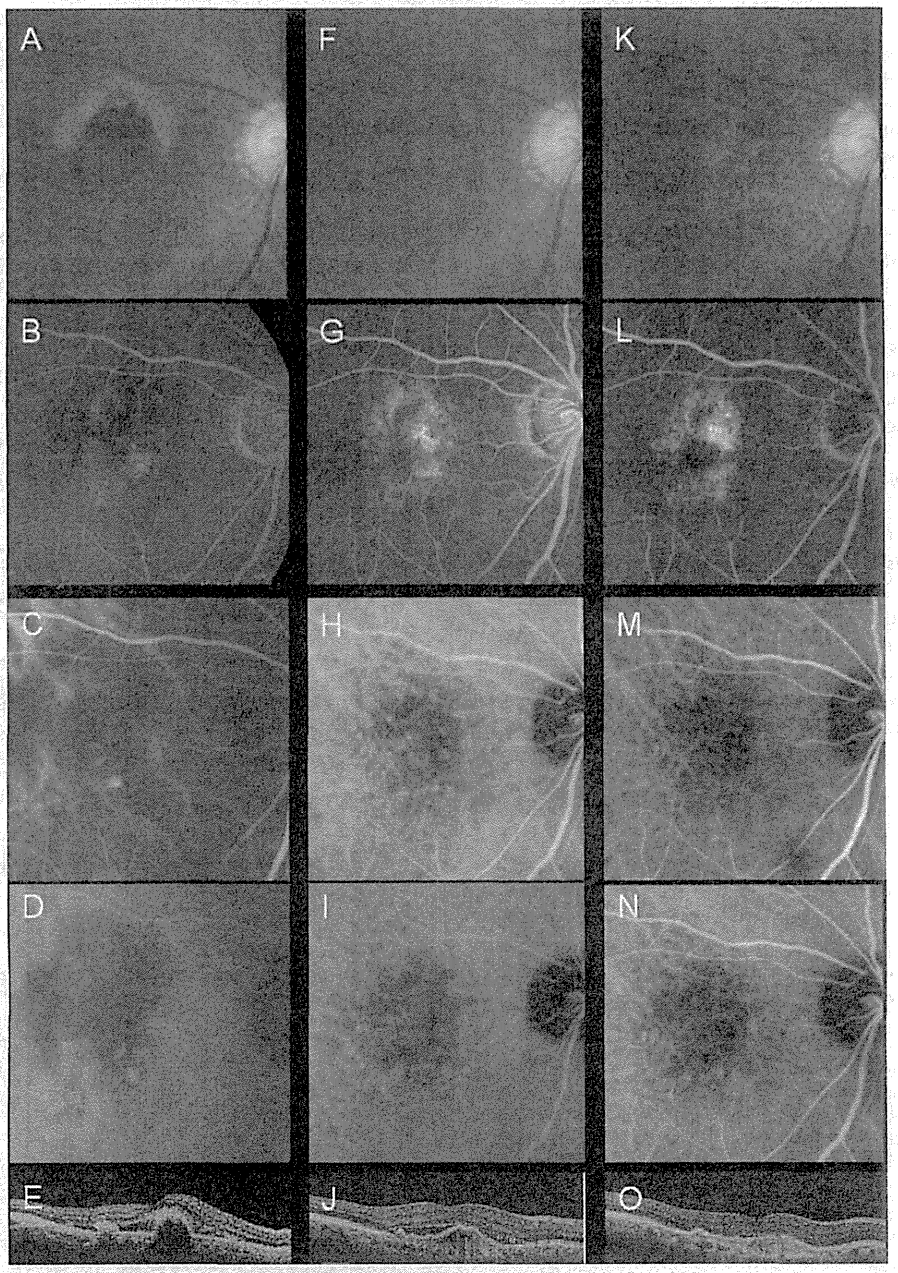

Figure 3 Fundus photograph, fluorescein angiography (FA), indocyanine green angiography (ICGA) and optical coherence tomography (OCT) findings before and at 12 and 36 months after triple therapy. (A) At baseline, fundus photograph demonstrates an orange-reddish nodule with a subretinal haemorrhage. (B) FA shows subfoveal hyperfluorescent leakage. (C, early phase; D, late phase). ICGA shows a branching vascular network that terminates in polypoidal lesions. (E) OCT demonstrates retinal pigment epithelium (RPE) detachment with subretinal fluid. (F) At 12 months after triple therapy, fundus photograph shows absorption of the subretinal haemorrhage. (G) FA demonstrates RPE window defect with mild leakage (H, early phase; I, late phase). ICGA shows incomplete regression of the polypoidal lesions. (J) OCT demonstrates flat RPE detachment with subretinal fluid. (K) At 36-month follow-up following additional antivascular endothelial growth factor agents, fundus photograph shows dry macula. (L) FA demonstrates tissue staining and window defect without leakage (M, early phase; N, late phase). ICGA shows complete regression of the polypoidal lesions. (O) OCT demonstrates no subretinal fluid accumulation.

proposed that prolongation of choroidal hypofluorescence through combination of TA or bevacizumab with PDT may reduce the incidence and duration of retreatment.[31] In addition, Yoshizawa *et al*[27] indicated that STTA is more preferable than IVTA with regards to adverse effects such as intraocular hypertension, cataracts, retinal detachment or endophthalmitis. Taken together, these findings suggest that STTA may be a useful and safe adjunct to enhance treatment efficacy for PCV.

Previous several investigations have reported the outcomes of triple therapy for the treatment of PCV. Nakata *et al*[9] reported the outcome of PDT combined with IVB (1.25 mg) and IVTA (2 mg) for PCV. They exhibited that the change in BCVA in the

triple therapy group was significantly better than in the PDT group. At 24 months, improvement in BCVA was seen in 10 eyes (41.7%) of the triple therapy group, although BCVA did not improve significantly. Yoshizawa *et al*[27] reported the efficacy of triple therapy consisting of PDT, IVB (1.25 mg) and STTA (40 mg). They showed that the mean logMAR BCVA improved significantly (0.70±0.50 at baseline; 0.37±0.40 at 12 months, $p<0.001$). Additionally, compared with baseline BCVA, 11 of 20 eyes (55.0%) with PCV had an increase of 0.3 or more in logMAR BCVA. Thus, triple therapy with IVB, PDT and STTA may be superior to any other treatments with regards to efficacy and safety, and may confer considerable patient value for PCV.

Our results suggest that initial PDT combined with IVB and STTA strongly decreases the disease activity of PCV, resulting in favourable visual outcomes and an extension of the treatment-free period after the initial therapy. The mean numbers of PDT, IVB or IVR and STTA treatments at month 36 were 1.32, 3.95 and 1.21, respectively. In the current study, we mainly used anti-VEGF (IVB or IVR) monotherapy as additional treatment because anti-VEGF therapy appears to have a treatment effect in PCV eyes.[32–35] This additional treatment strategy seems to be effective in safely reducing the number of treatments and maintaining long-term favourable visual outcome in PCV.

The limitations of this study include the small sample size, retrospective study design and lack of measurement of central retinal thickness by OCT. However, the 3-year follow-up of combination therapy for PCV is the longest period among previous comparative studies. Large prospective, randomised, multicentre studies and long-term follow-up are needed to clarify the best strategy for PCV treatment. Within these limitations, we conclude that initial triple therapy of a single session of PDT combined with IVB and STTA can maintain or improve visual acuity in patients with PCV over 36 months. It may be effective to change the treatment of IVB or IVR monotherapy in patients with regressed polypoidal lesions after combination therapy. Compared with double therapy, triple therapy for PCV may also extend treatment-free period and decrease the requirement for additional intravitreal anti-VEGF therapy.

Contributors Each author certifies that they have made substantial contribution to the work reported in this manuscript by participating in at least one of the following three areas: (1) substantial contributions to conception and design, acquisition of data or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content and (3) final approval of the version to be published.

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Competing interests None.

Patient consent Obtained.

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Three-year visual outcome of photodynamic therapy plus intravitreal bevacizumab with or without subtenon triamcinolone acetonide injections for polypoidal choroidal vasculopathy

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MUTATION REPORT

Novel *C8orf37* Mutations in Patients with Early-onset Retinal Dystrophy, Macular Atrophy, Cataracts, and High Myopia

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ABSTRACT

Purpose: More than 50 genes are reported as causative genes of autosomal recessive (ar) retinitis pigmentosa (RP) and cone-rod dystrophy (CRD). It is challenging to identify causative mutations for arRP and arCRD. The purpose of the present study was to investigate clinical and genetic features of two siblings with early-onset retinal dystrophy.

Methods: Whole-exome sequencing was conducted for the two affected siblings and their unaffected brother and mother from a Japanese family. We performed complete ophthalmic examinations, including visual acuity, funduscopy, visual-field testing, electroretinography and optical coherence tomography.

Results: Whole-exome sequencing analysis identified novel compound heterozygous mutations, a splice site mutation (c.374+2T>C in intron 4) and a deletion mutation (c.575delC [p.T192MfsX28] in exon 6) of chromosome 8 open reading frame 37 (*C8orf37*) gene, which encodes a ciliary protein, in both patients. The mother carried the truncating mutation, and the brother carried neither mutation. Ophthalmic examinations revealed diffuse retinal degeneration, macular atrophy, non-recordable electroretinography responses, cataracts, and high myopia in both patients, who could not be diagnosed with either RP or CRD because of the severe retinal degeneration and early onset disease. Longitudinal follow-up of the patients revealed highly progressive retinal degeneration, macular atrophy, and visual field loss.

Conclusions: Recessive *C8orf37* mutations have been identified in early to adolescent-onset arRP and arCRD with macular involvement. Our study identified two novel truncating mutations of the *C8orf37* gene in siblings with early-onset retinal dystrophy, macular atrophy, cataracts, and high myopia.

Keywords: *C8orf37*, early-onset retinal dystrophy, mutation, whole-exome sequencing

INTRODUCTION

Retinitis pigmentosa (RP) is the most common type of hereditary retinal dystrophy, and the prevalence of RP is approximately 1 per 3500–4000 persons.[1,2] RP is characterized by predominantly degenerated rod photoreceptor cells rather than cone photoreceptor cells, resulting in decreased rod responses as compared with cone responses in electroretinography (ERG).[2,3] In contrast to RP, cone-rod dystrophy (CRD) is characterized by predominantly degenerated cone photoreceptor cells rather than rod photoreceptor cells, resulting in decreased cone responses as compared with rod responses of ERG.[4,5]

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However, despite the fact that the first affected cell types are different between RP and CRD, it is very difficult to differentiate between RP and CRD at the point where both cone and rod photoreceptor cells are severely impaired.

In the RetNet database (https://sph.uth.edu/retnet/), 42 genes and 16 genes have been registered as causative genes of autosomal recessive (ar) RP and arCRD, respectively. However, it is challenging to investigate all of these candidate genes by Sanger sequencing. The recent technological development of exon capture with 99% coverage of all exons and its combination with next generation sequencing enables effective genetic studies for hereditary diseases[6–9] and is especially useful to identify a disease-causing mutation among multiple candidate genes.[10]

The present study examined one Japanese family including two siblings with early-onset retinal dystrophy, which could not be diagnosed with either RP or CRD because of severe retinal degeneration and early-onset disease. To identify a disease-causing mutation in the family, it was indispensable to investigate multiple candidate genes including RP- and CRD-causing genes. We employed a whole-exome sequence technique and identified novel compound heterozygous mutations in the *C8orf37* gene as disease-causing mutations.

PATIENTS AND METHODS

The study protocol was approved by the Institutional Review Board of The Jikei University School of Medicine and the National Hospital Organization at Tokyo Medical Center. The protocol adhered to the tenets of the Declaration of Helsinki, and informed consent was obtained from all participants.

Clinical Studies

We examined two sibling patients (patients II-2 and II-3) in a two-generation Japanese family (JU#0542) (Figure 1a). A detailed medical history was taken, and we performed ophthalmic examinations including decimal best-corrected visual acuity (BCVA), slit-lamp, fundus examinations, fluorescein angiography (FA) (VISUCAM NM/FA; Carl Zeiss Meditec AG, Dublin, CA), fundus autofluorescence imaging (FAI) (Spectralis HRA; Heidelberg Engineering, Heidelberg, Germany), and optical coherence tomography (OCT) (Cirrus HD-OCT; Carl Zeiss Meditec AG, Dublin, CA). A scotopic single flash or full-field ERG was performed; the procedure and conditions for ERG recording have been detailed previously.[11,12] Visual fields were assessed with a kinetic Goldmann perimetry (GP) (Haag Streit, Bern, Switzerland).

DNA Preparation and Exome Sequencing Analysis

Genomic DNA was extracted from blood samples. Whole-exome sequencing was performed in Macrogen Japan Corp. (Tokyo, Japan) by using a SureSelect XT Human All Exon kit V4+UTRs kit (Agilent Technologies, Santa Clara, CA) and by using an Illumina HiSeq2000 sequencer (Illumina, San Diego, CA). Obtained exome sequence data were compared with the reference human genome (hs37d5) and analyzed by using a portion of the previously described filtering method.[13] Then, we focused on only variants that could change the amino acid sequence initially. Subsequently, we filtered variants based on the criteria that the frequency of the variant was less than 1% in the 1000 Genomes database (http://www.1000genomes.org/) and the Human Genetic Variation Browser (http://www.genome.med.kyoto-u.ac.jp/SnpDB/about.html). The remaining variants were narrowed down by excluding variants that were found in the in-house database of exome data from seven people without ocular diseases. Finally, we screened the remaining variants by using the pattern of inheritance (homozygosity or compound heterozygosity). The confirmation of identified *C8orf37* mutations was performed by Sanger sequencing using the following two primer pairs; a forward primer, 5′-GCTTTCAATAGCTATCTCCCA AGA-3′ and a reverse primer, 5′-GTTGCAGTCC GGTGTACCTT-3′ for the exon4-intron4 boundary, and a forward primer, 5′-CACTCTCATGGATGCA TCTG-3′ and a reverse primer, 5′-CCAGCCTGAGT AACAATGAG-3′ for exon 6.

RESULTS

Ophthalmic Findings

The two affected siblings (patients II-2 and II-3) were referred to our department due to progressive loss of visual acuity. They reported loss of visual acuity from childhood. Both patients showed severely decreased visual acuity, high myopia, cataract, retinal degenerations with macular atrophy (Figures 2 and 3), severely constricted visual fields (Figure 4), and non-recordable ERG responses at the first examinations (37-year-old patient II-2 and 43-year-old patient II-3). Patient II-2 underwent cataract surgery with intraocular implantation in both eyes at the age of 39 years. At the last visit, the ophthalmic examinations showed progressive loss of visual acuity, retinal degenerations with macular atrophy (Figures 2 and 3), and constrictions of the visual fields (Figure 4) in both patients. In addition, patient II-3 showed progressed cataracts in both eyes. The ophthalmic findings of both patients are summarized in Table 1.

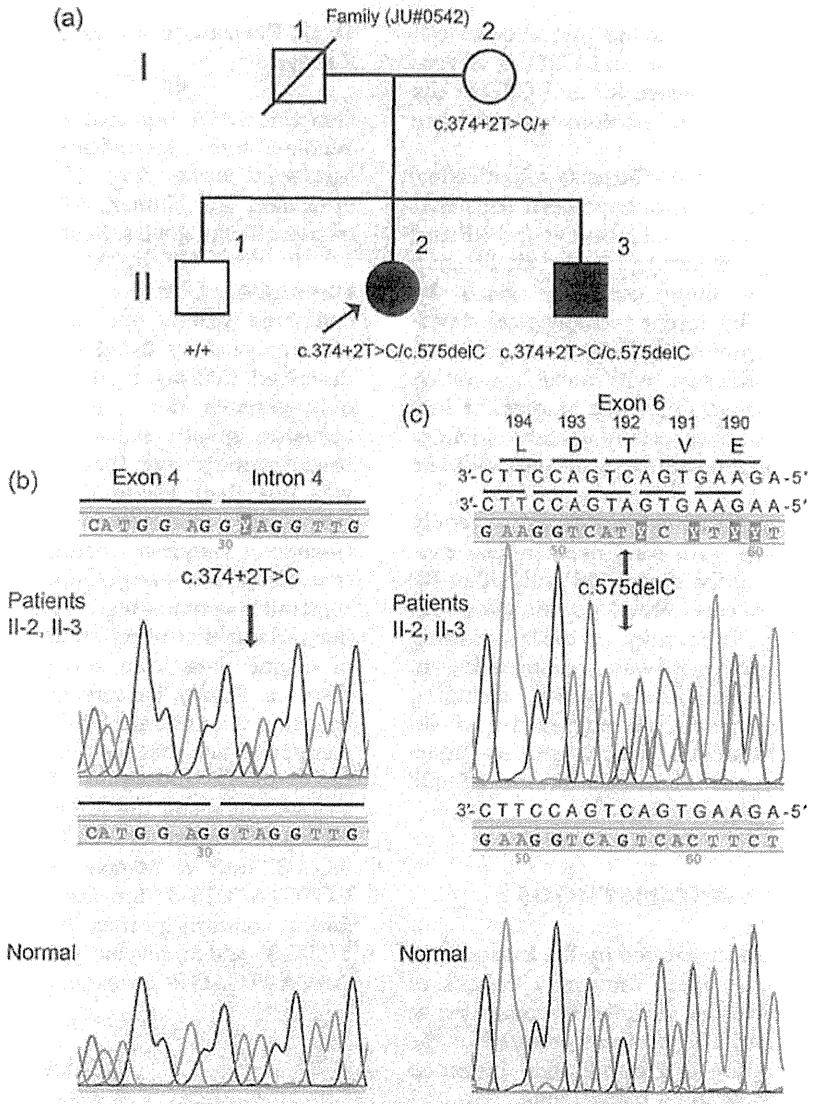

FIGURE 1. A Japanese family with early onset retinal degeneration and nucleotide sequence data of the novel *C8orf37* mutations. (a) Affected family members (male, solid square; female, solid circle) and unaffected family members (males, open squares; female, open circle) are shown. A slash symbol indicates a deceased person. (b) Partial nucleotide sequences of intron 4 in patients II-2 and II-3, and control. A heterozygous single-nucleotide mutation (c.374+2T>C) is shown only in the patients. (c) Partial complementary sequences of exon 6 using a reverse primer in patients II-2 and II-3, and control. A heterozygous deletion mutation (c.575delC) is confirmed only in the patients.

Non-ocular Medical History in the Two Affected Siblings

The elder sister (patient II-2) had a medical history of asthma in childhood, psychotic depression, and surgery for myoma uteri. The younger brother (patient II-3) reported tinnitus from 50 years of age. Neither patient had other systemic diseases such as renal dysfunction, cardiovascular disorders, polydactyly, obesity, hyperlipidemia, or impaired glucose tolerance.

Exome Sequencing Analysis and Identification of Mutations

To determine the disease-causing mutations, we performed whole exome sequencing in the two affected siblings (patients II-2 and II-3) and their unaffected mother (I-2) and brother (II-1). After the filtering steps (see the Methods section), only *C8orf37* variants were finally selected as the disease-causing mutations. In the two siblings, we identified novel compound heterozygous mutations, which were a

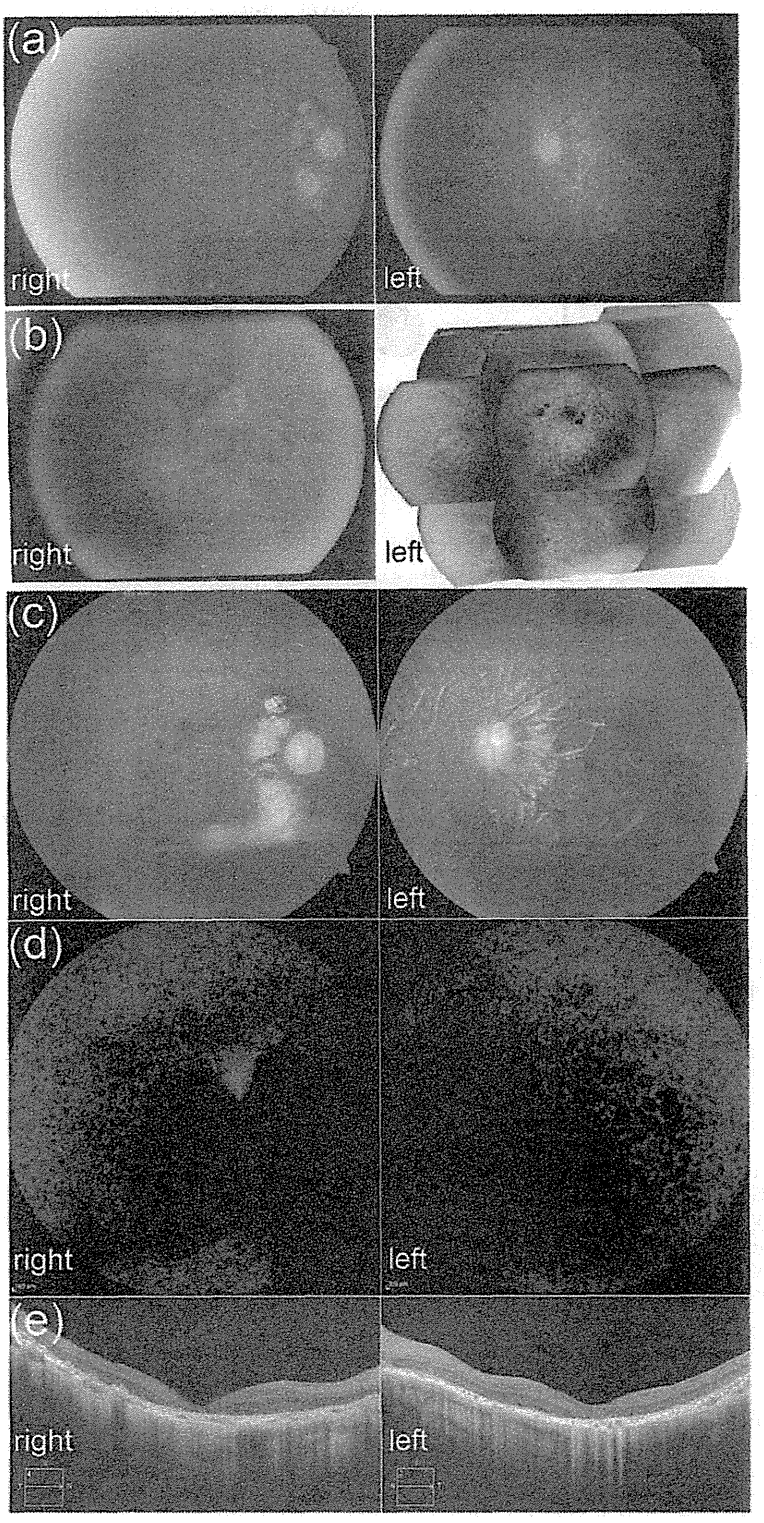

FIGURE 2. Fundus findings of patient II-2 at the age of 37 years (a and b) and at the age of 51 years (c, d and e). (a) Fundus photographs show retinal degeneration and attenuation of vessels in the midperiphery with macular degeneration in both eyes. Severe peripapillary atrophy was also shown in the right eye. (b) Fluorescein angiography (FA) in the right eye cannot be measured well due to severe cataract. FA in the left eye shows fluorescence block of the macular area, diffuse hyperfluorescence in the entire retina, and attenuation of vessels from the midperipheral to peripheral retina. (c) Fundus photographs show progressive chorioretinal atrophy with severe retinal degeneration, pigmentation, and attenuation of retinal vessels in the posterior area and more conspicuous macular degeneration in both eyes. (d) Fundus autofluorescence imaging of both eyes shows complete loss of autofluorescence in macular areas with diffuse loss of autofluorescence in the posterior pole. (e) Optical coherence tomography shows severe outer retinal layer thinning, the entire loss of the inner segment/outer segment line, and markedly thinning choroid in both eyes.

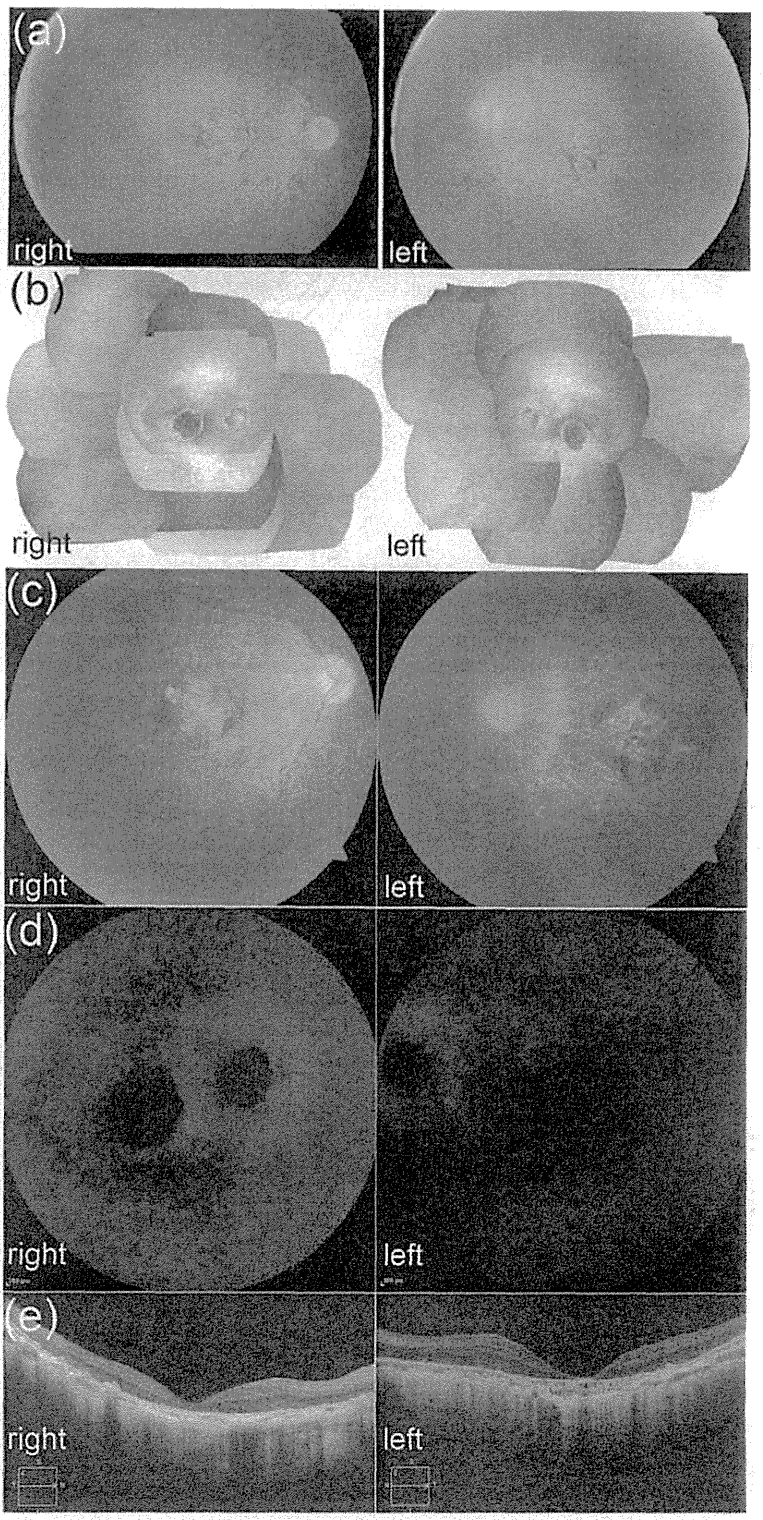

FIGURE 3. Fundus findings of patient II-3 at the age of 43 years (a and b) and at the age of 51 years (c, d and e). (a) Fundus examinations show retinal degeneration and the attenuation of vessels in the midperiphery of both eyes. Moreover, there is macular atrophy in both eyes. (b) Fluorescein angiography in both eyes shows fluorescence block of the macular area, diffuse hyperfluorescence with window defect in the entire retina, and attenuation of vessels from the midperipheral to peripheral retina. (c) Fundus examinations show progressed chorioretinal atrophy with retinal degeneration, pigmentation, and attenuation of retinal vessels in the posterior area and more conspicuous macular degeneration in both eyes. (d) Fundus autofluorescence imaging (FAI) of the right eye shows complete loss of autofluorescence in macular areas with diffuse loss of autofluorescence in the posterior pole. FAI of the left eye cannot be measured well due to severe cataract. (e) Optical coherence tomography shows severe outer retinal layer thinning, the entire loss of the inner segment/outer segment line, and marked thinning of the choroid in both eyes.

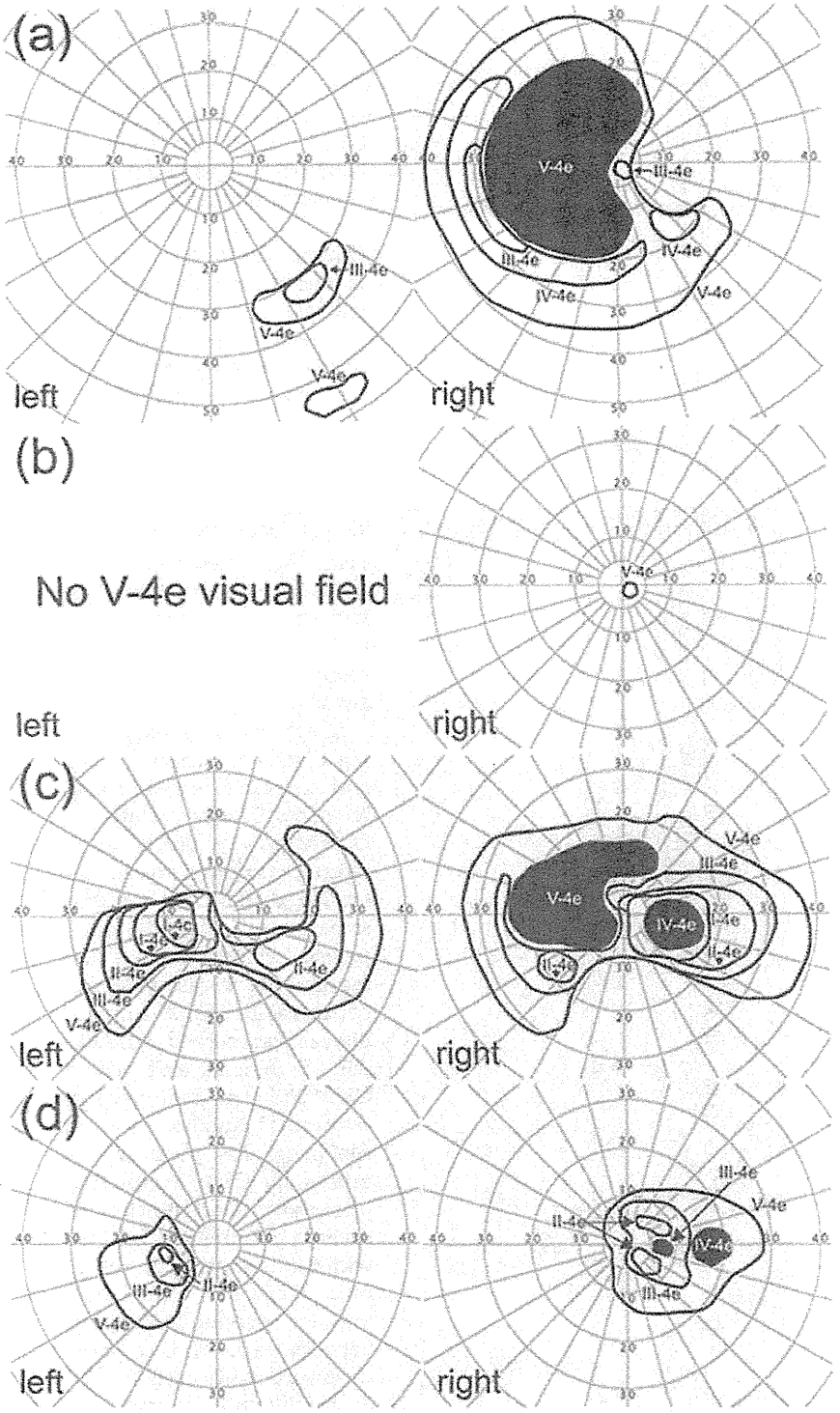

FIGURE 4. Visual fields assayed by Goldmann perimetry of patient II-2 and patient II-3. (a) The visual field of patient II-2 at the age of 37 years is severely constricted. The visual field of the right eye has less than 40 degrees remaining with the V-4e isopter and contains a V-4e scotoma in the central area. A highly limited visual field remains in the peripheral area of the left eye. (b) Visual fields of patient II-2 at the age of 50 years are severely constricted with less than 5-degree tunnel vision with the V-4e isopter in the right eye and no V-4e visual field in the left eye. (c) Visual fields of patient II-3 at the age of 43 years are severely constricted with less than 30 to 40 degrees remaining with the V-4e isopter in both eyes. (d) Visual fields of patient II-3 at the age of 51 years are constricted and are severely progressed to less than 10–30 degrees remaining in the right eye and less than 20 degrees remaining with visual field loss in the central area of the left eye with the V-4e isopters.