase 1 (*HK1*) gene is the cause of autosomal dominant retinitis pigmentosa (RP) 79. To date, only E874K mutation has been reported as the causative mutation in patients with nonsyndromic RP. As a Caucasian RP case with a pathological variant of *HK1* exhibiting pigmented paravenous retinochoroidal atrophy (PPRCA) phenotype was recently reported, we reviewed RP79 cases in our Japanese RP cohort. Consequently, 2 Japanese patients, who were diagnosed with RP79 by genetic tests in our RP cohort, were included in this study. Patient 1 was a 60-year-old woman. Fundus examination revealed symmetrical donut-shaped retinal degeneration, with pigment deposition avoiding the macula. Moreover, degeneration extended in a peripheral direction along the vessels like a starfish, and degeneration was observed around the veins and arteries. Patient 2 was a 75-year-old man. Fundus examination revealed symmetric macula-avoiding donut-shaped retinal degeneration, with paravenous protruding degeneration along the blood vessels like in case 1. Both Japanese cases, which belonged to two separate families, had the same HK1 pathogenic mutation, with a phenotype of PPRCA. Furthermore, atrophy along retinal arteries was noted. Reviewing previous nonsyndromic RP79 cases revealed symptoms that are believed to be those of PPRCA. Ultra-widefield fundus imaging, especially ultra-widefield fundus autofluorescence, has been useful in detecting PPRCA. If these devices become widely available,

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more cases may be discovered in the future because PPRCA can be used as a clue to suspect RP79, and Sanger sequencing may be used to identify pathogenic mutations in *HK1* at a lower cost and more easily than using whole-exome sequencing.

Introduction

Hexokinase 1 (*HK1*) gene is responsible for autosomal recessive hemolytic anemia, autosomal recessive Russe-type motor and sensory neuropathy, autosomal dominant (AD) neurodevelopmental disorders with visual defects and brain anomalies, and AD retinitis pigmentosa (RP) 79 (MIM ID*142600) [1]. Only one point mutation (NM_000188: exon 17: c.G2539A: p.E847K) has been reported to cause nonsyndromic RP due to *HK1* mutation. RP caused by *HK1* mutation is rare [2]. We have already reported a case of Japanese non-syndromic RP caused by *HK1* mutation with long-term follow-up data [3]. As a case report of the same mutation in *HK1* with pigmented paravenous retinochoroidal atrophy (PPRCA) was reported recently [4], we decided to re-examine our RP79 cases to determine if any case showed a similar phenotype. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534237).

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Patient 1 was a 60-year-old woman. In elementary school, macular degeneration was suspected; however, she did not undergo regular eye examinations because of the absence of specific symptoms. She had no history of any medical disease. In 2012, she was aware of metamorphopsia in her right eye and visited her previous doctor, who pointed out retinal degeneration in both eyes and referred her to our clinic. Her best corrected visual acuity at the initial examination was 1.2 (Snellen-equivalent [SE] 20/16, LogMAR-equivalent [LE] −0.1; C- 1.75/25°) OD and 1.2 (SE 20/16, LE −0.1; S + 0.25/C- 0.25/40°) OS. The interview revealed that no one in her family had a similar eye disease and that her parents were not consanguineously married (Fig. 1s). Fundus examination revealed symmetrical donut-shaped retinal degeneration, avoiding the macula with pigment deposition. Retinal degeneration was more widespread on the nasal side (Fig. 1a, b). In addition to these findings, we could recognize retinal degeneration, protruding starfish-like along the blood vessels toward the periphery. This degeneration occurred along both veins and arteries. The presence of PPRCA was previously reported by another group [3], but we also found peripheral protrusion of degeneration along both arteries and veins. After 11 years, ultra-widefield fundus imaging (UWFFI) showed firm retinal degeneration along the blood vessels extending to the periphery (Fig. 1c, d). Ultra-wide field fundus autofluorescence (UWFAF) further confirmed that retinal degeneration extended peripherally along the arteries and veins (Fig. 1e, f). The progression of retinal degeneration in the direction of the fovea has been gradual over the past 11 years (Fig. 1g–j). Goldmann perimetry showed little progression of the scotoma toward the center over 11 years, with bilateral expansion toward the temporal direction corresponding to fundus imaging (Fig. 1k–n). Electro-retinography detected waveforms in all measurement modes: photopic, scotopic, and 30-Hz flicker, but the amplitudes of both a and b waves were attenuated and the latencies

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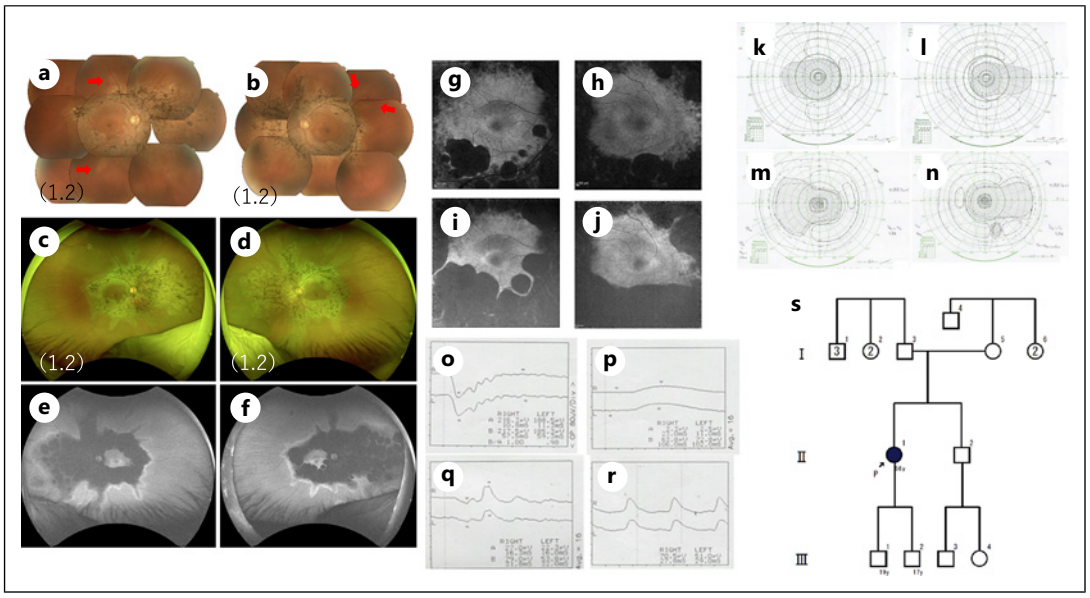

Fig. 1. Clinical findings in case 1. **a**, **b** Montage fundus imaging at the age of 50 years. **c**, **d** Ultra-widefield fundus imaging. **e**, **f** Ultra-widefield fundus autofluorescence at the age of 60 years. **g–j** Fundus autofluorescence at the ages of 49 (**g**, **h**) and 60 years (**i**, **j**). **k–n** Goldmann perimetry at the ages of 49 (**k**, **l**) and 60 years (**m**, **n**). **o–r** Electroretinograms at the age of 50 years: bright flash (**o**), scotopic (**p**), photopic (**q**), 30-Hz flicker (**r**). Upper rows: right, bottom rows: left. **s** Family tree of case 1. No one in the family has complained of eye disease.

were slightly prolonged. In bright-flash electroretinography, the b/a ratio was 1.0 in the right eye and 0.98 in the left eye, indicating a negative pattern (Fig. 1o–r) at the age of 50 years. Conventional optical coherence tomography (OCT) showed preserved macular retinal thickness and no macular edema (Fig. 2a–d). UWF OCT showed that the protruding areas of degeneration along the vessels showed a steep loss of the outer nuclear layer (Fig. 2e, f).

Patient 2 was a 75-year-old man. As his long-term follow-up data had already been reported as the first Japanese case of RP79 [3], we briefly describe the reported findings and progress data from a previous report. In 2022, his best corrected visual acuity was 1.2 (SE 20/16, LE −0.1: S +3.25/C −1.5/80°) OD and 0.7 (SE 20/16, LE −0.15: S +4.5/C −1.25/160°) OS. Interviews revealed three other family members had eye disease symptoms similar to those of the patient (Fig. 3i). The fundus photograph in 2012 revealed the widest angle among the montage fundus images taken so far (Fig. 3a, b). UWFFI performed in 2022 revealed symmetric macular-avoiding donut-shaped retinal degeneration, as in case 1, with paravascular-protruding degeneration along the veins and arteries (Fig. 3c, d). UWFAF more clearly confirmed the PPRCA findings (Fig. 3e, f). The visual field at the last visit in 2022 showed a donut-shaped scotoma consistent with degeneration; however, the central and most peripheral visual fields were preserved (Fig. 3g, h).

After written informed consent was obtained from both patients, whole-exome sequencing (WES) and direct sequencing of PCR products of the *HK1* gene were performed as described previously [2]. In both cases, *HK1* mutation (NM_000188: exon 17: c.2539G>A, p.E847K) was detected by WES and direct resequencing of PCR products. No candidate rare mutations (minor allele frequency <0.01) were found in either case, including the *CRB1* gene, except for *HK1* mutation.

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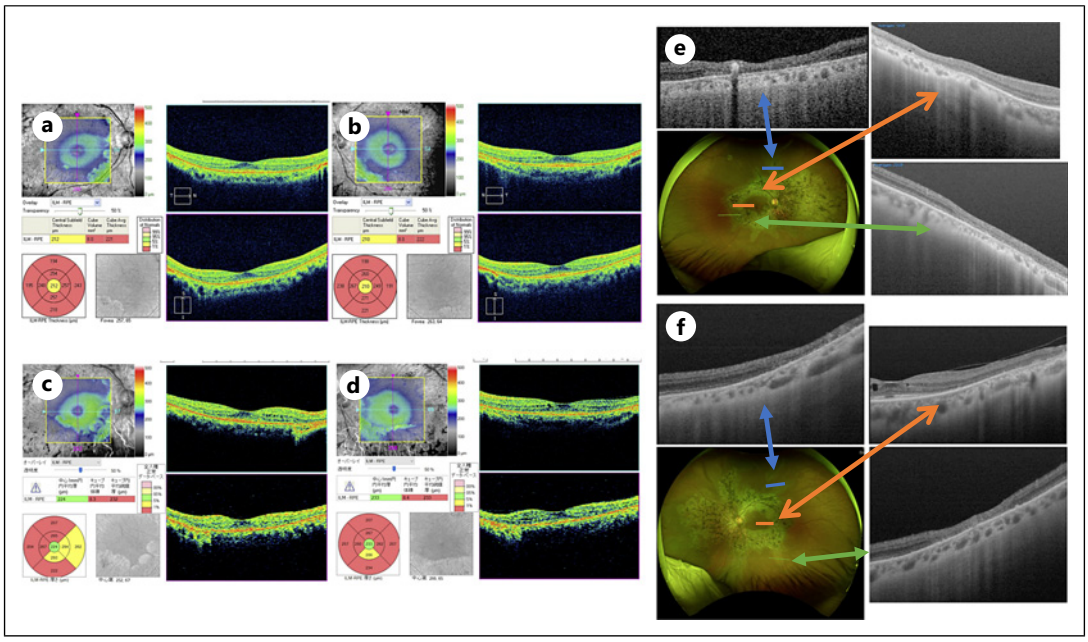

Fig. 2. OCT images in case 1. Conventional OCT at the ages of 49 (**a**, **b**) and 60 (**c**, **d**) years. **e**, **f** Ultra-widefield OCT. Double arrows of the same color indicate OCT images of colored line sites written above the ultra-widefield fundus imaging. The protruding areas of degeneration along the vessels showed a steep loss of the outer nuclear layer. **a**, **c**, **e** Right. **b**, **d**, **f** Left.

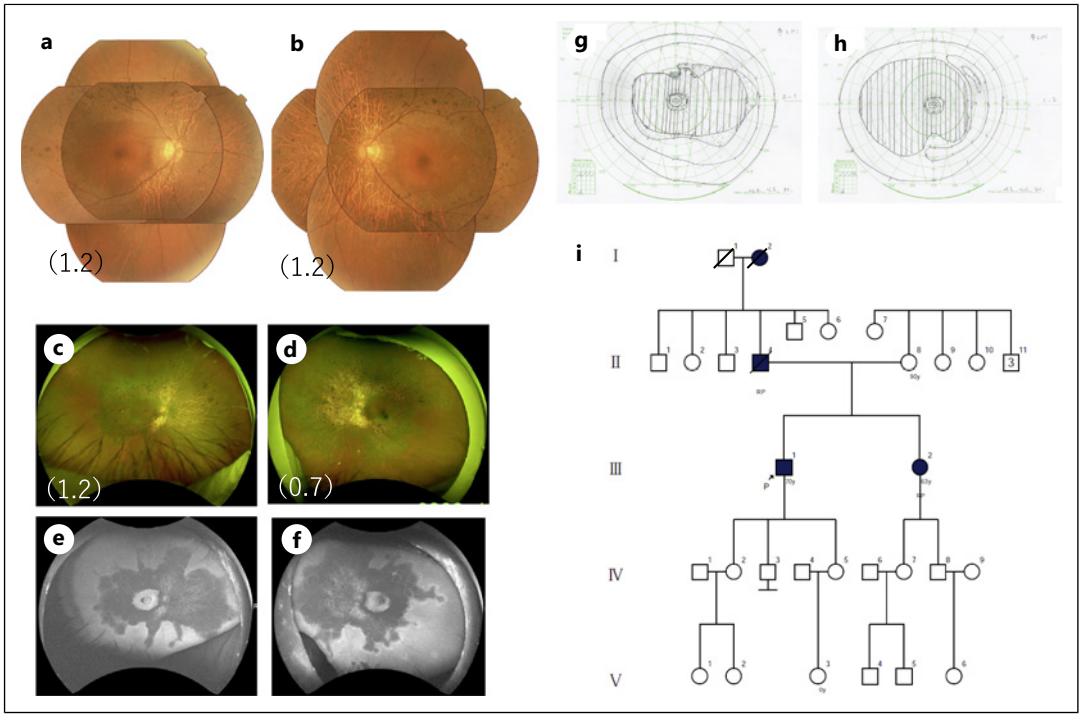

Fig. 3. Clinical findings in case 2. **a**, **b** Montage fundus imaging at the age of 65 years. **c**, **d** Ultra-widefield fundus imaging. **e**, **f** Ultra-widefield fundus autofluorescence at the age of 75 years. **g**, **h** Goldmann perimetry the age of 75 years. **a**, **c**, **e**, **g** Right. **b**, **d**, **f**, **h** Left. **i** Family tree of case 2. Autosomal dominant inheritance form was presumed but no eye disease was found after generation IV.

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Table 1. Review of previous reports

[Ref]	Case No.	Years old	Male/ female	Genotype	VA (right, left)	Ethnicity	Montage fundus imaging	UWFI or UWFAF	PPRCA or PPVRCA
Current report	1	60	F	p.E847K	1.2, 1.2	Japanese	Y	Y	Y
Current report, and [3]	2	75	M	p.E847K	1.0, 0.7	Japanese	Y	Y	Y
[5]	UTAD003-15	68	F	p.E847K	CF, 20/30	Caucasian	Y	N	N
	UTAD003-13	56	F	p.E847K	20/25, 20/20	Caucasian	Y	N	N
	UTAD003-16	34	M	p.E847K (homozygote)	CF, 20/200	Caucasian	Y	N	N
	UTAD003-21	61	F	p.E847K	20/20, 20/20	Caucasian	Y	N	N
	UTAD003-20	52	M	p.E847K	20/20, 20/20	Caucasian	Y	N	N
	UTAD636-10050	56	M	p.E847K	20/32, 20/80	Caucasian	Y	N	N
	UTAD952-10109	51	F	p.E847K	20/40, 20/50	Caucasian	Y	N	N
	MOGL1-5259	60	M	p.E847K	CF, 20/60	Caucasian	N	N	N
	MOGL1-515	45	M	p.E847K	20/20, 20/20	Caucasian	N	N	N
	MOGL1-5321	40	M	p.E847K	20/20, 20/20	Caucasian	N	N	N
[6]	Proband	59	F	p.E847K	0.1, 0.1	Caucasian	N	N	N
[7]	Family 1: II-1	54	F	p.E847K	HM, HM	Han Chinese	N	Y	N
	Family 1: II-2	50	F	p.E847K	20/25, 20/30	Han Chinese	N	Y	Y
	Family 1: II-3	48	M	p.E847K	20/30, 20/30	Han Chinese	N	Y	Y
[8]	I-2	80	F	NA	0.03, 0.05	Japanese	N	Y (low quality)	N
	II-3	49	F	p.E847K	1.0, 1.0	Japanese	N	Y	Y
	III-1	20	F	p.E847K	1.0, 1.0	Japanese	N	Y	Y
[4]	1	41	F	p.E847K	20/400, 20/80	Caucasian	N	Y	Y

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Discussion

This report presents two Japanese RP79 cases carrying p.E847K mutation in *HK1*. Nonsyndromic RP caused by a missense mutation in *HK1* is known as RP79. In previous reports, many cases have shown a pericentral RP phenotype with an excellent central visual prognosis (Table 1) [3–8]. There have also been reports of a patient with no subjective symptoms until the age of 52 years [4]. Our cases also showed the pericentral RP phenotype; central vision was relatively preserved until old age, and the progression of degeneration was slow. In addition, we observed retinal degeneration that extended in a peripheral direction along the vessels, as reported by Shah et al. [4]. However, in our case, retinal degeneration was observed along the arteries and veins. The mutation of *CRB1* is a well-known mutation related to the PPRCA phenotype, degenerating along the veins and spreading markedly to the periphery. Unlike the PPRCA phenotype of *CRB1* mutation, *HK1* mutation leads to degeneration along the veins and arteries, suggesting that it may degenerate by a mechanism different from that of *CRB1* mutation. UWF OCT imaging of the degenerative area along the vessels revealed a loss of the outer nuclear layer, with a clear boundary between the degenerative and nondegenerative areas and a steep loss rather than a gradual loss (Fig. 2e, f). This may indicate that the mutant HK1 protein in the blood vessels is weakly retinotoxic, but this requires further investigation. Until now, we could examine probands only and no family members have been examined. Nonsyndromic RP caused by *HK1* mutation is rare [2]. All observed cases that were reported with fundus photographs (before June 25, 2023) are presented in Table 1. Retinal degeneration protruding along blood vessels could be seen in 7 of 9 patients by UWFFI or UWFAF but could not be determined by montage fundus imaging alone. This indicated that UWFFI and UWFAF are useful in confirming the PPRCA phenotype. Although there are several causative genes for the PPRCA phenotype, such as *CRB1*, in cases of slow progression, retention of the macular area until a relatively old age, nasal predominant degeneration, atrophy along the arteries and veins in PPRCA, and presumed AD genetic form, it may be worthwhile to first perform direct sequence using the Sanger method for *HK1* mutation. This is because there is only one known causal mutation of *HK1* in RP79. Given that gene editing is being actively used to develop treatments for RP in the AD genetic form, and that clinical trials may be planned in the future, it makes sense to identify the RP79 family lineage.

This study has some limitations. First, it remains unknown whether RP79 always causes degeneration along the arteries and veins as this was a review of a small number of cases, including previous reports, and the mechanism by which degeneration along retinal vessels is caused has not yet been clarified. However, we have shown that PPRCA is one of the phenotypes of RP79 that is observed across racial lines and that UWFAF is very effective in its detection. This finding may lead to a definitive genetic diagnosis by the Sanger method without the need to perform WES or other methods.

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Statement of Ethics

This study was conducted in accordance with the Declaration of Helsinki. This study protocol was reviewed and approved by the Ethics Committee of Osaka University, approval number. 719-2, Osaka, Japan. Written informed consent was obtained from all participants for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S. Sato and T.M. performed patient recruitment, clinical follow-up, and informed consent. S. Sato and S.T. performed the genomic DNA purification and Sanger sequencing, respectively. S. Sato, T.M., and T.F. analyzed and interpreted the sequencing data. S. Sato, T.M., M.T., T.F., S. Sai, and K.N. performed the clinical data evaluation. S. Sato was a major contributor to writing the manuscript. All authors have read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. The data are not publicly available on legal or ethical grounds. Further inquiries can be directed to the corresponding author.

References

1 OMIM. [cited 2023 Jun 26]. Available from: https://www.omim.org/.
2 Fahim AT, Daiger SP, Weleber RG. In: Adam MP, Everman DB, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, et al, editors. Nonsyndromic retinitis pigmentosa overview. Seattle (WA); 1993.
3 Sato S, Morimoto T, Hotta K, Fujikado T, Nishida K. Eleven-year follow-up of a Japanese retinitis pigmentosa patient with an *HK1* gene mutation. Ophthalmic Genet. 2019;40(5):466–9.
4 Shah SM, Schimmenti LA, Chiang J, Iezzi R. Association of pigmented paravenous retinochoroidal atrophy with a pathogenic variant in the *HK1* gene. Retin Cases Brief Rep. 2022;16(6):770–4.
5 Sullivan LS, Koboldt DC, Bowne SJ, Lang S, Blanton SH, Cadena E, et al. A dominant mutation in hexokinase 1 (*HK1*) causes retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2014;55(11):7147–58.
6 Wang F, Wang Y, Zhang B, Zhao L, Lyubasyuk V, Wang K, et al. A missense mutation in *HK1* leads to autosomal dominant retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2014;55(11):7159–64.
7 Yuan Z, Li B, Xu M, Chang EY, Li H, Yang L, et al. The phenotypic variability of *HK1*-associated retinal dystrophy. Sci Rep. 2017;7(1):7051.
8 Kubota D, Matsumoto K, Hayashi M, Oishi N, Gocho K, Yamaki K, et al. High-resolution photoreceptor imaging analysis of patients with autosomal dominant retinitis pigmentosa (adRP) caused by *HK1* mutation. Ophthalmic Genet. 2020;41(6):629–38.