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# Autosomal recessive cone–rod dystrophy associated with compound heterozygous mutations in the *EYS* gene

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## Abstract

*Background* *EYS* mutations have been identified only in patients with autosomal recessive retinitis pigmentosa (arRP). This study was conducted to describe clinical and genetic features of a Japanese patient with autosomal recessive cone–rod dystrophy (arCRD) and *EYS* mutations.
*Methods* We performed complete ophthalmic examinations including full-field electroretinography (ERG). Genetic analysis using whole-exome sequencing and Sanger sequencing was performed to identify the disease-causing mutation in a 31-year-old male patient.
*Results* At the initial visit, the patient's decimal best-corrected visual acuity (BCVA) was 0.9 and 0.6 in his right and left eyes, respectively. Funduscopy indicated retinal degenerations were predominantly affected within the vascular arcades and preserved retinal vessels in the mid-periphery in both eyes. Visual field testing showed there were relative central scotomas and preserved peripheral visual fields in both eyes. ERG indicated there was a decreased pattern for both the rod and cone responses. At the age of 36 years, his BCVA decreased to 0.2 in both eyes. Optical coherence tomography showed marked retinal thinning of the macular regions in both eyes. Genetic analysis identified compound heterozygous truncating mutations (p.Y2935X and p.S1653KfsX2) in the *EYS* gene. His unaffected parents were heterozygous for each mutation.
*Conclusions* Our results demonstrated that *EYS* mutations can be the cause of not only arRP but also arCRD. Our findings extend the phenotypic spectrum of patients with *EYS* mutations.

**Keywords** *EYS* gene · Whole-exome sequencing · Genetics · Retinitis pigmentosa · Cone–rod dystrophy

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## Introduction

The eyes shut homolog (*EYS*) gene (Online Mendelian Inheritance in Man: *612424), largest gene known to be expressed in the human eye, spanning more than 2 Mb within the *RP25* locus (6q12). The human EYS protein is a homolog of the *Drosophila* eyes shut/ spacemaker (eys) protein, which is an extracellular matrix protein essential for photoreceptor development and morphology of the insect eye.

In 2008, mutations in the *EYS* gene were reported in patients with autosomal recessive retinitis pigmentosa (arRP) [1, 2]. The *EYS* mutations, which have been shown to be predominantly truncating mutations, have been described in patients with different ethnic origins and account for 5–16 % of arRP [3–7]. Thus, disruption of the EYS function has been identified as a frequent cause of arRP worldwide. With the exception for arRP, to date there have been no *EYS* mutations reported for any other phenotype.

Here, we report clinical and genetic features of a patient with autosomal recessive cone–rod dystrophy (arCRD) associated with compound heterozygous *EYS* mutations.

## Case report

A 31-year-old male patient (JU#0659) was referred to our hospital with a complaint of loss of visual acuity. He first reported a decreased visual acuity at the age of 29 years. Family history indicated that his parents had no previous reports of any ocular symptoms (Fig. 1). At his initial examination, decimal best-corrected visual acuity (BCVA) was 0.9 [with −6.00 diopter (dpt), cylinder (cyl) −1.25 dpt axis (Ax) 130°] in his right eye and 0.6 (with −4.50 dpt, cyl −0.75 dpt Ax 180°) in his left eye. Anterior segment examination showed no remarkable findings. Intraocular pressures were 16 mmHg in the right and 15 mmHg in the left eye. Funduscopy showed retinal degenerations within the vascular arcade in both eyes (Fig. 2a). Neither retinal degeneration nor attenuation of retinal vessels

### Family JU#0659



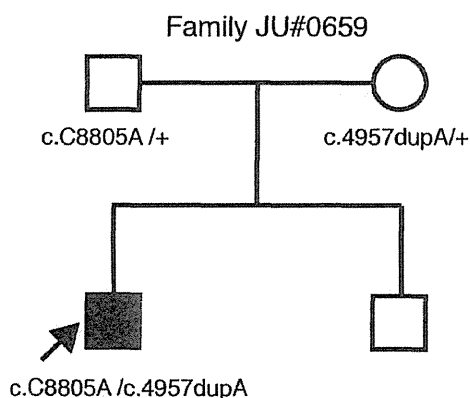c.C8805A /+            c.4957dupA/+

c.C8805A /c.4957dupA

Fig. 1 Pedigree of a Japanese family. Unaffected family members (males, *open squares*; females, *open circles*) and an affected proband (male, *solid square*) are shown
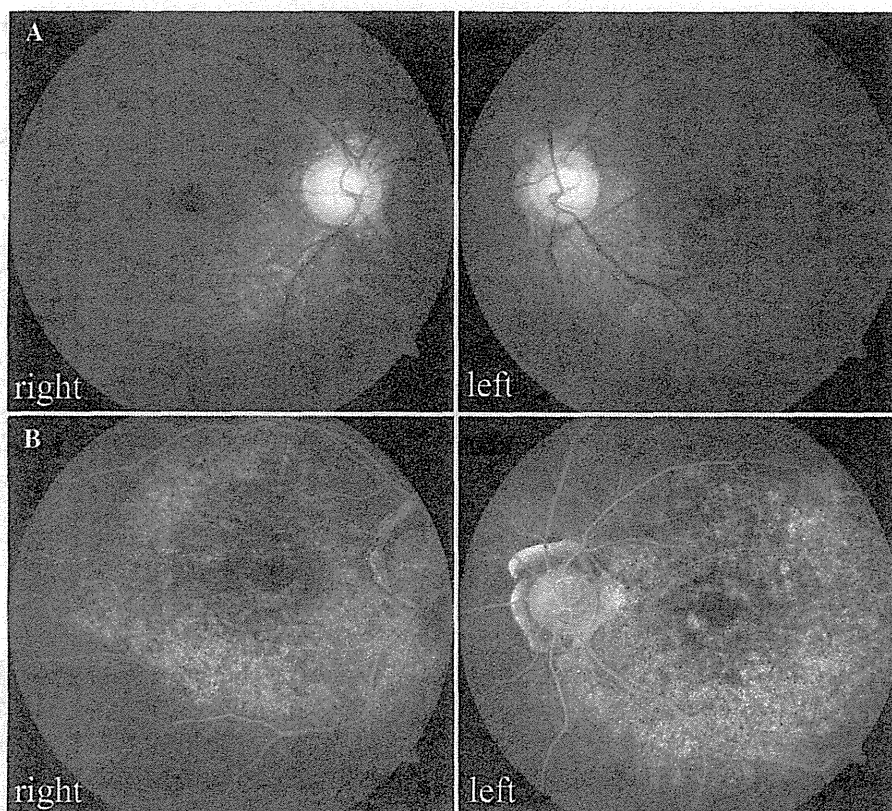
was observed in the periphery. Fluorescein angiography (VISUCAM NM/FA; Carl Zeiss Meditec AG, Dublin, CA, USA) showed a hyperfluorescence pattern due to a window defect within the vascular arcades of both eyes (Fig. 2b). At the age of 32 years, visual field testing using Goldmann kinetic perimetry (GP; Haag-Streit, Bern, Switzerland) showed bilateral central scotomas of the I-3e and I-4e isopters with relative sparing of the center, but preserved peripheral visual fields of the V-4e and I-4e isopters in both eyes (Fig. 3). Full-field electroretinography (ERG) was performed according to the protocols of the International Society for Clinical Electrophysiology of Vision. The procedure and conditions for ERG recording have been reported previously [8]. The ERG showed the rod, standard combined, cone, and 30-Hz flicker responses were bilaterally reduced to about one-third of those in a control, but the peak implicit time of each response was not delayed (Fig. 4).

At the age of 36 years, his BCVA decreased to 0.2 in both eyes. Funduscopic images using the Optos 200Tx imaging system (Optos PLC, Dunfermline, United Kingdom) showed retinal degenerations within the vascular arcades in both eyes, but relatively preserved mid-peripheral to peripheral retinal findings with no apparent attenuation of the retinal vessels (Fig. 5a). Fundus autofluorescence imaging (FAI) (Optos PLC) showed decreased autofluorescence within the vascular arcades but increased autofluorescence of the foveal area, and increased autofluorescence outside the vascular arcades in both eyes (Fig. 5b). Optical coherence tomography (OCT) (Cirrus HD-OCT; Carl Zeiss Meditec AG) showed retinal thinning with a visible foveal external limiting membrane line (Fig. 5c), and entire macular thinning in both eyes (Fig. 5d).

To identify disease-causing gene mutations, we performed whole-exome sequencing analysis as per a previously described method [9]. The obtained sequence data in the patient were compared with reference human genome sequences. Initially, we focused on only variants that could change the amino acid sequence. Subsequently, we filtered the remaining variants based on the criteria that a frequency of mutation was less than 1 % in the 1000-genome database (http://www.1000genomes.org). Finally, we screened variants residing within 207 retinal disease-associated genes published in the November 15, 2013

Fig. 2 Fundus photographs and fluorescein angiography images (FA) of the patient at the age of 31 years. a Fundus photographs show retinal degenerations within the vascular arcades in both eyes. b FA shows a hyperfluorescence pattern due to a window defect within the vascular arcades of both eyes
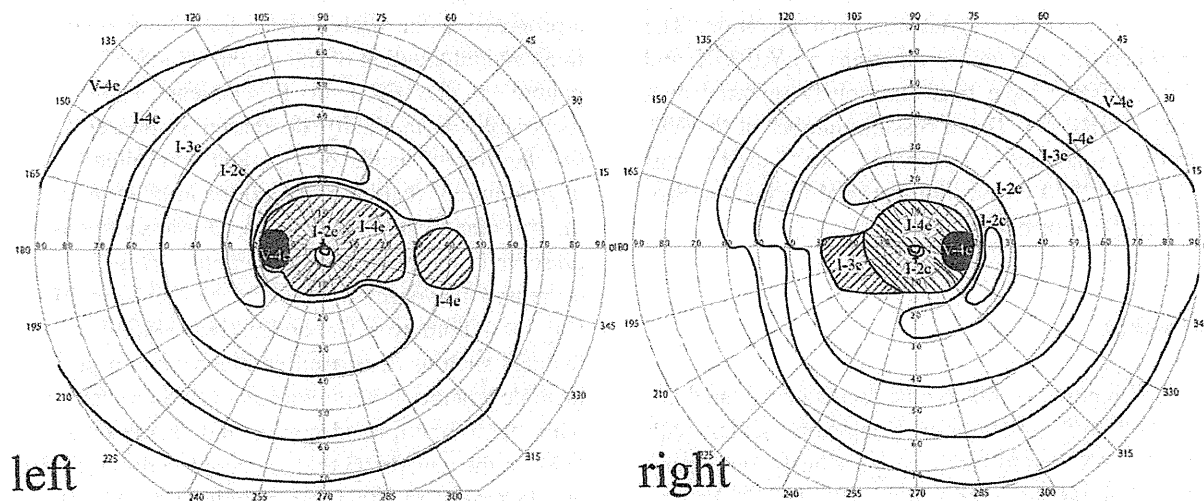


Fig. 3 Visual field testing using Goldmann kinetic perimetry (GP) at the age of 32 years. GP shows bilateral central scotomas of the I-3e and I-4e isopters with relative sparing of the center, but with preserved peripheral visual fields of the V-4e and I-4e isopters in both eyes

Fig. 4 Full-field electroretinography (ERG) at the age of 32 years. ERG shows that the rod, standard combined, cone, and 30-Hz flicker responses are bilaterally reduced to about one-third of those in a control, but the peak implicit time of each response is not delayed
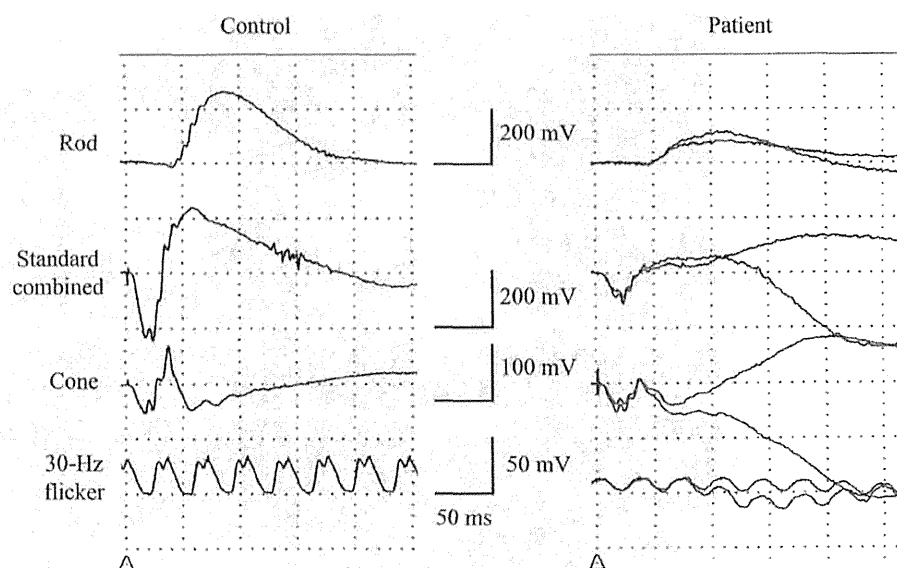
RetNet database (https://sph.uth.edu/retnet/). Based on the obtained data, known *EYS* mutations were identified in a compound heterozygous state as disease-causing mutations. In the other 206 genes, there were no mutations found in compound heterozygous or homozygous states. The identified *EYS* gene mutations were c.C8805A and c.4957dupA, which result in the truncating mutations p.Y2935X and p.S1653KfsX2, respectively. The findings were confirmed by Sanger sequencing. The patient's unaffected parents were heterozygous for each mutation. The compound heterozygous mutations (p.Y2935X and p.S1653KfsX2) have been previously reported as a cause of arRP [7]. The accession number of the *EYS* mRNA reference sequence we used was NM_001142800.1 from the National Center for Biotechnology Information.

## Discussion

In this report, whole-exome sequencing analysis identified *EYS* mutations in a Japanese patient with arCRD. *EYS* mutations have previously only been reported in patients with arRP [1, 2]. This is the first report that describes arCRD associated with compound heterozygous mutations in the *EYS* gene.

Previous studies have revealed that the EYS protein is expressed specifically in the human retina and is localized in the outer segment of the photoreceptor layers of the porcine retina [1, 2]. Although the function and structure of human EYS protein remain unclear, it has been suggested to be essential for photoreceptor morphogenesis [2]. In fact, *EYS* mutations give rise to RP phenotypes with thinning of the outer retinal layers [5, 7], which results from degeneration of both the rod and cone photoreceptors. Clinical features of patients with *EYS* mutations include a typical form of RP that is characterized by a progressive constricted visual field, bone pigmentations and attenuation of the retinal vessels [3–5]. The pattern of the ERG in RP patients shows nonrecordable or markedly decreased responses [3–5]. On the other hand, our patient exhibited retinal degenerations that were predominantly seen within the vascular arcades (Fig. 5a, b), central scotomas and preserved peripheral visual fields (Fig. 3), and decreased responses in the both rod and cone ERG (Fig. 4) in both eyes. Generally, CRD exhibits several features such as decreased central vision, a predominant degeneration of the macular region as compared with the mid-peripheral region, and decreased amplitudes in the cone ERG that are equal to or worse than the decreased rod ERG amplitudes [10, 11]. These characteristics of CRD were clearly consistent with the phenotype of our patient. Taken together, these findings indicated that the patient diagnosis was arCRD and not arRP.
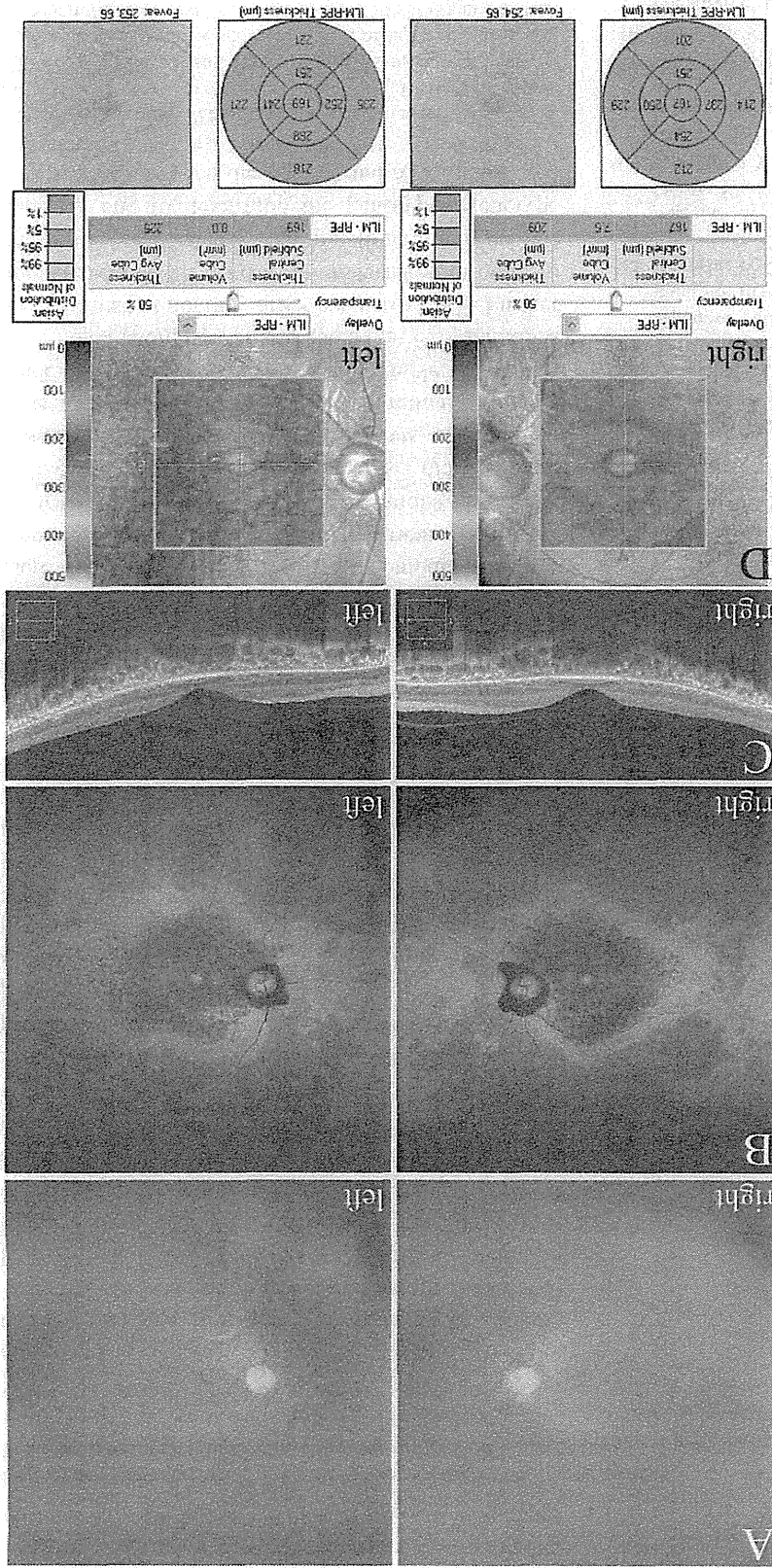
Whole-exome sequencing analysis disclosed that our patient had the *EYS* mutations, which demonstrates that the *EYS* mutations can be responsible for both the arCRD and the arRP phenotypes. Interestingly, mutations in the *ABCA4* [12–14], *CERKL* [15–18], and *C8orf37* [19, 20] genes have also been reported to be disease-causing mutations of both the arCRD and arRP phenotypes. With regard to the *ABCA4* gene mutations, the degree of functional damage caused by the various *ABCA4* mutation types can underlie the different degeneration patterns, for example, Stargardt disease (a type of macular dystrophy), arCRD or arRP [12–14]. The majority of patients with *CERKL* mutations exhibit arCRD [17, 18] and less frequently arRP [15, 16]. This is consistent with the fact that the CERKL protein is predominantly expressed in the cone photoreceptors [21]. In addition, different *C8orf37* mutations can cause either the arCRD or arRP phenotypes, which is consistent with the fact that the C8orf37 protein is expressed in both the rod and cone photoreceptors [19, 20]. However, this does not explain the pattern of the photoreceptor degeneration. On the other hand, the compound heterozygous *EYS* mutations (p.Y2935X and p.S1653KfsX2) that were found in our patient have also been reported in an arRP patient [7]. Although it is not understood why the same compound heterozygous mutations would underlie either the arCRD or arRP phenotypes, this finding suggests there is the presence of different modifier alleles between the arCRD or arRP patients with the compound heterozygous *EYS* mutations. Even so, our whole-exome sequencing analysis did not demonstrate any compound heterozygous or homozygous mutations in other 206 retinal disease-associated genes published in the RetNet database.

In conclusion, we demonstrated that *EYS* mutations are the cause of not only arRP but also arCRD. Further investigations will need to be undertaken in order to clarify the prevalence of *EYS* mutations among arCRD patients, and to determine the genotype–phenotype correlations between the arCRD and *EYS* mutations.

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# Occult macular dystrophy with bilateral chronic subfoveal serous retinal detachment associated with a novel *RP1L1* mutation (p.S1199P)

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Hisashi Yamada · Satoshi Katagiri · Yujiro Fujino · Yasuo Noda ·
Miwako Yoshimoto · Hidetoshi Kawashima

## Abstract

*Purpose* The purpose of this study was to present an atypical case of occult macular dystrophy (OMD) with bilateral chronic subfoveal serous retinal detachment (SRD).

*Methods* A 53-year-old man was ophthalmologically evaluated because of decreased visual acuity in both eyes. Genomic DNA was extracted from venous blood samples. Mutational analysis of the *retinitis pigmentosa 1-like 1* (*RP1L1*) gene was performed by Sanger sequencing.

*Results* Best-corrected visual acuity (BCVA) was 0.1 logMAR in both eyes until the age of 53, after which it gradually declined. Full-field electroretinography (ERG) was unremarkable, while multifocal ERG revealed a reduced central response in both eyes. Optical coherence tomography showed subfoveal SRD in both eyes, and fundus fluorescein angiography yielded unremarkable results. His brother and cousin had similar subjective symptoms. At age 58, his logMAR BCVA was 0.532 (OD) and 0.347 (OS). He was given 23 administrations of intravitreal bevacizumab (IVB; 1.25 mg) in both eyes alternately over a 2-year period and also underwent reduced-fluence photodynamic therapy in both eyes. Two years after the first administration of IVB, a reduction in SRD was obtained, and IVB was therefore discontinued. Three years after the first administration, logMAR BCVA was 0.155 (OD) and 0.523 (OS). Mutational analysis revealed a novel heterozygous missense mutation (p.S1199P).

*Conclusions* We describe in detail a case of bilateral chronic subfoveal SRD in an atypical OMD patient carrying a novel heterozygous *RP1L1* mutation

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(p.S1199P). Our results further extend the phenotypic spectrum of *RP1L1*-associated OMD.

**Keywords** Occult macular dystrophy · *RP1L1* · Serous retinal detachment · Intravitreal bevacizumab · Foveal cavitation

## Introduction

Occult macular dystrophy (OMD), first described in 1989 [1], is a rare autosomal dominant macular disease characterized by slow progressive loss of visual acuity, normal ophthalmoscopic and fluorescein angiographic findings, normal responses on full-field electroretinography (ERG) [2], and reduced amplitudes on focal macular ERG or multifocal ERG [2, 3]. In addition to autosomal dominant cases, however, sporadic cases have also been reported [3, 4]. Optical coherence tomography (OCT) findings have revealed outer retinal structural abnormalities in the foveal areas in both autosomal dominant and sporadic OMD patients [5–8]. The molecular basis of OMD was elucidated in 2010: heterozygous missense mutations (p.R45W [9–13], p.W960R [9], c.S1199C [14], p.Q2311P [13], p.S676C [13], and p.D1425H [13]) in the *retinitis pigmentosa 1-like 1* (*RP1L1*) gene were identified in autosomal dominant OMD. Here, we report an atypical case of OMD with bilateral chronic subfoveal serous retinal detachment (SRD) associated with a novel missense mutation in the *RP1L1* gene.

## Methods

### Ethics

The study was approved by the institutional review board of Tokyo Kosei Nenkin Hospital and The Jikei University School of Medicine. The protocol adhered to the tenets of the Declaration of Helsinki.

### Clinical investigation

A 47-year-old Japanese man (JU#0444) underwent a comprehensive ophthalmic examination, including decimal best-corrected visual acuity (BCVA), slitlamp biomicroscopy, dilated ophthalmoscopy, and fluorescein angiography (FA). We also performed indocyanine green angiography (ICGA) using a scanning laser ophthalmoscope Model 101 (Rodenstock Instruments, Munich, Germany). For retinal scan images, spectral-domain OCT (SD-OCT) (SPECTRALIS; Heidelberg Engineering GmbH, Heidelberg, Germany; and Cirrus HD-OCT Model 4000; Carl Zeiss Meditec AG, Oberkochen, Germany) was performed using the HD 5-line raster scan protocol and Macular Cube protocol (512 × 128 scan) to scan a 6 × 6-mm$^2$ area of the macula. Retinal thickness was measured manually from the inner limiting membrane to the limit of the outer retina without hanging down the photoreceptor outer segment. Retinal detachment thickness was measured manually from the limit of the outer retina and retinal pigment epithelium without hanging down the photoreceptor outer segment. BCVA, retinal thickness, and retinal detachment thickness were measured consistently during followups. Visual fields were assessed using a Humphrey Field Analyzer (Carl Zeiss Meditec AG) with the central 10-2 SITA-Standard program, and mean deviation (MD) and pattern standard deviation (PSD) were evaluated. Full-field ERG and multifocal ERG were performed according to the protocols of the International Society for Clinical Electrophysiology of Vision [15–17]. The procedure and conditions for full-field ERG and multifocal ERG recording have been detailed previously [18, 19]. Analysis of multifocal ERG data was performed using the Visual Evoked Response Imaging System (Electro Diagnostic Imaging Inc., San Mateo, CA). Electrooculography (EOG) was performed as described previously in accordance with the protocols of the International Society for Clinical Electrophysiology of Vision [20].

### Molecular genetic analysis

Genomic DNA was extracted from venous blood samples using the Gentra Puregene Blood kit (Qiagen, Hilden, Germany) and subjected to molecular analysis for Sanger sequencing. All coding exons (exon 2 to exon 4) in the *RP1L1* gene were amplified via polymerase chain reaction (PCR) using previously reported primers [21], all of which were produced by Operon Biotechnologies (Tokyo, Japan). The PCR products were purified with a QIAquick PCR Purification kit (Qiagen) and used as sequencing templates. Both strands were sequenced on an automated