elsevier_AJOPHT_9731

Clinical and Genetic Findings of Autosomal Recessive Bestrophinopathy in Japanese Cohort

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Supplemental Material available at AJO.com.

Purpose

To report the clinical and genetic findings of 9 Japanese patients with autosomal recessive bestrophinopathy (ARB).

Design

Retrospective, multicenter observational case series.

Methods

Nine ARB patients from 7 unrelated Japanese families that were examined in 3 institutions in Japan were studied. A series of ophthalmic examinations including fundus photography, spectral-domain optical coherence tomography, fundus autofluorescence, electrooculography (EOG), electroretinography, and the results of genetic analysis were reviewed.

Results

Genetic analyses identified 7 pathogenic variants in *BEST1* including 2 novel variants, c.478G>C (p.A160P) and c.948+1delG. Homozygous variants were found in 4 families and compound heterozygous variants were found in 3 families. Two patients were diagnosed as ARB only after the whole exome sequencing analyses. The Arden ratio of the EOG was less than 1.5 in all 7 patients tested. Vitelliform lesions typical for Best vitelliform macular dystrophy were not seen in any of the patients. Seven patients shared some of the previously described features of ARB: subretinal deposits, extensive subretinal fluid, and cystoid macular edema (CME). However, the other 2 patients with severe retinal degeneration lacked these features. Focal choroidal excavations were present bilaterally in 2 patients. One case had a marked reduction of the CME and expansion of subretinal deposits over an 8-year of follow-up period.

Conclusions

Japanese ARB patients had some but not all of the previously described features. Genetic analyses are essential to diagnose ARB correctly in consequence of considerable phenotypic variations.

The *BEST1* gene was first identified as the gene responsible for Best vitelliform macular dystrophy (BVMD) in 1998 (OMIM *607854; also known as *VMD2*).[1] *BEST1* encodes the bestrophin-1 protein, which consists of 585 amino acids and is located in the basolateral plasma membrane of the retinal pigment epithelial (RPE) cells.[2]

Variants of the *BEST1* gene cause a wide range of retinal diseases including BVMD, autosomal dominant vitreoretinochoroidopathy (ADVIRC), autosomal recessive bestrophinopathy (ARB), adult-onset vitelliform macular degeneration (AVMD), retinitis pigmentosa, and the microcornea, retinal dystrophy, cataract, and posterior staphyloma (MRCS) syndrome. BVMD is the most well known *BEST1*-associated retinal dystrophy, and its clinical features were first described by Best in 1905.[3] BVMD is usually caused by autosomal dominant variants of the *BEST1* gene with often incomplete penetrance.

As for ARB, Schatz and associates described a patient with retinopathy and biallelic variants of *BEST1* in 2006.[4] In 2008, Burgess and associates reported that ARB was a distinct retinal disease associated with biallelic variants in the *BEST1* gene.[5] ARB is caused by either compound heterozygous or homozygous mutations in the *BEST1* gene.

ARB is associated with a wide spectrum of fundus abnormalities. Multiple white flecks scattered over the posterior pole of the retina are clearly detected by fundus autofluorescence (FAF). Optical coherence tomography (OCT) images show an accumulation of fluid within and/or beneath the neurosensory retina. The electrooculography (EOG) light peak is absent or markedly reduced. Central visual disturbances and reduced amplitudes of electroretinograms (ERGs) are also associated with ARB. However, the visual acuity and full-field ERGs may remain relatively normal for a long period of time in some cases.[6] The results of several case studies have shown various phenotypes for ARB since the Burgess report.[6–10] Some cases had marked subretinal deposits while others had mainly RPE atrophy and scar lesions.[5,6,10] Because of the rarity of the disease and variable phenotypes, ARB has been reported mostly in a small number of cases and definitive clinical features of ARB have not been determined.

Thus, the purpose of this study was to describe the clinical and genetic findings of 9 Japanese patients with ARB. We show that the phenotypes of these patients varied considerably and examine the alterations of the FAF and spectral-domain OCT (SDOCT) images during the course of the disease in 1 patient followed for 8 years.

Methods

This is a retrospective, multicenter observational case series. The procedures used in this study adhered to the tenets of the Declaration of Helsinki, and an informed consent was obtained from the patients and relatives. An approval of the protocol of this study was obtained from the institutional review board of each institution (approval numbers: Nagoya University 2015-0072, Jikei University 24-231 6997, National Hospital Organization Tokyo -Medical Center R11-087 and R14-050).

The medical records of 9 patients from 7 unrelated Japanese families who were confirmed to carry biallelic pathogenic variants of the *BEST1* gene were reviewed. The medical histories and the results of the clinical examinations of the

patients and family members including the best-corrected visual acuity (BCVA), intraocular pressure measurements, slit-lamp examinations, and ophthalmoscopy were reviewed. Full-field ERGs were recorded from all patients, and EOGs were recorded from 7 patients, and these tests were performed conforming to the guidelines of the International Society for Clinical Electrophysiology of Vision (ISCEV) standards.[11,12] Patients also underwent fundus color photography, ~~fundus~~ FAF imaging (Spectralis HRA; Heidelberg Engineering, Heidelberg, Germany), and SDOCT imaging (Spectralis; Heidelberg Engineering, or Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, California, USA). Four patients (NA0050, JU0209, NA0044, and NA0062) underwent fluorescein angiography (FA) and 1 patient (NA0044) also underwent indocyanine green angiography (IA; Spectralis HRA; Heidelberg Engineering).

Identification of *BEST1* Variants

Mutations detection was performed by direct sequencing and/or whole exome sequencing. Primal direct sequencing was used in 7 patients from 6 families. Primal whole exome sequencing was performed on 2 patients (NA0044 and NA1044) from a family, followed by direct sequencing for confirmation. Co-segregation analysis was performed with direct sequencing in 6 families (family numbers I–IV; Supplemental Figure, available at AJO.com). Blood samples were obtained from all probands and their family members when available. Genomic DNA was extracted from peripheral blood leukocytes by a Gentra Puregene Blood Kit (Qiagen, Hilden, Germany). Direct sequencing of the *BEST1* gene was performed according to an established method (mRNA reference sequence: NM_004183.3).[13] The protein-coding exons, exons 2-11, of the *BEST1* gene were sequenced with an automated sequencer (3730xl DNA Analyzer; Applied Biosystems, Foster City, California, USA) with a BigDye Terminator Kit (V3.1, Applied Biosystems). Whole exome sequencing and targeted sequence analysis for the *BEST1* gene were done according to the published protocol of the National Institute of Sensory Organs, a customized analysis protocol for the Japanese population.[14] In silico bioinformatic analyses were performed to predict the pathogenicity of all of the identified *BEST1* variants that have been reported. The details of the in silico molecular genetic analyses are described as supplemental information (Supplemental Material available at AJO.com).

Results

The demographic and clinical characteristics of the 9 patients at the time of the diagnosis of ARB are shown in the Table. The pedigrees of the 9 patients are shown in the Supplemental Figure. All the patients were Japanese, and 2 families were consanguineous (Families I and VI). The mean age was 31 ± 10 years with a range of 14–45 years at the most recent examination. The age at the time of diagnosis varied from 12 to 35 years. The initial symptom of most of the patients was blurred vision, but 4 patients had good visual acuity of 20/20 or better at that time. The patients also complained of other symptoms, such as metamorphopsia, photophobia, night blindness, and floaters. One patient (KA160) had no symptoms and was found unexpectedly by fundus examination. The visual acuity at the time of diagnosis by gene analyses ranged from 20/20 to 20/200. Three patients (NA1050, JU773, and KA160) had visual acuity of 20/20 in at least 1 eye. The refractive errors ranged from hyperopia to mild myopia, with a range from −2.5 to +2.0 diopter. None of the patients had a shallow anterior chamber, and none had angle-closure glaucoma. The Arden ratio, light peak/dark trough, was severely reduced to less than 1.2 in all 7 patients who underwent EOG examinations. The amplitudes of the full-field scotopic and photopic ERGs were within normal range in 4 patients (NA1050, JU0773, NA0062, and KA160) and were reduced by different degrees in the other 5 patients. The 3 patients with poor visual acuity (NA1044, JU0209, and JU0645) had severely reduced ERGs. Fundus examinations of the parents were performed in 6 families (Families I–VI). The father of the JU0645 had vitelliruptive macular degeneration but the other parents showed no specific fundus abnormalities that would be considered to be related to BVMD or ARB.

Table Demographics and Clinical Characteristics of 9 Japanese Autosomal Recessive Bestrophinopathy Patients

Family Number, Case ID, Age (y), Sex	Age at Onset (y)	Symptoms at Onset	BCVA (OD,OS)	Spherical Equivalent (D) (OD,OS)	Arden Ratio of EOG (OD,OS)	Amplitudes of Full-Field ERG	Nucleotide Changes of *BEST1* Gene (Allele 1, Allele 2)	Amino Acid Changes (Allele 1, Allele 2)
I, NA1050, 27, F	22	Floaters	20/20, 20/25	+0.5, 0	1.1, 1.1	Normal	c.763C>T, c.763C>T	p.R255W, p.R255W
I, NA0050, 23, M	19	Night blindness, blurred vision	20/40, 20/32	+2.0, +1.5	1.0, 1.0	Moderate decrease	c.763C>T, c.763C>T	p.R255W, p.R255W
II, JU0209, 35, M	12	Blurred vision	20/100, 20/200	−0.5, −2.5	1.0, 1.0	Severe decrease	c.763C>T, c.763C>T	p.R255W, p.R255W
III, NA1044, 45, M	35	Blurred vision	20/80, 20/50	+1.0, +1.0	N/A	Severe decrease	c.73C>T, c.584C>T	p.R25W, p.A195V
III, NA0044, 42, F	41	Metamorphopsia, floaters	20/32, 20/25	0, −0.25	N/A	Mild decrease	c.73C>T, c.584C>T	p.R25W, p.A195V
IV, NA0062, 28, F	20	Photophobia, blurred vision	20/25, 20/25	0, −0.75	1.1, 1.1	Normal	c.102C>T,	p.G34G, p.A195V

							c.584C>T	
V, JU0773, 14, F	14	Metamorphopsia	20/20, 20/20	+1.0, +0.5	1.2, 1.2	Normal	c.478G>C, c.584C>T	p.A160P, p.A195V
VI, JU0645, 38, M	12	Blurred vision	20/125, 20/100	−0.75, 0	1.0, 1.1	Severe decrease	c.908A>G, c.908A>G	p.D303G, p.D303G
VII, KA160, 23, F	17	No complaint	20/20, 20/20	0, +0.25	1.0, 1.0	Normal	c.948+1delG, c.948+1delG	N/D

BCVA = best-corrected visual acuity; D = diopters; EOG = electrooculography; N/A = not available; N/D = not determined.

Analyses of *BEST1* Gene Mutations

The pathogenic variants of *BEST1* found in our cohorts are shown in the Table. Co-segregation analyses revealed heterozygous/homozygous status; 4 families had homozygous variants and 3 families had compound heterozygous variants. Seven different variants were found in our cohorts. Variants p.A195V and p.G34G (c.102C>T) have been reported to cause ARB with another variant in the compound heterozygous state. Four variants, p.R25W, p.A195V, p.R255W, and p.D303G, have been reported to be causative mutations for autosomal dominant BVMD. p.A160P (c.478G>C) and c.948+1delG were found in this study as new candidates of pathogenic variants. p.A160P was not listed in 5 different single nucleotide polymorphism databases, viz, dbSNP, EVS, ExAC, HGVD, and HTD. The in silico bioinformatic program predicted the pathogenicity of the new variant, p.A160P (PolyPhen-2~~,~~ as possibly damaging (0.777), SIFT as damaging (0.001), and PROVEAN as deleterious (−4.78). Variant c.948+1delG was predicted to result in a loss of a genuine splice donor site by the in silico prediction performed by the splice site prediction tools (HSF, NNSPLICE, and NetGene2).

Findings From Fundus Imaging

The fundus color photographs, FAF images, and OCT images of the left eye of the 9 patients are shown in Figure 1. The patients had similar abnormalities in both eyes, although the abnormalities varied considerably among the patients. ~~Seven~~Six of the patients had different degrees of central yellowish subretinal deposits in the fundus color images (NA1050, NA0050, ~~NA1044,~~ NA0044, NA0062, JU0773, and KA160). Vitelliform lesions, which are usually seen in eyes with BVMD, were not present in any of the patients, although the fundus of 2 cases resembled that of the vitelliruptive stage of BVMD, with massive subretinal deposits (NA0062 and JU0773). Three patients (JU209, NA1044, and JU0645) had prominent RPE atrophy, which appeared as diffuse grayish green scars over the posterior pole.

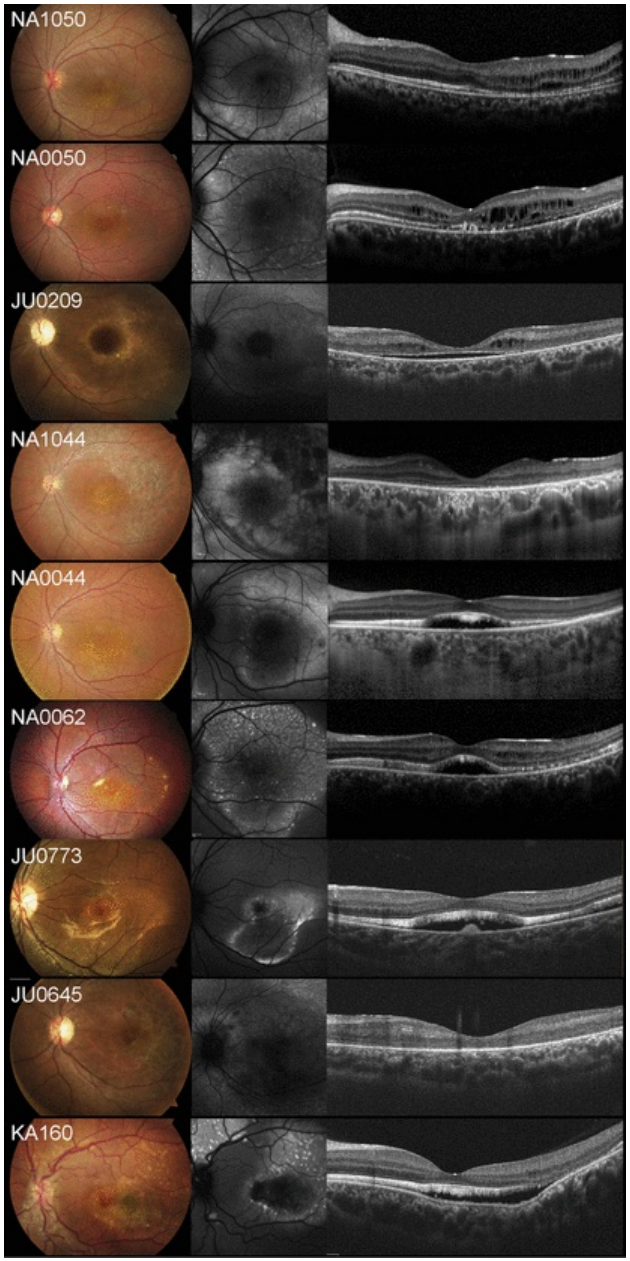

Figure 1 Fundus color photographs, fundus autofluorescence (FAF) images, and spectral-domain optical coherence tomography (SDOCT) images of the left eye of the 9 patients with autosomal recessive bestrophinopathy (ARB). Six of the 9 patients had yellowish white subretinal deposits (NA1050, NA0050, NA0044, NA0062, JU0773, and KA160). The subretinal deposits were detected in the FAF images as abnormal hyperautofluorescence. SDOCT images showed cystoid edema in 4 patients (NA1050, NA 0050, JU0209, and NA0062) and serous retinal detachment with elongated photoreceptor outer segment in 4 patients (NA0044, NA0062, JU0773, and KA160). The ellipsoid zone was not observed in 3 patients (JU0209, NA1044, and JU0645), who had severe atrophy of the retinal pigment epithelium.

The FAF images showed different types of abnormalities with a mixture of hyper- and hypoautofluorescence throughout the posterior pole in all of the patients. Subretinal deposits were detected as hyperautofluorescent spots in the FAF images and were

more recognizable than in the color photographs of the fundus. The areas of atrophic RPE were detected as hypoautofluorescent areas.

The SDOCT images showed different kinds of abnormalities. Cystoid edema was seen in 4 patients (NA1050, NA0050, JU0209, and NA0062) in the SDOCT images. The edema was diffusely spread over the macular area and mainly within the inner nuclear layer (INL).

Four patients (NA0044, NA0062, JU0773, and KA160) had serous retinal detachments with elongated photoreceptor outer segments. One patient (JU0209) also had serous retinal detachment, but the ellipsoid zone (EZ) was absent, with a severe thinning of the outer nuclear layer. The EZ was also not observed in 2 patients, NA1044 and JU0645, who had severe RPE atrophy. A disruption of the EZ was seen adjacent to an area of serous detachment in 2 patients (NA0044 and KA160) and under the cystoid edema in 2 patients (NA1050, NA0050). The SDOCT images also showed focal choroidal excavations bilaterally in 2 patients (KA160 in Figure 1 and NA0044 in Figure 2). One patient (NA0044) had multiple choroidal excavations and pigment epithelial detachments that corresponded with the areas of increased choroidal vascular permeability in the IA images (Figure 2). Fluorescein angiography showed patchy hyperfluorescence over the posterior pole in the early phase in 4 cases, which indicated the presence of window defects owing to the RPE atrophy. A pooling of fluorescein dye in the cystoid spaces was seen in the late phase in 2 patients (NA0044 and NA0062; images of NA0044 are shown in Figure 2).

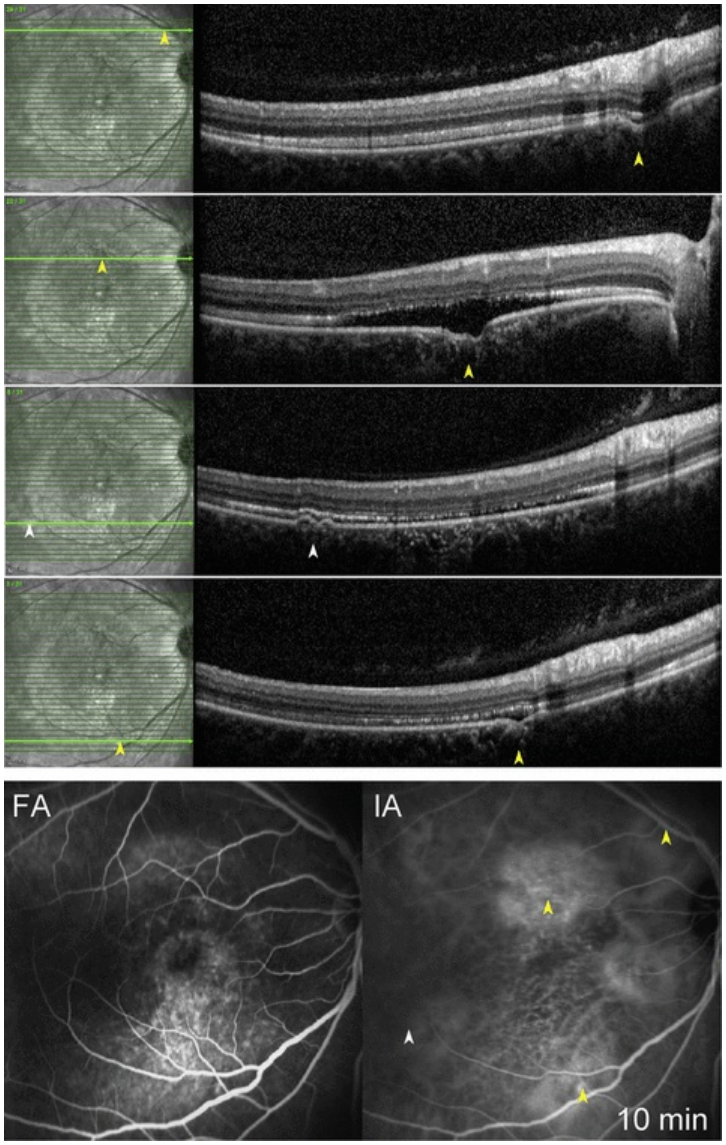

Figure 2 Fundus images of Patient NA0044 with multiple focal choroidal excavations. (Top) Spectral-domain optical coherence tomography images show focal choroidal excavations and retinal pigment epithelial detachments. (Bottom left) Pooling of fluorescein dye in the cystoid spaces can be seen in the late phase of fluorescein angiography (FA). (Bottom right) The focal choroidal excavations and retinal pigment epithelial detachments are located within or adjacent to increased choroidal vascular permeability areas that can be seen by indocyanine green angiography (IA). Yellow arrowheads indicate the locations of the focal choroidal excavations and white arrowheads indicate the retinal pigment epithelial detachments.

Case With 8-Year Follow-up

Case NA0062 had marked changes in the fundus images over an 8-year period in spite of only minor changes of her BCVA, which decreased from 20/20 to 20/25 (Figure 3). The yellowish subretinal deposits shown in the fundus color images in 2007 were decreased in 2015. On the other hand, the areas of hyperautofluorescence were expanded in 2015. Cystoid macular edema was present in both INL and outer nuclear layer (ONL) in 2007, but the edema in the ONL disappeared almost completely in 2015.

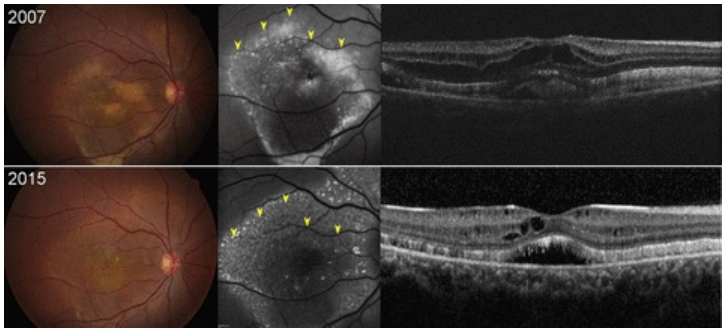

Figure 3 Changes of fundus images in Patient NA0062, who was followed for 8 years. Fundus photographs and fundus autofluorescence (FAF) and spectral-domain optical coherence tomography (SDOCT) images in 2007 (Top) and in 2015 (Bottom) are shown. The edge of the abnormal hyperautofluorescent area in the FAF images of 2007 is indicated by yellow arrowheads in both FAF images of 2007 and 2015. During the 8-year follow-up, these yellowish subretinal deposits became less detectable in the fundus color photographs, although the abnormal hyperautofluorescence areas were clearly detected in the FAF images and the area was expanded. SDOCT image showed marked retinal edema and subretinal fluids in 2007, but they were decreased in 2015.

Discussion

We have presented the clinical characteristics and genetic findings of 9 Japanese patients in 7 unrelated families with ARB. The visual acuities and amplitudes of the ERGs ranged from normal to severely reduced, but the EOGs were abnormal in all of the 7 patients examined.

The appearance of the fundus of the patients was comparable to those reported in earlier studies on ARB: yellowish subretinal deposits scattered over the posterior pole, accumulation of subretinal fluid beneath the macula, and cystoid macular edema.[5] However, from the findings of the patient (NA0062) followed for 8 years, the distribution of subretinal deposits and cystoid edema can change during the course of the disease. In addition, there were 3 cases with severe retinal degeneration (JU0209, NA1044, and JU0645), and 2 of these lacked those features (NA1044 and JU0645). We believe that the subretinal deposits and cystoid edema can be reduced in the advanced stages of ARB, as in these cases.

The refractive errors were relatively more hyperopic than the average of the Japanese population.[15] However, angle-closure glaucoma related to the shorter axial lengths and shallower anterior chamber[5–7] was not common in our patients.

The differential diagnosis of ARB is difficult. Several patients were misdiagnosed with central serous chorioretinopathy (CSC), juvenile X-linked retinoschisis, macular degeneration, and BVMD, as they had similar clinical features. The differential diagnosis between ARB and BVMD can also be challenging. The ocular findings in some cases of extensive and/or multifocal legions in BVMD seemed to overlap those of ARB.[16] Fundus images of 2 patients (JU0773 and NA0062) resembled the vitelliruptive phase of BVMD and, in fact, NA0062 had been initially diagnosed as being BVMD before the biallelic variants of *BEST1* gene were detected. It would also be difficult to diagnose in such cases, as the 3 patients with severely damaged photoreceptor layers (JU0209, NA1044, and JU0645) demonstrated. Patients NA1044 and NA0044 had been diagnosed with central serous chorioretinopathy and macular degeneration of unknown etiology, respectively, and were confirmed to be ARB only after the whole exome analysis showed biallelic variants of *BEST1*. Patient JU0645 had severe retinal degeneration and was confirmed to have biallelic variants of the *BEST1* gene because his father had vitelliruptive lesion and was diagnosed with BVMD.

Taken together, our findings indicate that gene analysis is essential for the diagnosis of ARB.

Variants of *BEST1* Gene

Two new pathogenic variants, p.A160P and c.948+1delG, were found. These variants were predicted to be pathogenic by in silico analysis. A homozygous variant, p.R255W, was detected in 3 cases of 2 families. A heterozygous variant of p.R255W has been reported in a Chinese patient with BVMD,[17] and it was also reported in the compound heterozygous state in 2 Chinese patients with the BVMD phenotype.[18] The high prevalence of the p.R255W variant in Asians suggests a difference in the spectrum of *BEST1* variants among Asians and other ethnic groups. Compound heterozygous variants including p.A195V were detected in 4 cases of 3 families. The p.A195V variant in a compound heterozygous state with the other mutations has been reported as a causative variant of ARB in other studies from other countries.[19–22] Thus, p.A195V might be one of the major variants of ARB worldwide.

The region between amino acid 290 and 316 in exon 8, which includes the acidic domain, has been reported to be one of the hot spots of the disease-causing variants of BVMD in the heterozygous state.[23] The p.D303G variant was reported to cause BVMD in cases with autosomal dominant inheritance,[22] and the father of JU0645, who had p.D303G variant heterozygously, had vitelliruptive lesions. However, JU0645, who had a homozygous variant of p.D303G, had severe panretinal degeneration, which is different from BVMD. These results support the idea that some of the variants that cause BVMD in the heterozygous state can cause more diffuse and severe retinal degeneration in the homozygous state. The c.102C>T variant resulted in synonymous changes, p.G34G, but this variant was reported to be a damaging mutation that creates a cryptic splice donor site at 52 nucleotides upstream of the genuine splice donor site.[24]

Genotype-Phenotype Correlation

Although our sample size was small, the 3 patients with homozygous variants of p.R255W had macular edema mainly and less subretinal fluid compared with the other patients. These findings suggest the existence of a genotype-phenotype association. However, the mechanisms of how the *BEST1* variants' effects on function alter the phenotypes in patients with ARB are still debatable. ARB was proposed to have a null phenotype of the bestrophin-1 protein function as a Cl^- channel originally.[5] However, a combination of the *BEST1* variants found in an ARB patient was reported not to affect the Cl^- currents in human-induced pluripotent stem cell–derived RPE cells.[25] Other in vitro study has shown that several variants abolished the correct trafficking, promote early degradation, or induce aggresome-like inclusion bodies of bestrophin-1 and concluded that a missense variant associated with ARB has a pathogenic influence beyond a simple loss of function.[26] A study of a larger cohort will be needed to determine a definitive genotype-phenotype correlation.

Correlation of Spectral-Domain Optical Coherence Tomography Findings With Visual Acuity

The EZ was clearly detected at the fovea in the 5 patients who had visual acuity better than 20/32 (NA1050, NA0044, JU0773, NA0062, and KA160). Three patients (JU0209, NA1044, and JU0645), who had a thinning of the ONL and an absence of the EZ in the SDOCT images, had poor visual acuity and a marked decrease of the amplitudes of the ERGs. A thinning of the ONL and disruption of the EZ in the OCT images indicated photoreceptor degeneration, as in other retinal diseases,[27,28] though the mechanism(s) causing the degeneration might be different. The photoreceptor degeneration in the eyes with ARB is assumed to be secondary to the ongoing RPE dysfunction because bestrophin-1 is present in the RPE specifically and not in the other retinal tissues.[2]

The mechanisms causing the photoreceptor damages in eyes with ARB may be similar to those in eyes with chronic CSC because ARB and chronic CSC share some characteristics: prolonged serous retinal detachments, elongation of the photoreceptor outer segments,[29] and focal choroidal excavations.[30] An elongation of the photoreceptor outer segments was seen within the area of serous retinal detachment in 4 patients (NA0044, JU0773, NA0062, and KA160). This elongation might result from defective phagocytosis of the photoreceptor outer segments by the RPE. These patients had relatively good visual acuity (ranged from 20/32 to 20/20); however, the persistent presence of subretinal fluid might cause photoreceptor degeneration in ARB, as reported in chronic CSC.[31] The finding that disruptions of the EZ were found adjacent to the area of the serous retinal detachment in 2 patients (NA0044 and KA160) supports this idea.

A fragmentation of the EZ was observed beneath the macular edema in 3 patients (NA1050, NA0050, and NA0062). The macular edema may also aggravate the photoreceptor damage, as in diabetic macular edema[32] and cystoid macular edema associated with retinal vein occlusion.[33]

There are limitations in this study. One limitation is the small sample size that was used to try to describe the genotype-phenotype correlations. Another limitation is that the pathogenic effect of the new variants was only predicted by the in silico analyses. Additional studies of a larger number of cohorts are required.

In conclusion, we identified 7 *BEST1* variants, 2 of which were new, in 9 cases of Japanese patients with biallelic variants of *BEST1*. We have presented additional data that show that ARB patients had a broad range of morphologic abnormalities with the possibility that they may change over time, as detected by multimodal imaging. Genetic analyses are essential to diagnose ARB correctly because there are considerable phenotypic variations.

Funding/Support: This work was supported in part by JSPS KAKENHI Grant Numbers 25462709 to S.U., 25462738 to T.A., 30255525 and 26462674 to K.T., and grant for Practical Research Project for Rare/Intractable Diseases from the Japan Agency for Medical Research and Development (AMED) to T.I. (15ek0109072h0002). Financial disclosures: Shinji Ueno: Santen Pharmaceutical Co, Ltd, Japan (Grant); Novartis Pharma K.K., Japan (Grant). Yasuki Ito: Aichi Ophthalmologists Association, Japan (Honorarium for lecturing); Alcon Japan Ltd, Japan (Honoraria for lecturing); Bayer Health Care, Japan (Honoraria for lecturing); Canon Life Care Solutions Inc, Japan (Honoraria for lecturing); Carl Zeiss Meditec Co, Ltd, Japan (Honorarium for lecturing); Kowa Pharmaceutical Company LTD, Japan (Honoraria for lecturing); Novartis Pharma K.K., Japan (Honoraria for lecturing); Okazaki City Medical Association, Japan (Honoraria for lecturing); Pfizer Japan Inc, Japan (Honoraria for lecturing); Santen Pharmaceutical Co, Ltd, Japan (Honoraria for lecturing). Hiroshi Tsuneoka: Santen Pharmaceutical Co, Ltd, Japan (Grant); Bayer Yakuhin, Ltd, Japan (Grant); Pfizer Japan Inc; Novartis Pharma K.K., Japan (Grant); Senju Pharmaceutical Co, Ltd, Japan (Grant); Abbott Medical Optics Inc, Japan (Grant); Wakamoto Pharmaceutical Co, Ltd, Japan (Grant); R-Tech Ueno, Ltd., Japan (Grant); Alcon Japan Ltd, Japan (Grant); DAIICHI SANKYO COMPANY, LIMITED, Japan (Grant); Mitsubishi Tanabe Pharma Corporation, Japan (Grant); HOYA CORPORATION, Japan (Grant); NIDEK CO, LTD, Japan (Grant); Otsuka Pharmaceutical Co, Ltd, Japan (Grant); MSD K.K., Japan (Grant). Hiroko Terasaki: Astellas Pharma Inc, Japan (Honorarium for lecturing); Otsuka Pharmaceutical Co, Ltd, Japan (Honoraria for lecturing, Grant); ONO PHARMACEUTICAL CO, LTD, Japan (Consulting); SANWA KAGAKU KENKYUSHO CO, LTD, Japan (Honorarium for lecturing); NIDEK CO, LTD, Japan (Honorarium for lecturing); KOWA PHARMACEUTICAL COMPANY LTD, Japan (Honoraria for lecturing, Grant); Santen Pharmaceutical Co, Ltd, Japan (Honoraria for lecturing, Grant); Senju Pharmaceutical Co, Ltd, Japan (Honoraria for lecturing, Grant); Alcon Japan Ltd, Japan (Honoraria for lecturing, Grant); Novartis Pharma K.K., Japan (Honoraria for lecturing, Grant); Bayer Health Care, Japan (Honoraria for lecturing, Consulting, travel expenses); Pfizer Japan Inc, Japan (Honoraria for lecturing, Grant); ROHTO Pharmaceutical Co, Ltd, Japan (Rohto Award Selection Committee); WAKAMOTO Co, Ltd, Japan (Honoraria for lecturing, Grant); AICHI OPHTHALMOLOGISTS ASSOCIATION, Japan (Honorarium for lecturing); Carl Zeiss Meditec Co, Ltd, Japan (Honorarium for lecturing); Nitten Pharmaceutical Co, Ltd, Japan (Writing assistance, Honorarium for lecturing); Takeda Pharmaceutical Company Limited, Japan (Honorarium for lecturing); Chiba Ophthalmologist Association, Japan (Honorarium for lecturing, travel expense); Japan Medical Association, Japan (Honorarium for lecturing, travel expense); Fukushima Ophthalmologist Association, Japan (Honorarium for lecturing, travel expense); HOYA CORPORATION, Japan (Grant). The following authors have no financial disclosures: Ayami Nakanishi, Takaaki Hayashi, Satoshi Katagiri, Taro Kominami,

Tamaki Gekka, Yoichiro Masuda, Kei Shinoda, Akito Hirakata, Makoto, Inoue, Kaoru Fujinami, Kazushige Tsunoda, and Takeshi Iwata. All authors attest that they meet the current ICMJE criteria for authorship.

The authors thank Professor Duco Hamasaki of the Bascom Palmer Eye Institute for the discussions and editing the final version of the manuscript.

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Supplemental Data

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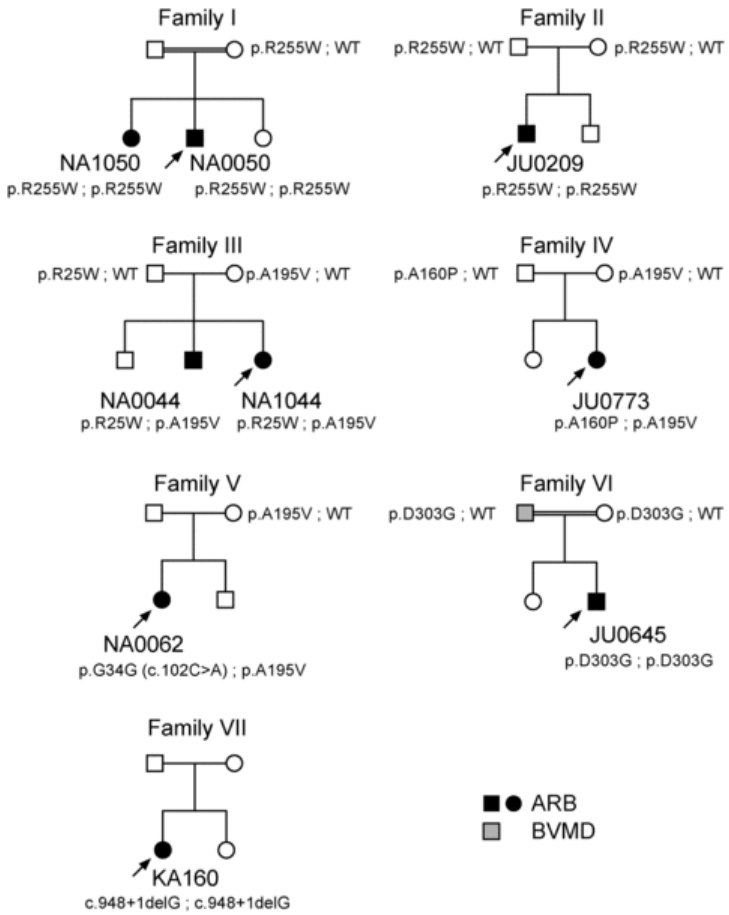

Supplemental Figure Pedigree charts of 9 autosomal recessive bestrophinopathy patients in 7 families. Parents of Families I and IV were consanguineous. The father of Family IV had vitelliruptive macular degeneration. The other parents showed no specific fundus abnormalities that would be considered the relation with Best vitelliform macular dystrophy or autosomal recessive bestrophinopathy.

Multimedia Component 1

Supplemental information

Queries and Answers

Query: In supplemental information under the topic “In Silico Molecular Genetic Analysis”, Please note sentence “The allelic frequency was estimated with reference to 6 databases”states that 6 databases were referenced, but you list only 5; Also, access date is missing for HTD.

Answer: The number of databases was 5 as you pointed out, we corrected it and also add the access date for HTD. The revised text is attached (Title: Supplemental information 052516).

Query: Please confirm that given names and surnames have been identified correctly.

Answer: We confirmed the names are identified correctly.