



Expanding the phenotype of *IBA57* mutations: related leukodystrophy can remain asymptomatic

Kohei Hamanaka¹ · Satoko Miyatake^{1,2} · Ayelet Zerem³ · Dorit Lev⁴ · Luba Blumkin³ · Kenji Yokochi⁵ · Atsushi Fujita¹ · Eri Imagawa¹ · Kazuhiro Iwama¹ · Mitsuko Nakashima⁶ · Satomi Mitsuhashi¹ · Takeshi Mizuguchi¹ · Atsushi Takata¹ · Noriko Miyake¹ · Hiroto Saito⁶ · Marjo S. van der Knaap⁷ · Tally Lerman-Sagie³ · Naomichi Matsumoto¹

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Abstract

Biallelic mutations in *IBA57* cause a mitochondrial disorder with a broad phenotypic spectrum that ranges from severe intellectual disability to adolescent-onset spastic paraplegia. Only 21 *IBA57* mutations have been reported, therefore the phenotypic spectrum of *IBA57*-related mitochondrial disease has not yet been fully elucidated. In this study, we performed whole-exome sequencing on a Sephardi Jewish and Japanese family with leukodystrophy. We identified four novel biallelic variants in *IBA57* in the two families: one frameshift insertion and three missense variants. The three missense variants were predicted to be disease-causing by multiple in silico tools. The 29-year-old Sephardi Jewish male had infantile-onset optic atrophy with clinically asymptomatic leukodystrophy involving periventricular white matter. The 19-year-old younger brother, with the same compound heterozygous *IBA57* variants, had a similar clinical course until 7 years of age. However, he then developed a rapidly progressive spastic paraparesis following a febrile illness. A 7-year-old Japanese girl had developmental regression, spastic quadriplegia, and abnormal periventricular white matter signal on brain magnetic resonance imaging performed at 8 months of age. She had febrile convulsions at the age of 18 months and later developed epilepsy. In summary, we have identified four novel *IBA57* mutations in two unrelated families. Consequently, we describe a patient with infantile-onset optic atrophy and asymptomatic white matter involvement, thus broadening the phenotypic spectrum of biallelic *IBA57* mutations.

Introduction

IBA57 (MIM# 615316) encodes a protein involved in the synthesis of mitochondrial [4Fe-4S] cluster proteins

[1]. The [4Fe-4S] cluster is a cofactor of multiple mitochondrial enzymes: respiratory chain complexes (RCC) I and II, mitochondrial aconitase, and lipoic acid synthetase (LIAS). As a cofactor, LIAS transfers lipoic acid to multiple enzymes for mitochondrial energy metabolism [2]. Therefore, loss-of-function mutations in *IBA57* or other genes related to [4Fe-4S] cluster synthesis can lead to multiple defects in mitochondrial enzymes, termed multiple mitochondrial dysfunction syndrome

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✉ Naomichi Matsumoto
naomat@yokohama-cu.ac.jp

¹ Department of Human Genetics, Yokohama City University Graduate School of Medicine, Yokohama, Japan

² Clinical Genetics Department, Yokohama City University Hospital, Yokohama, Japan

³ Pediatric Neurology Unit, Metabolic-Neurogenetic Clinic, Wolfson Medical Center, Holon, and Sackler School of Medicine, Tel Aviv University, Tel-Aviv, Israel

⁴ Institute of Medical Genetics, Metabolic-Neurogenetic Clinic, Wolfson Medical Center, Holon, and Sackler School of Medicine, Tel Aviv University, Tel-Aviv, Israel

⁵ Department of Pediatric Neurology, Mikatahara General Hospital, Hamamatsu, Japan

⁶ Department of Biochemistry, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan

⁷ Department of Child Neurology, VU University Medical Centre, Amsterdam, Netherlands

(MMDS [MIM# 605711, 614299, 615330, 616370, 617613]) [3–7].

IBA57-mutated MMDS is associated with a broad spectrum of neurological impairments. The most severe cases demonstrate psychomotor delay or regression, hypotonia, respiratory failure, seizures, and cavitating leukoencephalopathy, leading to an early death [4, 8]. Milder cases show childhood- to adolescent-onset spastic paraplegia, optic atrophy, distal neuropathy (SPOAN [MIM# 609541]) and cavitating leukoencephalopathy [9].

Since only 21 *IBA57* mutations have been reported to date [4, 8–12], the phenotypic spectrum of biallelic *IBA57* mutations has not been fully elucidated. Here, we report two families harbouring four novel *IBA57* mutations and describe new clinical and radiological features.

Materials and methods

Study participants

Three individuals from two families with leukodystrophy were included in the study: Family 1 had two affected brothers and was from Israel, while Family 2 had one affected girl and was from Japan. Clinical information was obtained from their medical records. Informed consent was obtained from the parents in both families. The study was approved by the institutional review board of Yokohama City University School of Medicine (Yokohama, Japan).

Whole-exome sequencing

Whole-exome sequencing (WES) was performed using DNA from the proband of Families 1 and 2 as previously described [13]. In brief, genomic DNA was captured with a SureSelect Human All Exon V5 Kit (Santa Clara, CA, United States, Agilent Technologies) and sequenced on an Illumina HiSeq 2500 (San Diego, CA, United States, Illumina) with 101-bp paired-end reads. Reads were aligned to the human reference genome (GRCh37.1/hg19) using Novoalign v3.02.13 (<http://www.novocraft.com/>). PCR (polymerase chain reaction) duplicates were removed using Picard (<http://broadinstitute.github.io/picard/>). Local realignments around indels and base quality score recalibration were performed with the Genome Analysis Toolkit (GATK) 3.7-0 (<http://www.broadinstitute.org/gatk/>). Variants were called by GATK UnifiedGenotyper and filtered according to GATK Best Practices. Common variants registered in dbSNP135 (minor allele frequency >0.01) that were not flagged as having clinical associations were excluded. Included variants were annotated using ANNOVAR (2016nov) (<http://www.openbioinformatics.org/a>

[nnoovar/](#)). For each proband from Families 1 and 2, mean depth of coverage against RefSeq coding sequence by WES was 84× and 69×, with 92% and 89% of coding sequence covered by 20 reads or more, respectively.

Sanger sequencing

IBA57 variants were analyzed by Sanger sequencing using standard methods. Primer sequences were: TGCTAGG GCTGCTGACCAATGAAC (forward) and ACCCTTGA GCTTCCACCCATC (reverse) for c.335T>C; CAGAGC TCTTTGCGTTGG (forward) and ATCGGTGCTGGTGA TAATCC (reverse) for c.386A>T and c.588dup; and GGAGCTGGACGATGTTCAAT (forward) and AAGAA CCGGACAGGGAAGAG (reverse) for c.731A>C. PCR products were purified by Exonuclease I and sequenced with BigDye Terminator v3.1 Cycle Sequencing kit (Foster City, CA, United States, Applied Biosystems) on a 3500 DNA Sequencing Analyzer (Carlsbad, CA, United States, Life Technologies).

In silico analysis

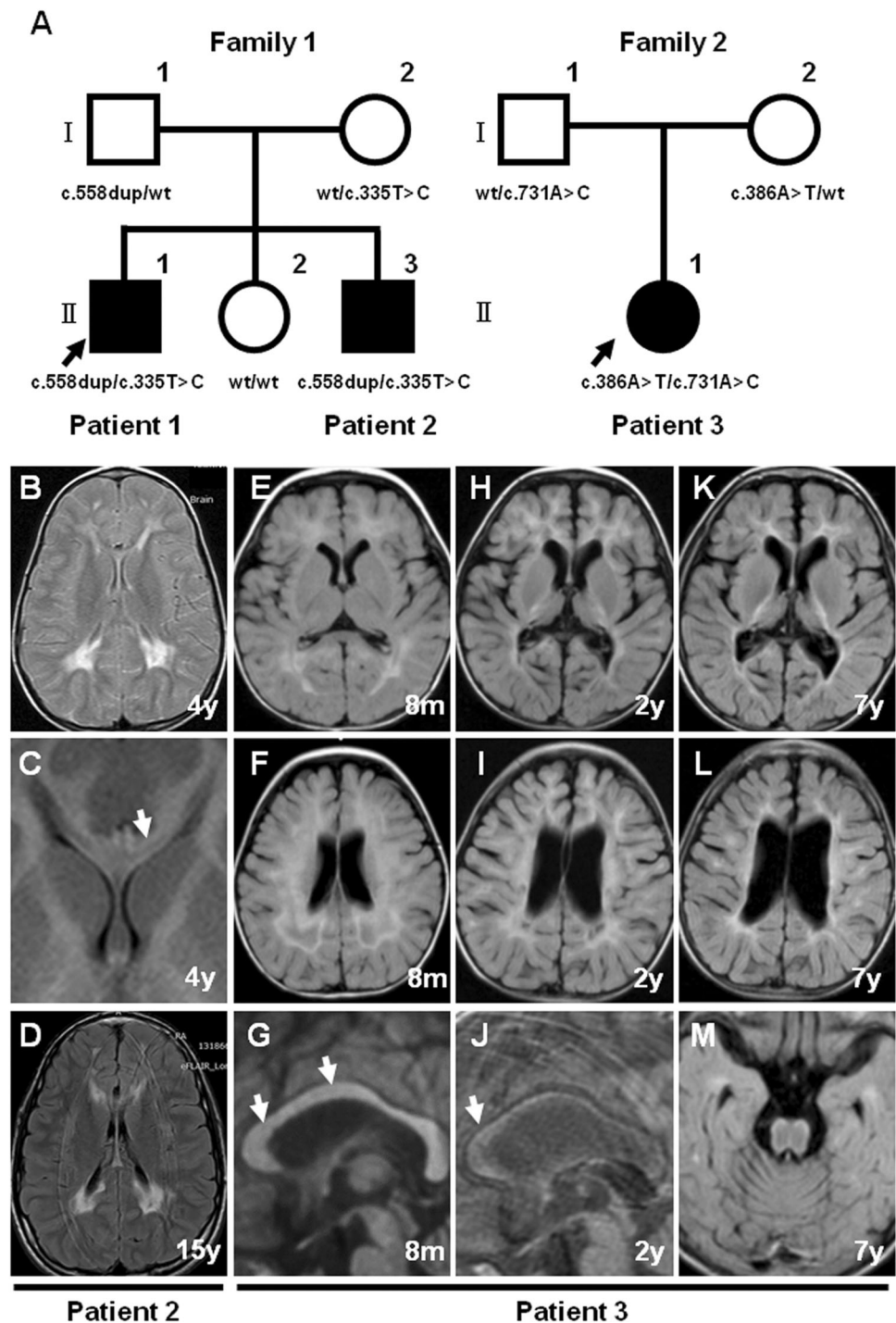
Pathogenicity of missense variants was predicted using the following software: SIFT (<http://sift.jcvi.org>), PolyPhen-2 (<http://genetics.bwh.harvard.edu/pph2/>), and MutationTaster (<http://www.mutationtaster.org/>). Flanking amino acids at missense variants were aligned between species by ClustalW (<http://www.genome.jp/tools-bin/clustalw>). References for amino acid sequences were: *Homo sapiens*: NP_001010867.1; *Macaca mulatta*: XP_001083460.1; *Mus musculus*: NP_776146.1; *Gallus gallus*: NP_001026129.2; *Xenopus tropicalis*: XP_002939357.1; and *Danio rerio*: NP_001070103.2.

Results

Clinical studies

Family 1 of Sephardi Jewish origin has two affected siblings whose early life has been previously described by Vinkler et al. [14] (Fig. 1a). Briefly, Patient 1 (II-1) was a 29-year-old man at the time of this study, and showed infantile-onset optic atrophy associated with completely asymptomatic cerebral white matter signal abnormalities by magnetic resonance imaging (MRI). He developed normally. Reduced vision was first noted at the age of 20 months. Within the following 2 weeks, he completely lost his vision. Ophthalmologic examination revealed no abnormalities in the anterior segment of his eyes. Funduscopy examination revealed pale discs with a normal retina and no vascular changes. Electroretinogram

Fig. 1 Clinical findings in Families 1 and 2. **a** Pedigrees of Families 1 and 2. *IBA57* variants are shown below each individual. Arrows, probands; squares, males; circles, females; closed symbols, affected; and open symbols, unaffected; wt, wild-type sequence of *IBA57*. **b–k** Brain fluid-attenuated inversion recovery (FLAIR) (b, d, e, f, h, i, k, l, and m) and T1-weighted (c, g, and j) images in Patient 2 (b–d) and Patient 3 (e–m). Ages when the images were obtained are indicated at the right bottom of each image: y indicates years, m indicates months. White matter volume loss was observed (b and d). The middle blade of the corpus callosum was affected (arrow) (c, g, and j). Rarefaction, cystic degeneration, and rapid loss of white matter volume were detected (e, f, h, i, k, and l). The anterior portion of the pons was affected (m)



showed normal findings. Visual evoked potentials (VEP) indicated a prolonged latency with low amplitudes. Brain MRI performed at 2 years of age showed high signal intensity in bilateral periventricular white matter on T2-weighted images. Follow-up brain MRI at the age of 14 years did not demonstrate any progression. Currently, he has no neurological features and works as a musician and teacher.

Patient 2 is a 19-year-old male and the younger brother (II-2) of Patient 1 (Fig. 1a). He showed a similar clinical course as Patient 1 in early childhood, with visual loss and asymptomatic white matter changes on brain MRI at the age of 18 months. Ophthalmologic examination revealed marked visual loss, a sluggish pupillary response to light, and pendular nystagmus. Funduscopic examination revealed diffuse pallor in both discs with a normal retina.

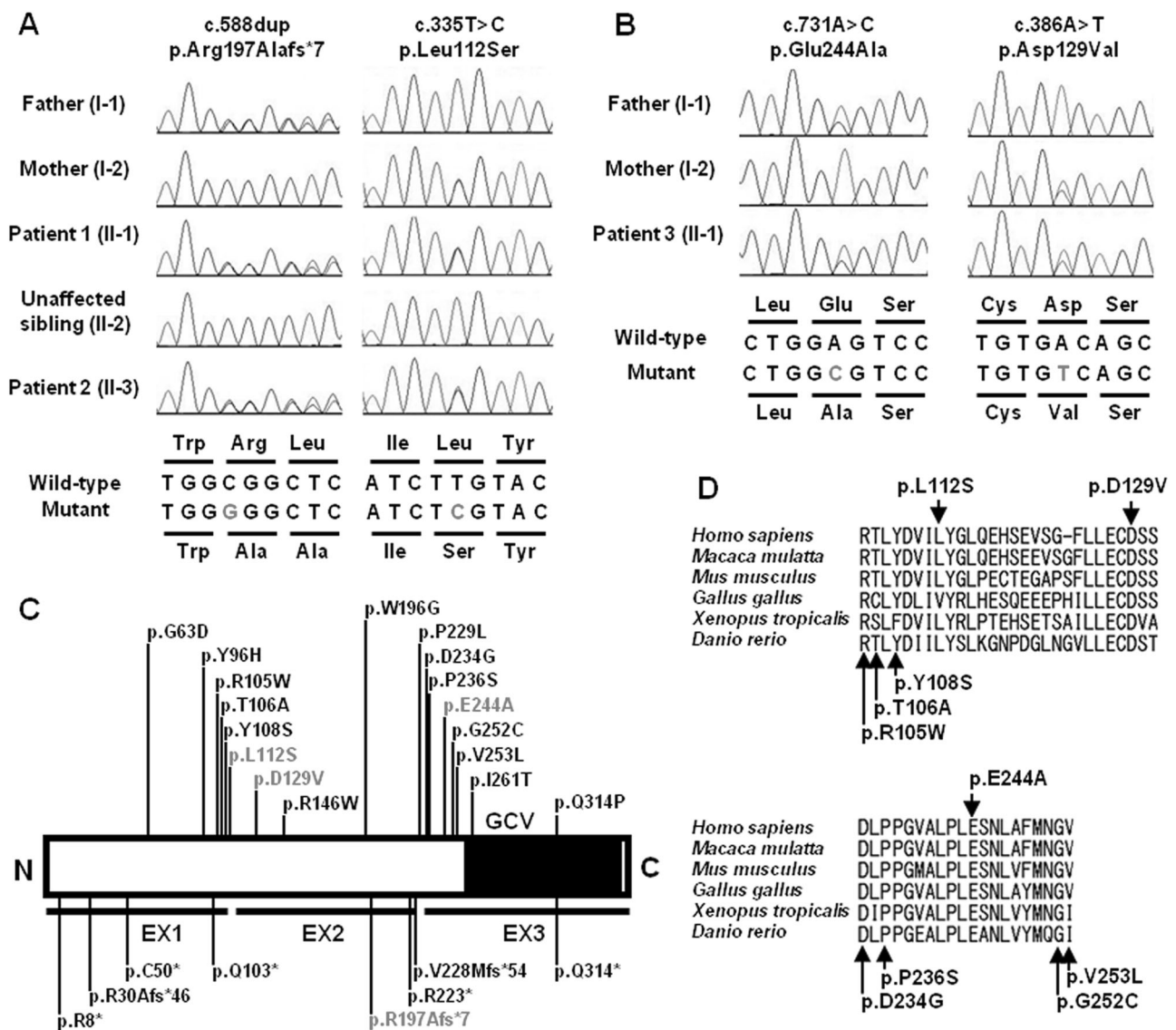


Fig. 2 Genetic findings in Families 1 and 2. Electropherograms of *IBA57* variants in Families 1 (a) and 2 (b). Wild-type and mutant nucleotide and amino acid sequences are depicted below. Substituted or duplicated nucleotides are coloured red. **c** Schematic of *IBA57* protein (NP_001010867.1). Mutated amino acids identified in this study and those reported previously are indicated: missense mutations are shown above and truncating mutations below the protein structure.

Variants identified in this study are coloured red. The GCV domain region is shown as a black-filled box. The corresponding coding exons are shown below the protein structure: EX, exon; N, N-terminus; C, C-terminus; and GCV, glycine cleavage T-protein C-terminal barrel domain. **d** Conservation of amino acids. Variants identified in this study and those reported previously are depicted above and below the alignment, respectively

VEP showed a prolonged latency with very low amplitudes. Brain MRI showed thin optic nerves and signal abnormalities in periventricular white matter and middle blade of the corpus callosum (Fig. 1b, c, and S1A). Mitochondrial dysfunction was suspected due to association of optic atrophy with white matter involvement. Consequently, a skeletal muscle biopsy was performed at 4 years of age revealing no ragged-red fibres and normal staining of oxidative enzymes, namely, nicotinamide adenine dinucleotide-tetrazolium reductase, succinate dehydrogenase, and cytochrome c oxidase staining. Biochemical

studies demonstrated normal RCC activity. At the age of 5 years, he developed seizures, which were controlled with anti-epileptic drugs. At the age of 7 years, after a *Shigella* infection, he rapidly developed spasticity and weakness of his legs leading to a spastic gait. Brain MRI was repeated, revealing that the white matter abnormalities observed at 18 months of age had not progressed. Brain MRI at 15 years of age showed partial white matter rarefaction, a thin corpus callosum, and white matter volume loss (Fig. 1d). Currently he has borderline intelligence, learning disabilities, and anxiety. He attends a special school for

Table 1 Allele frequency and in silico prediction of *IBA57* variants

Family	Variants	ExAC ^a	ESP6500 ^b	ToMMo ^c	SIFT	PolyPhen2	Mutation Taster
1	c.335T>C	–	–	–	Damaging	Probably damaging	Disease causing
	c.588dup	–	–	–	NA	NA	NA
2	c.386A>T	–	–	–	Tolerated	Probably damaging	Disease causing
	c.731A>C	–	–	–	Damaging	Probably damaging	Disease causing

NA not available, – not registered

^aExome Aggregation Consortium

^bESP6500: NHLBI Exome Sequencing Project Exome Variant Server

^cTohoku Medical Megabank Organization

children with cerebral palsy. His neurological examination has been stable since his acute deterioration.

Patient 3 (II-1 in Family 2) is a 7-year-old Japanese girl with developmental regression, spastic quadriplegia, and seizures (Fig. 1a). Her developmental milestones were initially normal. However, developmental regression was noticed at the age of 7 months: she lost head control and stopped reaching out for toys and rolling over. She frequently became drowsy with no clear cause. Neurological examination revealed spasticity with increased deep tendon reflexes in all four limbs. Lactate and pyruvate levels were normal in blood and cerebrospinal fluid. Brain MRI at the age of 8 months showed cerebral white matter involvement, periventricular rarefaction, and corpus callosum involvement at the middle blade (Fig. 1e, f, g, and S1B). She developed febrile seizures at the age of 18 months. Brain MRI performed at 2 years of age detected significant loss of white matter volume and cystic degeneration of periventricular white matter, showing progression of white matter changes (Fig. 1h, i, and j). Abnormal signal intensity in the posterior limb of the internal capsule (Fig. 1h) and an atrophic cerebellum were observed. The thalamus had also atrophied and demonstrated abnormal signal intensity (Fig. 1h). From 4 years of age, she developed complex partial seizures that are controlled by carbamazepine and levetiracetam. To date, she is bedridden with no head control or voluntary movements. She can only understand a few words. Brain MRI at 7 years of age showed further white matter loss, suggesting that the white matter lesions are still gradually progressing, albeit not as rapidly as before (Fig. 1k and l). The anterior portion of the pons showed abnormal signal intensity (Fig. 1m). There is no involvement of U fibres (Fig. 1k and l).

Genetic analysis

WES was performed on two patients, as previously described: Patient 1 in Family 1 and Patient 3 in Family 2. We identified two heterozygous variants in *IBA57* (NM_001010867.2), namely c.335T>C (p.Leu112Ser) and c.588dup (p.Arg197Alafs*7) in Patient 1 and c.386A>T (p.

Asp129Val) and c.731A>C (p.Glu244Ala) in Patient 3. In both families, Sanger sequencing of the patients and parents confirmed that the variants were compound heterozygous: c.335T>C (maternally derived) and c.588dup (paternally derived) in Patient 1; and c.386A>T (maternal) and c.731A>C (paternal) in Patient 3 (Fig. 2a and b). In Family 1, the compound heterozygous variants identified in Patient 1 were shared with his affected brother (Patient 2). All the identified variants are novel (Fig. 2c) and not in publicly available human variation databases (Table 1). The missense variants were predicted as disease-causing by two or more in silico web-based tools (Table 1). The substituted amino acids are highly conserved among species (from fish to human) (Fig. 2d and Table 1). To confirm the pathogenicity of the variants, we would like to test respiratory chain enzyme deficiency or other enzymes containing [4Fe-4S] in the biopsied muscles of Patient 2. However, those from Patient 2 were used up and not left.

Discussion

Here, we describe four novel *IBA57* variants in two families. The frameshift variant in Family 1 is located at the penultimate exon, >50-bp from the last nucleotide of this exon (Fig. 2c). Consequently, transcripts from this allele are most likely to be degraded via nonsense-mediated mRNA decay. The other three missense variants are located at possible mutation hotspots of previously reported missense mutations (Fig. 2c). Thus, the four variants are most likely to be pathogenic mutations.

Family 1 showed a milder phenotype than previously reported cases of *IBA57* mutations [4, 8–10, 12] and intra-familial variability. Patient 1 exhibited isolated infantile-onset optic atrophy with asymptomatic brain white matter involvement. Abnormal vision has been reported in an *IBA57*-related family with SPOAN [9]. This family demonstrated childhood-onset spastic paraparesis and distal neuropathy, followed by adolescent-onset optic atrophy. Blindness has also been reported in a few *IBA57*-related cases with severe developmental delay, abnormal

VEP, and early death [8]. Compared with these families, Patient 1 has developed normally and been healthy except for optic atrophy. Interestingly, Patient 2, the younger brother of Patient 1, shares the same mutations, but has a different clinical course. In addition to infantile-onset optic atrophy, he rapidly developed spastic paraparesis. However, the disease was most likely exacerbated by a febrile illness at the age of 7 years because the disease has not progressed since the initial event.

Why was the phenotype of Patient 1 mild? Surprisingly, Patient 2 had normal RCC enzyme activity and was suspected clinically of having MMDS. All previously reported cases show low activity in both or either RCC I and II [4, 8–10, 12], and residual RCC enzyme activity defines disease severity [4, 9, 12]. The relatively milder phenotype of Patient 1, compared with previously reported cases [4, 8–10, 12], can possibly be explained by retained RCC enzyme activity levels.

Concurrence of optic atrophy and white matter involvement, as seen in Patient 1, has also been described in other mitochondrial diseases such as other types of MMDS, Leigh syndrome (MIM# 256000), as well as Kearns–Sayre syndrome (MIM# 530000) [3, 15–17]. These diseases show a wide variety of symptoms, with a distinct clinical picture from Patient 1. The only mitochondrial disease that resembles the phenotype of Patient 1 is Leber's hereditary optic neuropathy (LHON [MIM# 535000]). LHON is caused by mitochondrial DNA mutations and characterized by optic atrophy with onset from early childhood to late adulthood. LHON can concur with white matter involvement. Clinical symptoms and MRI of such cases usually resemble multiple sclerosis and are different from those of Patient 1 [18, 19]. A similar clinical presentation was described by Lev et al. [20], in a rare case of LHON with periventricular white matter involvement and no other symptoms. However, in this case, decreased vision was not as severe at 14 years of age. Thus, isolated infantile-onset optic atrophy with asymptomatic white matter involvement in *IBA57*-related disease is a distinct phenotype.

Patient 3 had a severe phenotype compared with Patients 1 and 2. Patient 3 showed psychomotor regression and spastic quadriplegia within 1 year after birth, while epilepsy developed after a febrile illness. Brain MRI showed progressive, significant loss of white matter volume. Although white matter abnormalities by MRI might have been augmented by febrile illness, the overall phenotype is consistent with the most severe cases previously reported [8, 12].

Patient 3 was initially diagnosed with vanishing white matter disease (VWM [MIM# 603896]) because of shared features: chronic progressive neurological symptoms, rapid deterioration after febrile illness, and cystic degeneration of periventricular white matter [21]. However, Patient 3 has profound intellectual disability, which is not described in

VWM disease. MRI images demonstrate white matter rarefaction and cystic degeneration, which are reminiscent of VWM disease (Fig. 1f and i) [21]. However, several findings are atypical and suggestive of MMDS. First, the rim of patchy multifocal white matter abnormalities is well delineated and remain patchy over time (Fig. 1e, h, and k). In contrast, they are typically more diffuse in VWM [21]. Second, severe white matter atrophy occurred from an early disease stage (Fig. 1f, i, and l). Such atrophy can be noticed in VWM with late, but not infantile, onset [22]. Third, thalamic atrophy occurred from an early disease stage (Fig. 1h and k). This finding has previously been observed in an *IBA57*-mutated case [8] and is not typically seen in VWM [23]. Fourth, the middle blade of the corpus callosum is preferentially affected (Fig. 1g and j). This feature may be suggestive of MMDS [3, 10–12, 15, 24], while the inner blade is preferentially affected in VWM. MMDS can present with MRI findings similar to VWM, making it difficult for clinicians to accurately diagnose. Our case demonstrates that the well delineated rim of patchy white matter lesions and preferential involvement of the middle blade of the corpus callosum may be useful features to distinguish the two entities.

Patients 2 and 3 showed rapid progression following a febrile illness. In patients with *IBA57* mutations, it has been repeatedly reported that neurological symptoms rapidly progress following stress such as vaccination or head trauma [8, 9]. Similarly, stress-induced rapid neurological deterioration is reported in cases of MMDS caused by mutations in other genes essential for [4Fe-4S] cluster synthesis [25–27]. Our cases and these reports suggest that exogenous stress to the brain can have a significant deleterious effect on white matter.

In conclusion, we describe two families with four novel *IBA57* mutations. Consequently, we have broadened the clinical spectrum of *IBA57* mutations by presenting a previously undescribed phenotype of infantile-onset isolated optic atrophy associated with asymptomatic white matter involvement. Furthermore, we illustrate that brain MRI images of MMDS can be similar to VWM, but have unique features that can be used for differentiation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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