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Autosomal dominant optic atrophy with *OPA1* gene mutations accompanied by auditory neuropathy and other systemic complications in a Japanese cohort

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Purpose: This study aimed to describe the genetic and clinical characteristics of four Japanese patients with autosomal dominant optic atrophy (DOA) accompanied by auditory neuropathy and other systemic complications (i.e., DOA-plus disease).

Methods: Four patients from four independent families underwent comprehensive ophthalmic and auditory examinations and were diagnosed with DOA-plus disease. The disease-causing gene variants in the *OPA1* gene were identified by direct sequencing. The genetic and clinical data of 48 DOA patients without systemic complications—that is, with simple DOA—were compared to those of DOA-plus patients.

Results: DOA-plus patients noticed a decrease in vision before the age of 14 and hearing impairment 3 to 13 years after the development of visual symptoms. Two patients had progressive external ophthalmoplegia, and one patient had vestibular dysfunction and ataxia. The DOA-plus phenotypes accounted for 13.3% (4/30) of the families with the *OPA1* gene mutations. Each DOA-plus patient harbored one of the monoallelic mutations in the *OPA1* gene: c.1334G>A, p.R445H, c.1618A>C, p.T540P, and c.892A>C, p.S298R. Missense mutations accounted for 100% (4/4) of the DOA-plus families and only 11.5% (3/26) of the families with simple DOA.

Conclusions: All the patients with the DOA-plus phenotype carried one of the missense mutations in the *OPA1* gene. They all had typical ocular symptoms and signs of DOA in their first or second decade, and other systemic complications—such as auditory neuropathy, vestibular dysfunction, and ataxia—followed the ocular symptoms. We should consider the occurrence of extraocular complications in cases with DOA, especially when they carry the missense mutations in the *OPA1* gene.

Autosomal dominant optic atrophy (DOA; OMIM 165500) is one of the major causes of inherited optic nerve disorders and is characterized by a slow, progressive reduction of visual acuity, by central visual field defects, and by the temporal pallor of the optic disc. Abnormalities in the *OPA1* gene (Gene ID: 165500; OMIM 605290) are a major cause of DOA [1-4], and mutations in the *OPA1* gene account for 32.1–89.5% of all DOA cases [3,5-10]. *OPA1* encodes a dynamin-related GTPase that is located in the mitochondrial intermembrane space, and it plays a key role in controlling the balance of mitochondrial fusion and fission. To date, more than 200 *OPA1* variants have been reported to cause DOA [11], including missense mutations, nonsense mutations, insertion/deletion, splice site mutations, and large-scale *OPA1* rearrangements [5-9,12,13].

The severity of DOA varies considerably, and the visual acuity ranges from normal to hand motion [10,14]. This variability is observed both within and among families. It should be noted that there is a subset of patients with DOA who have extraocular symptoms, such as, auditory neuropathy, ataxia, myopathy, neuropathy, and progressive external

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ophthalmoplegia (PEO) [15,16]. Yu-Wai-Man et al. [17] reported that patients with extraocular features accounted for 17.2% of all *OPA1* mutation carriers in the British population. They named this ocular condition the "DOA-plus" phenotype [17]. The majority of cases involving the DOA-plus phenotype were associated with missense mutations affecting the GTPase domain, and the most common extraocular manifestation was auditory neuropathy [17,18]. Auditory neuropathy is a type of hearing disorder that was reported by Kaga [19,20] and Starr [21], and it is characterized by mild to moderate hearing loss, poor speech discrimination, normal otoacoustic emission, and the absence or severe deterioration of the auditory brainstem response (ABR). Since the initial discovery of a case with DOA accompanied by hearing loss by Shimizu et al. [15] and the association of DOA with auditory neuropathy by Amati-Bonneau et al. [16], many cases with *OPA1* mutations have been reported to have the DOA-plus phenotype in the European population. However, there have been few reports of DOA-plus disease in the Japanese and Asian populations, and little is known about its natural course and clinical features. Thus, the purpose of this study was to determine the genotypes and clinical courses of both the ocular and extraocular signs and symptoms of four Asian patients from four independent families with the DOA-plus phenotype.

METHODS

Four patients (cases 1, 2, 3, and 4; Figure 1) from four independent families who were diagnosed with DOA were examined at the National Institute of Sensory Organs (NISO). The genetic data of Case 2 [15,22] and Case 3 [23] and part of ophthalmological data of Case 2 [15] were reported by co-authors.

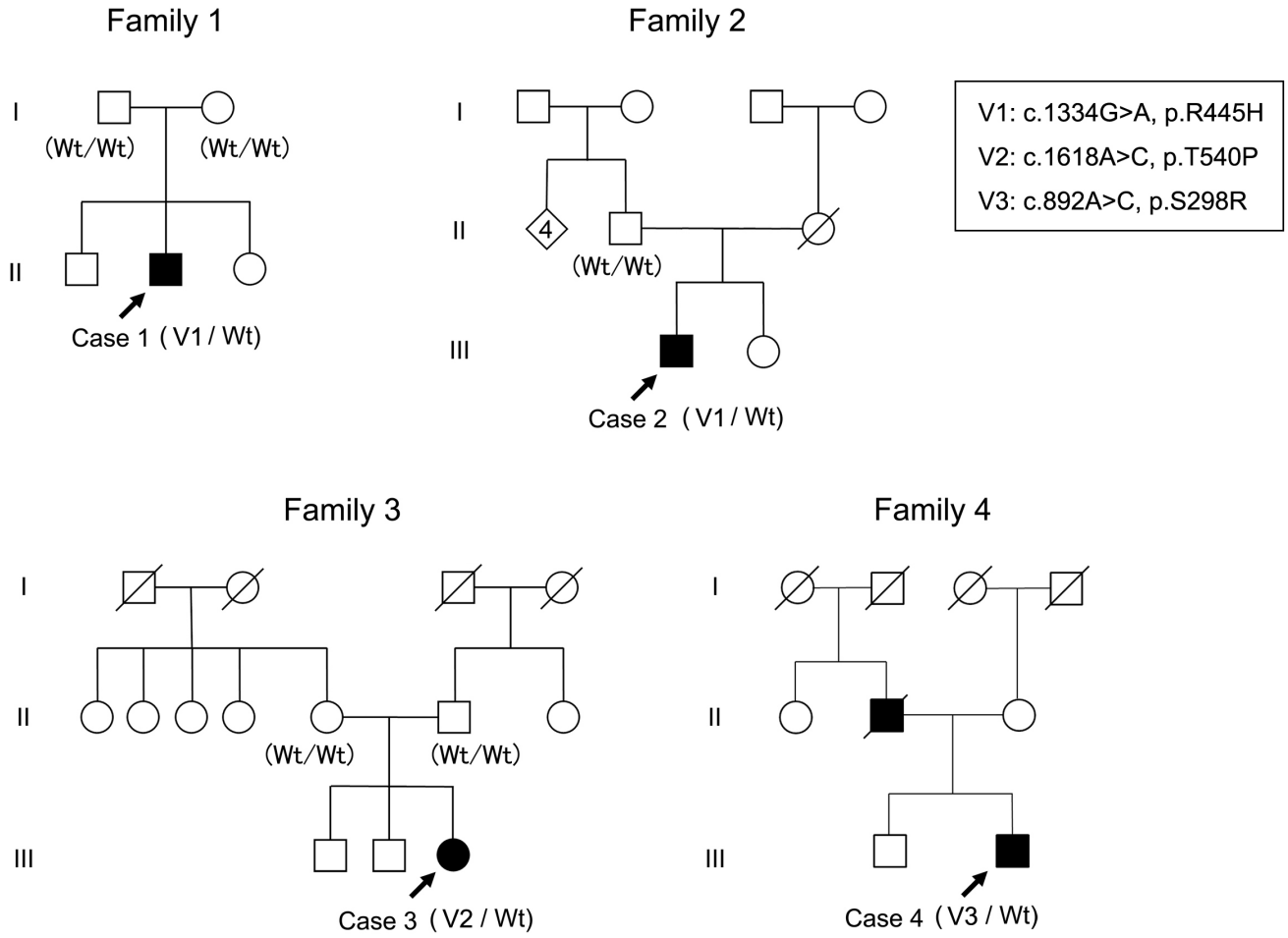

Figure 1. Pedigrees of four families affected by dominant optic atrophy (DOA)-plus disease. The proband is indicated by an arrow. Wt refers to the wild-type of the *OPA1* gene.

To investigate the genotype-phenotype correlation of DOA, the genetic and clinical features of the four cases were compared with those of forty-eight DOA patients (27 men and 21 women) from twenty-six families without systemic disorders, defined as 'simple DOA'. Patients with Simple DOA were recruited from the National Institute of Sensory Organs (NISO) and the Jikei University between January 2003 and September 2017. For the comparison of visual acuity between DOA-plus and age-matched simple DOA patients, data of the right eyes were used.

The procedures used were approved by the ethics committees of each institution, and all procedures were performed in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all the patients for all the procedures.

Clinical assessments: Detailed medical histories were obtained, and comprehensive ophthalmological examinations were performed on all patients. The ophthalmological assessments included measurements of the best-corrected visual acuity (BCVA), visual field tests using Goldmann perimetry, ophthalmoscopic examinations through dilated pupils, color fundus photography, optical coherence tomography (OCT), and pattern-reversal visual evoked potentials (VEPs). The OCT images were obtained with a spectral domain OCT device (Cirrus HD-OCT, version 5.1; Carl Zeiss Meditec, Dublin, CA), and pattern VEPs were elicited by 1.0° and 0.25° checks, in accordance with the standard protocol of the International Society for Clinical Electrophysiology of Vision (ISCEV; LE4000; Tomey Corporation, Aichi, Japan) [24].

The auditory assessments included pure-tone audiometry (125–8000 Hz), speech audiometry (audiometer AA-75; Rion Co., Tokyo, Japan), distortion product otoacoustic emission (DPOAE) testing using the ILO-92 system (Otodynamics Ltd., Hatfield, UK), and ABR using the Neuropack system (Nihon Kohden Corp., Tokyo, Japan) [22]. The DPOAE test is an examination of the outer hair cell function, and patients with auditory neuropathy are characterized as having normal DPOAE.

Genetic examinations: The genetic analysis of the *OPA1* gene in cases 1, 3, and 4 was done by T. Matsunaga and that of Case 2 by S. Shimizu (Table 1). The procedures used for the genetic analysis have previously been described in detail [15,23]. In brief, genomic DNA was extracted from leukocytes of the peripheral blood, and exons 1 through 30 were amplified and directly sequenced. The genetic analyses were performed on both the proband and the parents in cases 1 and 3, on the proband and his father in Case 2, and on only the proband in Case 4 (Figure 1). For patients with simple DOA, the sequence of the *OPA1* gene was performed separately by Jikei University (Appendix 1). The screening of *OPA1* variants was performed using Sanger sequencing for the coding region of the *OPA1* gene [25], the multiplex ligation-dependent probe amplification method [12], or target gene panel sequencing using a modification of a previously reported method [26] or under the same conditions as previously reported [27]. The modifications involved the use of newly designed amplicon-specific primer sequences for the *OPA1* gene (Appendix 1) and the use of the Illumina MiSeq platform (San Diego, CA) instead of the 454 Genome Sequencer FLX system (Roche Diagnostics Corp., Basel, Switzerland). The confirmation and segregation of identified *OPA1* variants were performed using Sanger sequencing. The nomenclature of the variants was based on the *OPA1* cDNA sequence of NM_015560.2.

RESULTS

Case 1: The proband was a 24-year-old man who noticed a decrease in his vision bilaterally at age 14 and consulted a local ophthalmologist (Table 2). No ocular abnormalities were detected to explain his decreased vision. His vision slowly deteriorated until age 20 and became stable thereafter. He noticed hearing impairments at age 17 and was diagnosed with auditory neuropathy at age 21 at a local hospital. He was referred to the NISO for genetic examination at age 23, and a heterozygous mutation of the *OPA1* gene (c.1334G>A, p.R445H) was found (Table 1). He had no family history of either visual or auditory impairments (Figure 1). A segregation analysis of this family revealed that the proband in Case 1 had a de novo mutation.

Ophthalmological examinations at age 24 showed that his decimal BCVA was 0.3 oculus dexter (OD) and 0.5 oculus sinister (OS) (Table 3). The pupillary light reflexes were normal in both eyes, but a relative afferent pupillary defect (RAPD) was present in the right eye. The eye positions and eye movements were normal. There was no ptosis in either eye. Goldmann visual field examinations showed central and paracentral scotomas and the enlargement of Marriott's blind spot bilaterally (Figure 2). The color discrimination tests, which included the Ishihara test, Tokyo Medical College test, and Panel-D 15, were normal. Ophthalmoscopic examinations showed temporal pallor of the optic disc bilaterally (Figure 3). OCT showed a thinning of the nerve fiber layer (NFL) and ganglion cell layer (GCL) between the optic disc and the fovea, but micro retinal cysts were not observed (Figure 4). The N75 and P100 components of the pattern-reversal VEPs were extinguished in both eyes.

Auditory examinations showed a bilateral sensorineural hearing loss of approximately 20–40 dB HL by pure-tone audiometry (Table 4). The maximum speech discrimination

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Table 1. Results of in silico genetic analysis of 3 OPA1 variants*1.

Variant ID	HGVS.c	HGVS.p	Position (GRCh 38)	HGVD (%)*2	2kJPN (%)	GnomAD allele frequency (%)						Prediction			Conservation score		dbSNP ID
						East Asian	South Asian	European (Non-finish)	Latino	African	Total	SIFT	Polyphen2 HDIV	Mutation taster	PhyloP	PhastCons	
V1	c.1334G>A	p.Arg445His	3:193643996	0	0	0	0	0	0	0	0	Deleterious	Probably damaging	Disease causing	6.014	1	rs80356529
V2	c.1618A>C	p.Thr540Pro	3:193647093	0	0	0	0	0	0	0	0	Deleterious	Probably damaging	Disease causing	4.904	1	ND*3
V3	c.892A>C	p.Ser298Arg	3:193637973	0	0	0	0	0	0	0	0	Deleterious	Probably damaging	Disease causing	4.884	1	ND

*1Reference: ENST00000392438, NM_015560.2, GRCh38.p12. *2In silico bioinformatic analyses were performed with three allele frequency databases, three software prediction programs, and conservation scores; HGVD (accessed on May 10, 2019), 2kJPN (https://ijgvd.megabank.tohoku.ac.jp/download_2kjpn/; accessed on May 10, 2019), gnomAD Browser (accessed on May 10, 2019), PolyPhen2 (accessed on May 10, 2019), SIFT (accessed on May 10, 2019), and mutation taster (accessed on May 10, 2019), primate PhyloP scores and phastCons scores provided by UCSC (accessed on May 10, 2019). *3ND, not detected.

Table 2. General clinical features of four patients with DOA-plus disease.

Case	Variant ID	Age	Sex	Family history	Clinical features				
					Optic atrophy	Auditory neuropathy	Vestibular dysfunction	Ataxia / Myopathy/ Neuropathy	Progressive external ophthalmoplegia
1	V1	24	M	-	+	+	-	-	-
2	V1	33	M	-	+	+	+	+	+
3	V2	31	F	-	+	+	-	-	+
4	V3	37	M	+	+	+	-	-	-

scores were 45% in right ear and 20% in left ear. ABRs were absent at 100 dB nHL stimulation bilaterally, but DPOAEs were normal in both ears. Cochlear implant was undertaken in his left ear at age 26, and his ability to participate in auditory–verbal communications improved significantly.

Case 2: The proband was a 33-year-old man who noticed a decrease in his vision bilaterally at age 10 and consulted a local ophthalmologist (Table 2). The ocular examinations found no ocular abnormalities to explain his reduced vision. He noticed hearing impairment at age 15. At age 16, bilateral optic nerve abnormality was detected at a local hospital, and his BCVA was 0.4 OU. Genetic analysis for Leber hereditary optic neuropathy was performed, but no mutation was detected in the mitochondrial gene. At age 17, he noticed an unsteadiness while riding a bicycle due to vestibular dysfunction. His vision gradually deteriorated, and he visited the Teikyo University Hospital at age 19, where genetic tests revealed a heterozygous mutation in the *OPA1* gene (c.1334G>A, p.R445H) [15] (Table 1). He was later diagnosed with auditory neuropathy at age 28 at Keio University. At the same time, he noticed difficulty in walking due to weakness in his lower extremities. He had no family history of either visual or auditory impairment (Figure 1).

Ophthalmological examinations at age 33 showed that his decimal BCVA was 0.2 OD and 0.09 OS (Table 3). The pupillary light reflexes were normal in both eyes. The eye positions were normal, but there was a limitation of elevation, depression, and abduction in both eyes. There was no ptosis in either eye.

Goldmann visual field testing revealed central and paracentral scotomas, and the enlargement of Marriott's blind spots bilaterally (Figure 2). The color discrimination tests, which included the Ishihara test, Tokyo Medical College test, and Panel-D 15, were normal. OCT showed a thinning of the NFL and GCL between the optic disc and the fovea, but micro retinal cysts were not observed (Figure 4). The N75 and P100 components of the pattern-reversal VEPs were extinguished in both eyes.

Table 3. Ocular findings of four patients with DOA-plus phenotype.

Case	Age of onset	Chief complaint	Best corrected decimal VA	Goldmann perimetry	Funduscopic appearance	OCT	Pattern VEP
1	14	Decreased VA	(0.3)/(0.5)	Central and paracentral scotoma, OU	Temporal pallor of optic disc, OU	Thinning of NFL and GCL in the papillomacular bundle, OU	Extinguished responses of N75 and P100, OU
2	10	Decreased VA	(0.2)/(0.09)	Central and paracentral scotoma, OU Enlargement of blind spot, OU	Temporal pallor of optic disc, OU	Thinning of NFL and GCL in the papillomacular bundle, OU	Severely reduced responses of N75 and P100, OU
3	3	Decreased VA	(0.03)/(0.03)	Large central scotoma, OU	Moderate and diffuse pallor of optic disc, OU	Thinning of NFL and GCL in the papillomacular bundle, OU	Extinguished responses of N75 and P100, OU
4	6	Decreased VA	(0.04)/(0.03)	Central and paracentral scotoma, OU	Moderate and diffuse pallor of optic disc, OU	Thinning of NFL and GCL in the papillomacular bundle, OU	Extinguished responses of N75 and P100, OU

VA; visual acuity, OCT; optical coherence tomography, VEP; visually evoked potential, NFL; nerve fiber layer, GCL; ganglion cell layer

A bilateral sensorineural hearing loss of approximately 60 dB HL was found by pure-tone audiometry (Table 4). The maximum speech discrimination scores were 20% in both ears. ABRs were absent at 100 dB nHL stimulation bilaterally, but DPOAEs were normal at all frequencies tested in both ears.

Case 3: The proband was a 30-year-old woman. Her poor visual acuity was detected at age 3, and a local ophthalmologist diagnosed her with bilateral optic atrophy of unknown origin (Table 2). She noticed hearing impairment at age 16. She was referred to the NISO at age 28 and was diagnosed with auditory neuropathy. Genetic tests revealed a heterozygous mutation in the *OPA1* gene (c.1618A>C, p.T540P) [23]

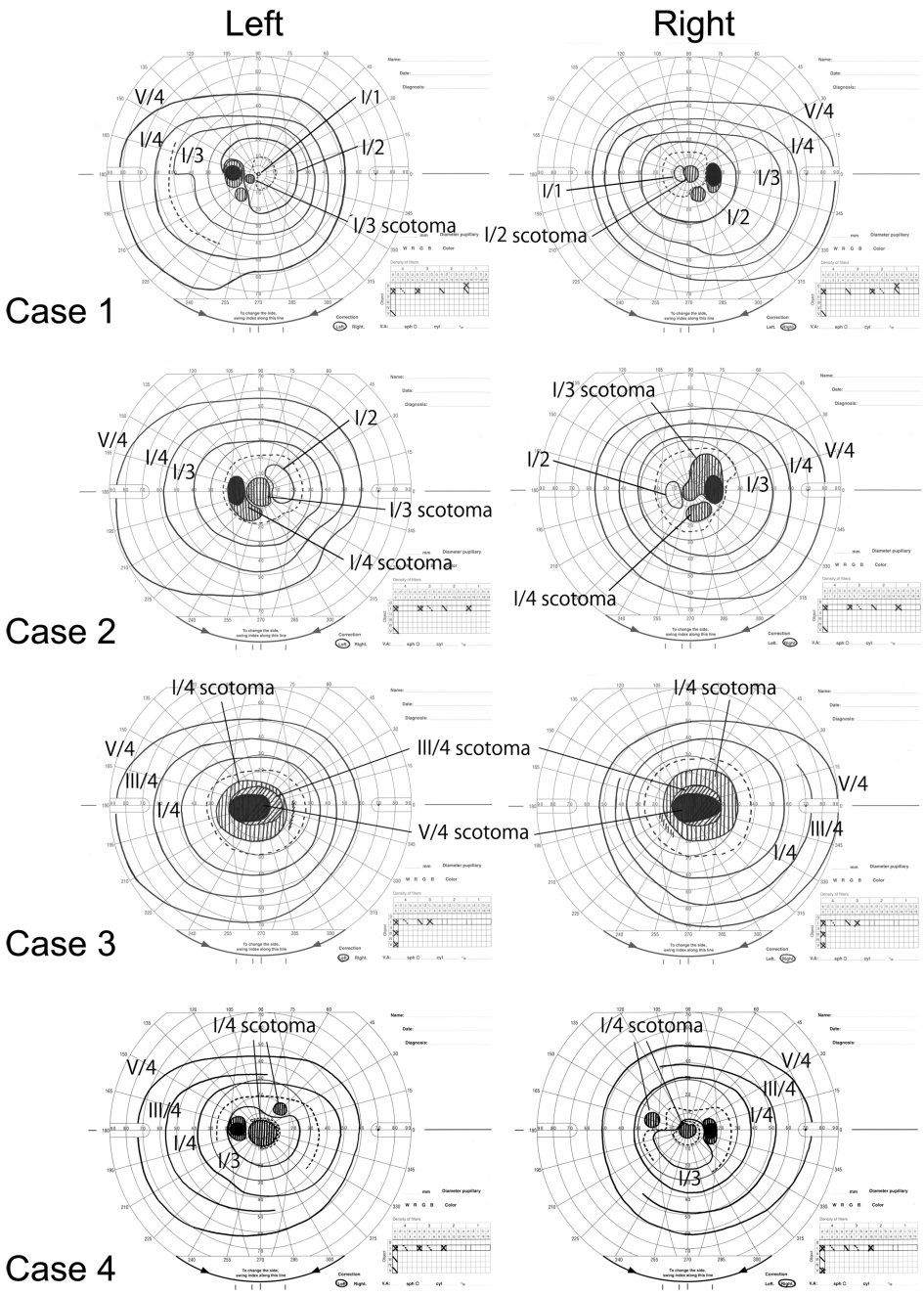

Figure 2. Results of Goldmann visual field tests. Central and paracentral scotomas, and the enlargement of Marriott's blind spots were present in all DOA-plus cases.

(Table 1). She had no family history of either visual or auditory impairments (Figure 1). A segregation analysis of her family revealed that Case 3 had a de novo mutation.

Ophthalmological examinations at age 31 showed that her BCVA was 0.03 in both eyes (Table 3). The pupillary light reflexes were normal in both eyes. Horizontal nystagmus was present in both eyes, and a limitation of adduction was observed in the left eye. A mild ptosis of the right eye was present, with a margin-to-reflex distance of 1.0 mm in the right eye and 2.5 mm in the left eye.

Goldmann visual field tests revealed a large central scotoma bilaterally (Figure 2). She could not read any plates of either the Ishihara test or Tokyo Medical College test. OCT showed a thinning of the NFL and GCL between the optic

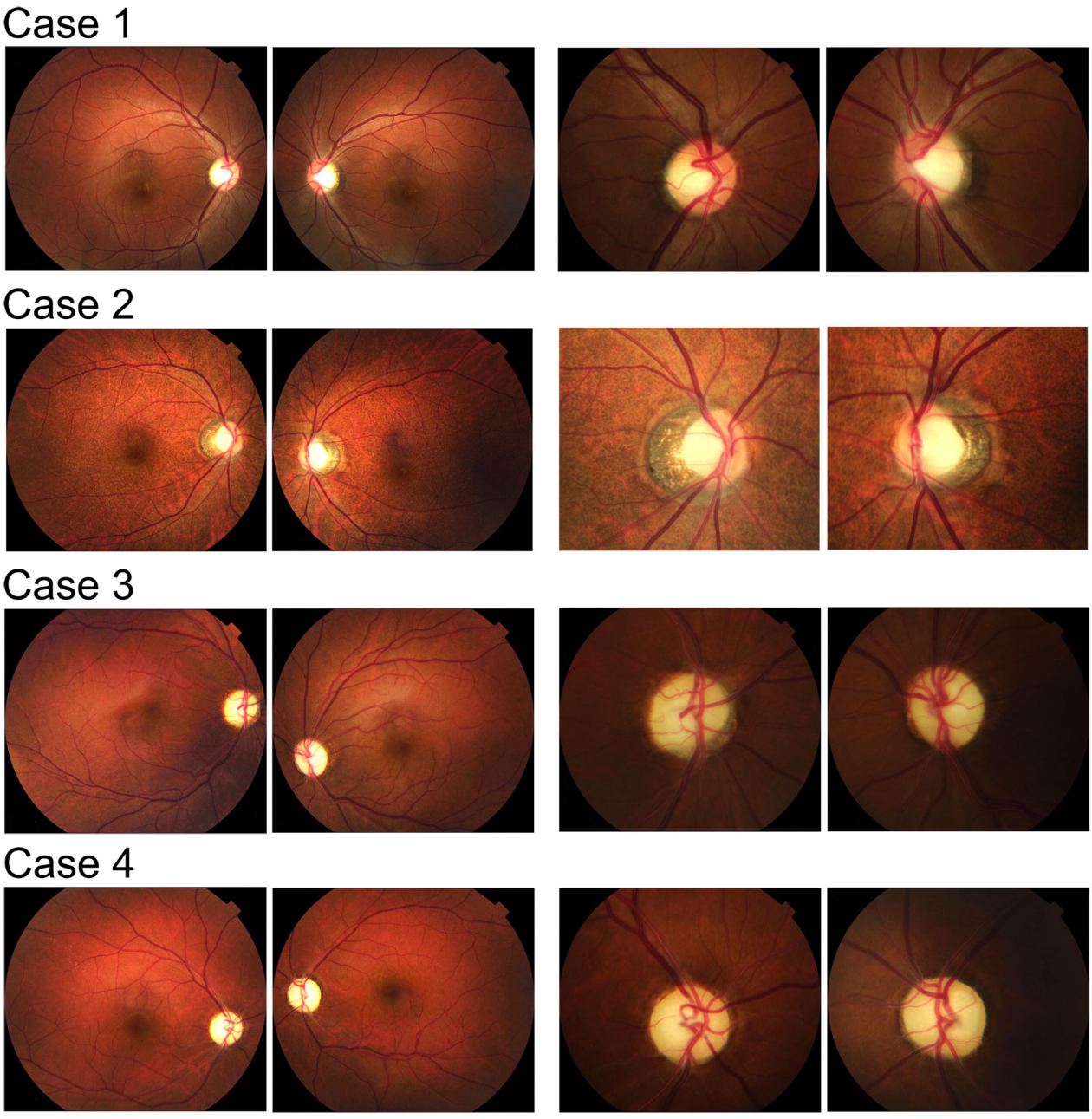

Figure 3. Fundus photographs of the four DOA-plus patients with enlarged optic discs in the left columns. Diffuse or temporal pallor of the optic disc was present in all cases.

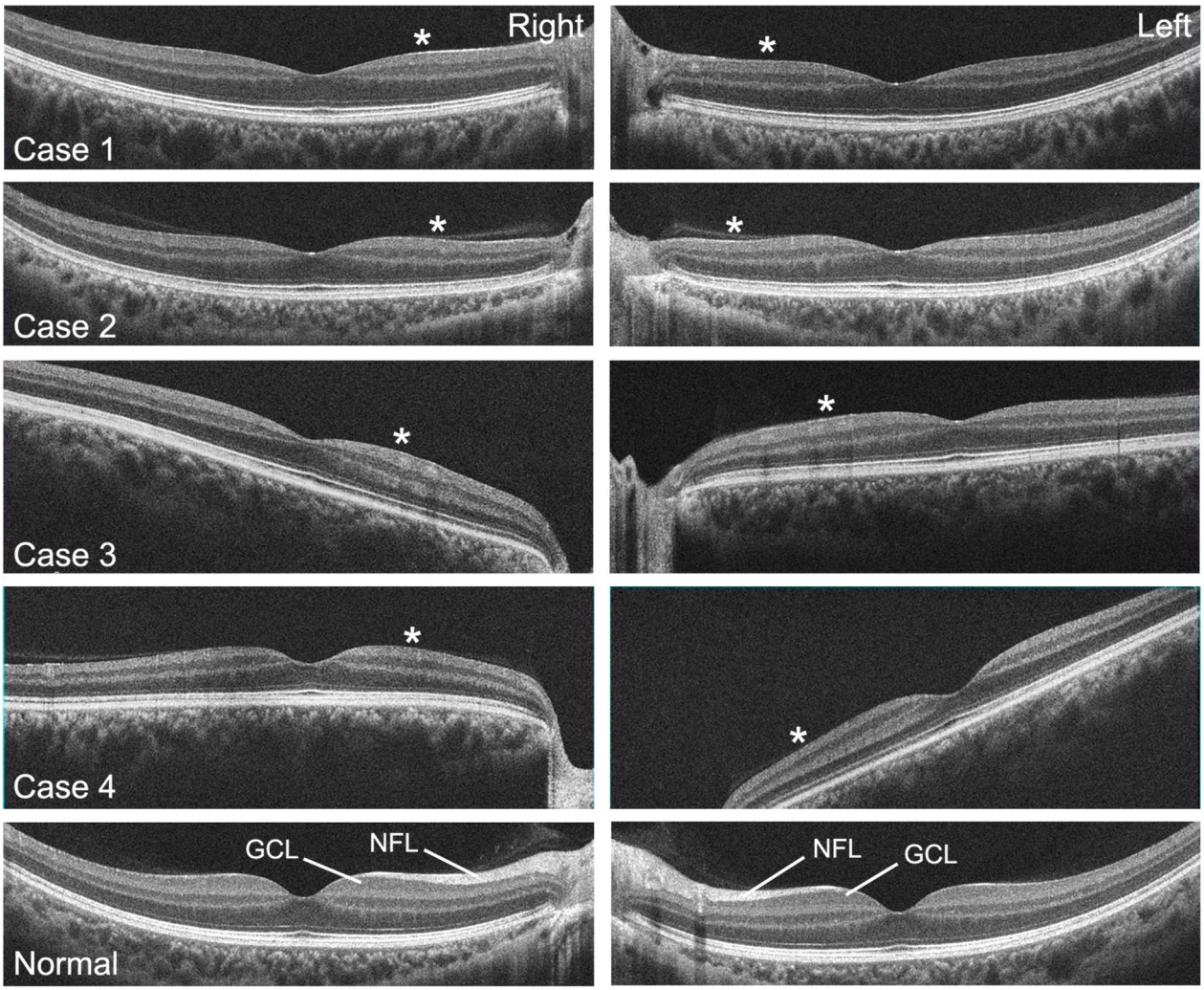

Figure 4. Optical coherence tomographic (OCT) images along the horizontal meridian. An example of a normal 19-year-old woman is shown at the bottom. In all cases, a thinning of the nerve fiber layer (NFL) and ganglion cell layer (GCL) was observed between the optic disc and the fovea (asterisk).

Table 4. Auditory findings of four patients with DOA-plus phenotype.

Case	Age of onset	Chief complaint	Audiometric tests	Maximum speech discrimination scores	DPOAE	ABR
1	17	Hearing impairment	A bilateral sensorineural hearing loss of approximately 20–40 dB	45% in right ear, 20% in left ear	Normal	Absent bilaterally
2	15	Hearing impairment	A bilateral sensorineural hearing loss of approximately 60 dB	20% in both ears	Normal	Absent bilaterally
3	16	Hearing impairment	A bilateral sensorineural hearing loss of approximately 50 dB in right, and 40 dB in left	40% in right ear, 30% in left ear	Normal	Absent bilaterally
4	16	Hearing impairment	A bilateral sensorineural hearing loss of approximately 70 dB in right, and 60 dB in left	0% in both ears	Normal	Absent bilaterally

DPOAE; distortion product otoacoustic emission, ABR; auditory brainstem responses

disc and the fovea, but micro retinal cysts were not observed (Figure 3). The N75 and P100 components of the pattern-reversal VEPs were extinguished in both eyes.

A bilateral sensorineural hearing loss of approximately 50 dB HL in the right ear and 40 dB HL in the left ear was found by pure-tone audiometry (Table 4). The maximum speech discrimination scores were 40% in the right ear and 30% in the left ear. ABRs were absent at 95 dB nHL stimulation bilaterally, but DPOAEs were normal in both ears.

Case 4: The proband was a 37-year-old man whose low visual acuity was detected at age 6, and a local ophthalmologist diagnosed him with bilateral optic atrophy of unknown origin (Table 2). He noticed hearing impairment at age 16, and he was later diagnosed with auditory neuropathy at age 31. Genetic tests revealed a novel heterozygous mutation in the *OPA1* gene (c.892A>C, p.S298R; Table 1). His father had both visual and hearing impairments before age 20, but he died at age 68 without undergoing detailed ophthalmological examination (Figure 1).

Ophthalmological examinations at age 37 showed that the patient's BCVA was 0.04 OD and 0.03 OS (Table 3). The pupillary light reflexes were normal in both eyes. He had exotropia in his right eye, but the eye movements were normal in both eyes. There was no ptosis in either eye.

Goldmann visual field tests revealed central and paracentral scotomas bilaterally (Figure 2). He could not detect the characters of any of the Ishihara test plates. OCT showed a thinning of the NFL and GCL between the optic disc and the fovea, but micro retinal cysts were not observed (Figure 3). The N75 and P100 components of the pattern-reversal VEPs were extinguished.

A bilateral sensorineural hearing loss of approximately 70 dB HL in the right ear and 60 dB HL in the left ear was found by pure-tone audiometry (Table 4). The maximum speech discrimination scores were 0% in both ears. ABRs were absent at 100 dB nHL stimulation bilaterally, but DPOAEs were normal in both ears. Cochlear implant was undertaken in his left ear at age 37, and his ability to participate in auditory–verbal communications improved significantly.

Comparison between cases with and without systemic disorders: The clinical and genetic records of 48 cases from 26 families with simple DOA were reviewed and compared with the four DOA-plus cases [12,13,28]. The mean ± standard deviation (SD) age at the time of the examination of DOA-plus disease was 31.3 ± 3.9 years and of simple DOA was 37.3 ± 17.7. All the cases had heterozygous pathogenic variants in the *OPA1* gene, and the variants are listed in Appendix 2. All the DOA-plus cases had missense mutations, whereas splice site mutations were most common in simple DOA. Missense mutations accounted for only 11.5% (3/26) of the simple DOA cases.

The BCVA of the four DOA-plus cases were compared to age-matched simple DOA cases who were no older than 50 years (38/48 cases). The mean age ± SD of the DOA-plus cases was 31.3 ± 3.9 years and of the simple DOA cases was 30.4 ± 12.7 years ($p = 0.40$, Student *t* test). The mean BCVA of the four eyes of the DOA-plus cases was 1.04 ± 0.43 logarithm of the Minimum Angle of Resolution (LogMAR) units and that for the 38 eyes of the simple DOA cases was 0.55 ± 0.34 LogMAR units ($p = 0.07$, Student *t* test).

DISCUSSION

DOA is one of the major causes of inherited optic nerve disorders, and even before the major genetic cause of DOA was determined to be the *OPA1* gene [1,2], a subset of patients with DOA had been shown to have extraocular symptoms such as hearing loss [14,29-32]. The *OPA1* gene was first considered to be causative of DOA with extraocular symptoms by Shimizu [15] and Amati-Bonneau [16], who both showed that a missense mutation in the GTPase domain, R445H, was causative of optic neuropathy and hearing loss. Since then, several cases with this complex phenotype have been detected, mainly in the European population [17,18,33-38]. Yu-Wai-Man et al. reported their findings on a large multi-center study of 104 DOA patients from 45 independent families. They presented a detailed DOA-plus phenotype, which was associated with varying combinations of hearing loss, ataxia, myopathy, peripheral neuropathy, and PEO [17].

The OPA1 protein is located within the inner mitochondrial membrane and is critical for the fusion of mitochondria. Pathogenic *OPA1* mutations result in marked mitochondrial network fragmentation [18], which then decreases the stability of the mitochondrial respiratory chain complexes [35,39,40]. *OPA1* mutations also cause mitochondrial genome instability, which leads to the accumulation of multiple mtDNA deletions in the affected tissues [33,41]. Patients with DOA-plus phenotypes have significantly higher levels of these somatic mtDNA abnormalities, and these abnormalities may lead to the development of the more severe neuromuscular complications [17]. However, the variations in the manifestations of DOA-plus patients indicate the existence of other factors modulating the changes induced by the primary *OPA1* mutation. Although very rare, optic atrophy and auditory neuropathy are known to co-occur through other genetic causes, such as autosomal recessive optic atrophy and auditory

neuropathy with mutations of the *TMEM126A* gene (Gene ID: 612989; OMIM 612988) [42].

Ocular signs and symptoms: The decimal BCVA of the four DOA-plus cases varied from 0.03 (Case 3, OU) to 0.5 (Case 1, OS), and the age of onset varied from 3 years (Case 3) to 14 years (Case 1). It is well known that the ocular signs and symptoms of DOA vary considerably, and the variations observed in the DOA-plus cases are comparable to those of simple DOA. In all the DOA-plus cases, ophthalmoscopy showed temporal or diffuse pallor of the optic discs, OCT showed a thinning of the NFL and GCL in the papillomacular bundle, and pattern-reversal VEPs were severely reduced or extinguished. Microcystic changes in the inner nuclear layer were found in some cases with DOA [43], but our cases with DOA-plus did not show any cystic changes. In addition, the BCVA of the DOA-plus cases were not significantly different from that of age-matched simple DOA cases. These findings indicate that the visual signs and symptoms do not significantly differ between DOA-plus and simple DOA cases, at least until the fourth decade of life. However, the multicenter study by Yu-Wai-Man et al. indicated that individuals with DOA-plus phenotypes had significantly worse vision than did those with simple DOA phenotypes [17]. In our four cases of DOA-plus, there was a tendency to have lower BCVAs, and it is possible that statistical significance may arise if the number of DOA-plus patients is increased.

Auditory signs and symptoms: Among the extraocular disorders other than optic neuropathy caused by the *OPA1* gene mutations, sensorineural hearing impairment was reported in 62.5% of the *OPA1* mutation carriers and was the second most frequent major clinical feature in DOA-plus patients [17]. Auditory neuropathy is a hearing disorder characterized by the absence or severe deterioration of the ABR in the presence of normal cochlear outer hair cell function, as determined by the DPOAE test [19-21]. It has been reported that in 42% of patients with auditory neuropathy, it is associated with hereditary neurologic disorders, while in 10% of patients, it is associated with toxic, metabolic, immunological, and infectious causes. The cause is unknown in 48% of patients [44].

Several genes are involved in the pathology of auditory neuropathy, including *OPA1* [18,22] and those encoding *DIAPH3* (Gene ID: 609129; OMIM 614567) and OTOF (Gene ID: 601071; OMIM 603681) [45,46]. Mutations in *OTOF* is the most common cause in Japanese patients with congenital auditory neuropathy [47]. In patients who have the p.R445H mutation in the *OPA1* gene, progressive hearing impairment begins in childhood, and audiological examinations show features of auditory neuropathy [18,44].

All four of our cases had bilateral hearing loss in their second decade of life, and they presented with features typical of auditory neuropathy due to the *OPA1* gene mutations (Table 4). Two patients (cases 1 and 4) underwent cochlear implant and recovered the ability to engage in auditory–verbal communication. It is noteworthy that Case 2 noticed not only hearing loss but also unsteadiness while riding a bicycle at the age of 17. Although he did not clearly complain of a balance dysfunction, vestibular function tests revealed that Case 2 had impaired vestibular function accompanied by auditory neuropathy [22].

Ataxia, myopathy, neuropathy, and PEO: PEO was reported in 46.2% of the patients who were *OPA1* mutation carriers and was the third most common major clinical feature in DOA-plus patients [17]. Among our four patients, a limitation of elevation, depression, and abduction in both eyes was observed in Case 2, and horizontal nystagmus in both eyes and a limitation of adduction in the left eye were observed in Case 3 (Table 2). Case 3 also had mild ptosis of the right eye. These signs are thought to be part of PEO; however, neither patient noticed any disabilities related to these disorders and thus, the age of onset was not clear. Case 2 noticed difficulty in walking due to weakness of the lower extremities at age 28. It is likely that this was due to myopathy or neuropathy related to the *OPA1* mutation, but detailed examination by a neurologist had not been performed on this patient.

Complications during natural course of disease process: Yu-Wai-Man et al. reported that in 104 DOA-plus patients from 45 independent families, optic nerve dysfunction was present in 85.6%, deafness in 62.5%, PEO in 46.2%, myopathy in 35.6%, ataxia in 21.8%, and neuropathy in 21.8% [17,35,37]. They reported that optic nerve dysfunction was usually detected in the first or second decade of life, followed by auditory dysfunction in the second or third decade. Other signs, such as ataxia, myopathy, neuropathy, and PEO developed after the third decade of life.

In our four cases, optic nerve dysfunction occurred in the first to second decade of life, and auditory dysfunction occurred later in the second decade of life (Figure 5). In Case 2, myopathy or neuropathy occurred in the third decade. Although the onset of PEO was uncertain, the course of complications was comparable to that observed in the European population [17].

Genotypical comparisons between DOA-plus and simple DOA: The majority of the reported mutations in the *OPA1* gene resulted in a loss of function, and haploinsufficiency is a major disease mechanism for DOA pathogenesis [5,7,11,48]. However, missense mutations within the GTPase domain have been reported to cause DOA via a dominant negative

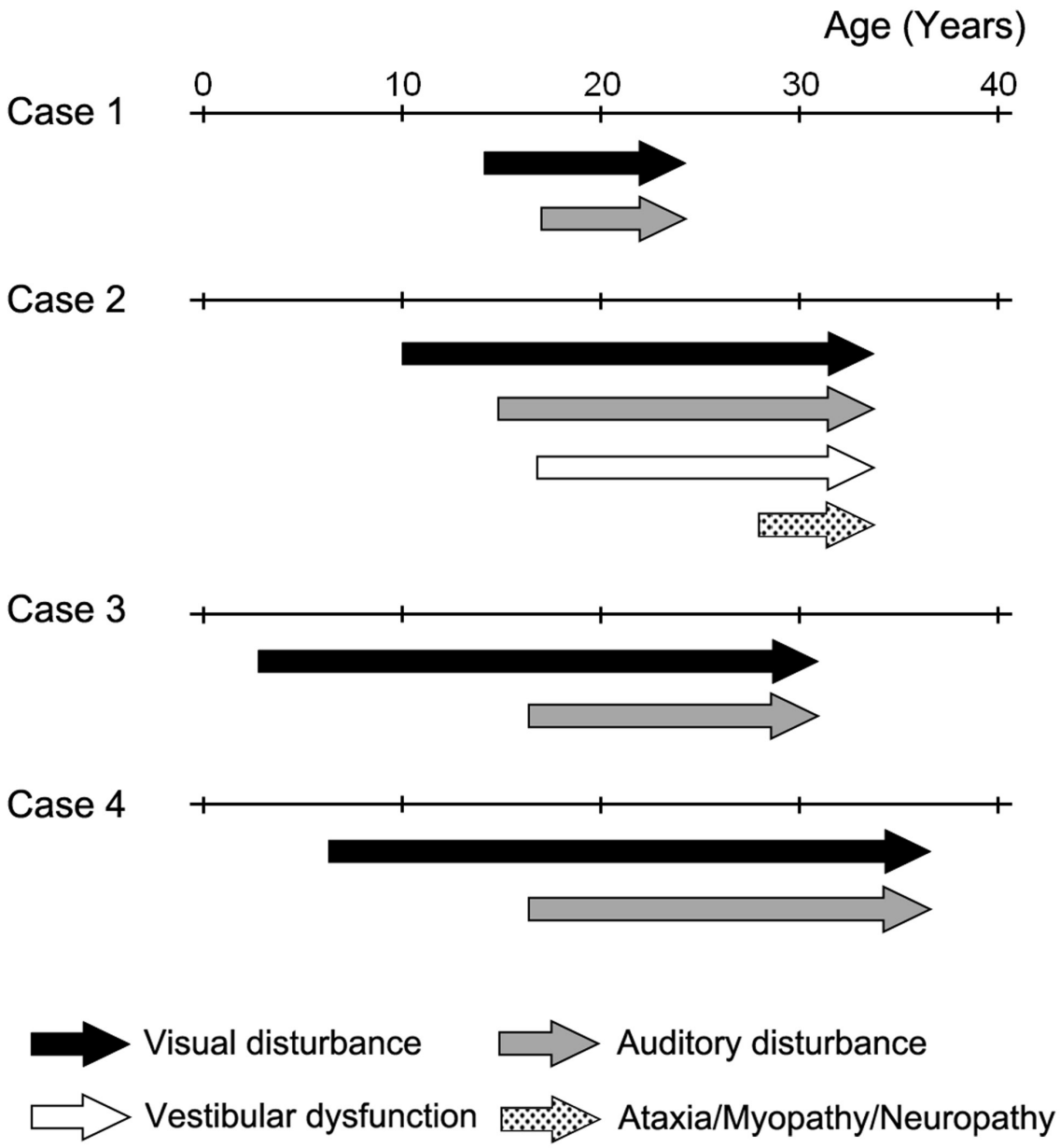

Figure 5. Progress of ocular and extraocular signs in patients with the DOA-plus phenotype. The horizontal axis shows age. Visual disturbance preceded auditory disturbance in all cases. In Case 2, the symptoms of vestibular dysfunction and ataxia followed those of auditory disturbances. Cases 2 and 3 had PEO, but we did not show it in the figure because the onset of PEO was not clear in either patient.

effect [33], and DOA patients with missense mutations exhibit more severe phenotypes than those with deletion/truncation mutations associated with haploinsufficiency [17,49]. There is a two- to threefold increase in the risk of having DOA-plus features when missense mutations are located within the GTPase domain [17]. In our cohort, the cases with DOA-plus phenotypes had missense mutations in either the GTPase domain (cases 1, 2, and 4) or the dynamin central domain (Case 3). As for the type of variant, missense mutations accounted for 100% (4/4) in DOA-plus cases but for only 11.5% (3/26) in simple DOA cases (Appendix 2). The p.R445H-mutation in cases 1 and 2 is most commonly found

in the DOA-plus phenotype. This mutation may impair GTP hydrolysis and interfere with nucleotide binding and affinity, which would then affect the hydrolysis rate of the GTPase domain [33]. Namba et al. [23] demonstrated, using molecular modeling, that the p.T540P mutation in Case 3 decreased the GTP binding ability because of the destabilization of loop-l4, which caused a decrease in GTPase activity [23].

Prevalence of DOA-plus among all patients with OPA1 mutations: Yu-Wai-Man et al. estimated that the prevalence of DOA-plus patients among all *OPA1* mutation carriers was 17.2% in the Northern England population [17]. Similarly, Ferre et al. [11] estimated it to be 10% in the French and Spanish populations [11]. In our cohort, the DOA-plus families accounted for 13.3% (4/30) of all the families with *OPA1* gene mutations.

According to the locus-specific database of *OPA1* mutations compiled by Ferre et al., 27% (55/204) of *OPA1* mutations were missense mutations [11,48], whereas missense mutations accounted for only 17.5% (7/30) of families in our total cohort (Table 1 and Appendix 2). The difference in the incidence of DOA-plus may arise from genotypical characteristics of the Japanese population; however, the size of our cohort was small, making it difficult to draw any strong conclusions.

Biallelic mutations in the *OPA1* gene are known to cause Behr syndrome, which is characterized by early-onset optic atrophy accompanied by spinocerebellar degeneration resulting in ataxia, pyramidal signs, peripheral neuropathy, and developmental delay [50,51]. This disorder is clinically heterogeneous, and our cases also showed clinical features common with autosomal recessive Behr syndrome. In our cohort, however, none of either the DOA-plus or simple DOA patients had biallelic pathogenic variants in the *OPA1* gene.

There are limitations in our study. First, the total number of DOA patients was 52 from 30 families, meaning it is not a large enough sample from which to compare genetic and clinical features among different ethnicities. Second, the onset of extraocular complications was unclear in some cases, even for the patients themselves, and it was difficult to conclusively describe the natural courses of the DOA-plus phenotype.

In conclusion, all the patients with the DOA-plus phenotype had a missense mutation in the *OPA1* gene. These patients had the typical ocular signs and symptoms of DOA in their first or second decade of life, and other systemic complications, such as auditory neuropathy, vestibular dysfunction, and ataxia, followed the ocular symptoms. Considering that patients with auditory neuropathy are known to recover their auditory–verbal communications through the use of cochlear implant [52], we should carefully observe the occurrence of extraocular complications in cases with DOA especially when missense mutations in the *OPA1* gene are present.

APPENDIX 1. SUPPLEMENTARY TABLE 1.

To access the data, click or select the words "Appendix 1."

APPENDIX 2. SUPPLEMENTARY TABLE 2.

To access the data, click or select the words "Appendix 2."

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