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Clinical short communication

Bilateral striatal necrosis caused by a founder mitochondrial 14459G > A mutation in two independent Japanese families

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ABSTRACT

Bilateral striatal necrosis (BSN) has many causes and is characterized by unique clinical and neuroradiological features. Herein, we report a clinical and genetic analysis of three BSN cases from two independent Japanese families harboring a mitochondrial DNA (mtDNA) 14459G > A mutation located in a coding region of the NADH dehydrogenase subunit 6 gene. In the first family, two male siblings from non-consanguineous parents exhibited similar phenotypes, with infantile-onset generalized dystonia. A third sporadic case involved a male patient with a comparatively milder phenotype characterized by juvenile-onset mild truncal ataxia and parkinsonism. Cerebral magnetic resonance imaging of these cases revealed abnormal signal intensities along the bilateral putaminal area and enlarged lateral ventricle anterior horns caused by caudate nuclear atrophy, particularly in the sibling pair. The sibling-pair cases shared a homoplasmic 14459G > A mutation, and the sporadic case showed heteroplasmy of the same mutation. Additionally, all three cases harbored the 14605A > G single nucleotide polymorphism, which was previously reported as a rare synonymous variation (4.3%) in a Japanese population. Plasmid sequencing revealed a genetic linkage of these two DNA substitutions, suggesting that the three patients shared a genetic founder. Although our mtDNA analysis was only accessible using leukocytes, clinical severity might be associated with homoplasmy or heteroplasmy. In summary, it is important to evaluate potential mtDNA defects in BSN cases, regardless of familial occurrence.

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1. Introduction

Bilateral striatal necrosis (BSN) is characterized by a unique clinical phenotype and neuroradiological features. The pathogenesis of BSN is heterogeneous and its presence has been associated with various acquired and hereditary conditions [1], including mitochondrial disorders such as Leigh syndrome, Leber's hereditary optic neuropathy (LHON) with dystonia, and myoclonic epilepsy with ragged red fibers [2–6]. Mitochondrial BSNs are caused by mutations in both mitochondrial and nuclear genes associated with the maintenance of mitochondrial function [2–13]. Here we report a clinical and genetic analysis of three BSN cases from two independent Japanese families harboring the mitochondrial DNA (mtDNA) 14459G > A mutation.

2. Clinical presentation

2.1. Patient A-1

A 42-year-old Japanese man was admitted to our hospital with slowly progressive, generalized dystonia (Fig. 1A). He had no history of remarkable perinatal abnormalities or complications with standing and walking at an early age. However, he began to drag his left foot at age 5, after which his gait disturbance progressed slowly. He was confined to a wheelchair at age 13 and was required to live in a nursing home at age 18. On admission to our hospital, a neurological examination revealed dysarthria with stuttering, mild dysphagia, moderate rigidity in his left upper and lower limbs, and generalized dystonia. He was unable to stand up from sitting or to walk without assistance. Other neurological findings, such as diminished visual acuity, hearing loss, and muscle weakness and atrophy, were not confirmed. Scores for the Mini-Mental State Examination (MMSE) was 30 (out of 30), the Montreal Cognitive Assessment was 24 (out of 30), and the Frontal Assessment Battery was 15 (out of 18). The needle electromyogram showed normal

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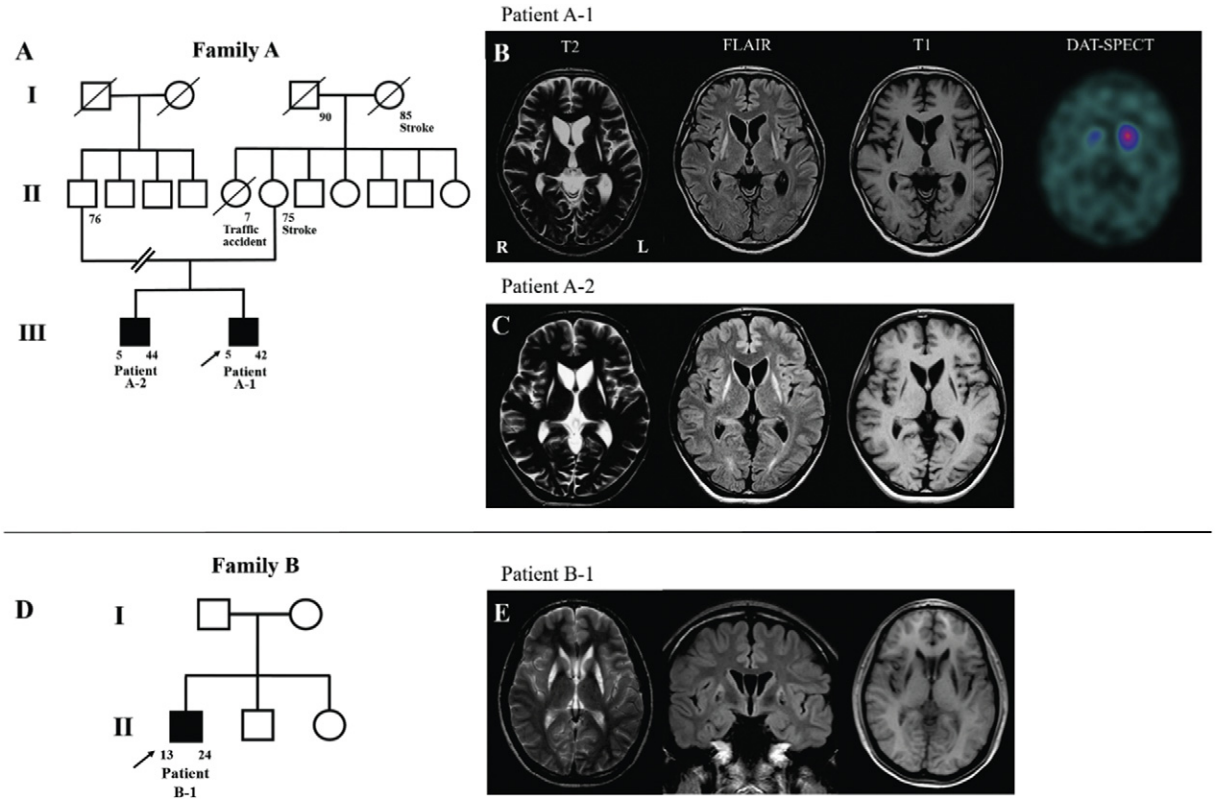

Fig. 1. Pedigrees of two families affected by bilateral striatal necrosis (BSN) and neuroradiological findings of three patients Pedigrees of Patients A-1 and A-2 from Family A and Patient B-1 from Family B are shown in (**A**) and (**D**), respectively. Squares and circles represent males and females, respectively. Shaded and unshaded symbols represent affected and unaffected individuals, respectively. Symbols with diagonal lines denote deceased individuals. The numbers in the lower left corners represent the age of onset and those in the lower right corners represent the current age or age at death. Magnetic resonance images of Patients A-1 and A-2 reveal high signal intensities along the bilateral putaminal area on both T2-weighted (T2) and fluid-attenuated inversion recovery (FLAIR) images, and low signal intensities on T1-weighted images (T1). The enlarged lateral ventricles anterior horns were caused by caudate nuclear atrophy (**B, C**). Dopamine transporter imaging with ^{123}I–ioflupane single photon emission computed tomography revealed severely reduced uptake in the right striatum and mildly reduced uptake in the left putamen in Patient A-1 (**B**). In Family B, no family member exhibited a neurological disorder similar to that of Patient B-1 (**D**). Magnetic resonance images of Patient B-1 (**E**) show high signal intensities along the bilateral putaminal area on T2-weighted, low signal intensities on T1-weighted, and cystic changes on FLAIR images, with lesser enlargement of the lateral ventricle anterior horns relative to Patient A-1 (**B**) or A-2 (**C**).

findings, and muscle biopsy was not performed. The results of laboratory tests including lactic acid and pyruvic acid were unremarkable for both peripheral blood and cerebrospinal fluid.

Cerebral magnetic resonance imaging (MRI) revealed high signal intensity along the bilateral putaminal area on both T2-weighted (T2) and fluid-attenuated inversion recovery (FLAIR) images, and corresponding low signal intensity on T1-weighted images (T1) (Fig. 1B). Bilateral enlargement of the lateral ventricle anterior horns, which was more pronounced on the right side, was attributed to caudate nuclear atrophy (Fig. 1B). Single photon emission computed tomography using ^{99m}Tc-ethyl cysteinate dimer showed hypoperfusion in the bilateral putaminal regions (data not shown). Dopamine transporter imaging with ^{123}I–ioflupane single photon emission computed tomography indicated severely and mildly reduced tracer uptake in the right striatum and left putamen, respectively (Fig. 1B). The patient was treated with levodopa (600 mg/day), but did not exhibit clinical improvement.

2.2. Patient A-2

A 44-year-old Japanese man (Fig. 1A) presented with a similar clinical course, neurological findings, and age at onset (5 years) as that of his younger brother, Patient A-1, but was unable to speak, stand, or walk due to severe generalized dystonia. Cerebral MRI of Patient A-2 revealed high signal intensity along the bilateral putaminal area on both T2 and FLAIR images, corresponding low signal intensity on T1 images, and proportional enlargement of the lateral ventricle anterior horns (Fig. 1C), similar to those in Patient A-1. Beyond these brothers, Family A had no history of neurological disorders (Fig. 1A).

2.3. Patient B-1

A 24-year-old Japanese man visited a neurology clinic with a loss of manual coordination and truncal instability. He had no history of abnormalities during his perinatal and developmental periods and no family history of similar symptoms (Fig. 1D). However, he first experienced gait instability at age 13 and initial evaluations of serum iron, ferritin, copper, and ceruloplasmin levels at that time were all normal. He had been unable to complete an educational program at the junior college because of poor achievement and was working as a home aid. A neurological examination revealed a low voice, slurred speech, mildly increased muscle tone in all limbs, and mild truncal ataxia. Other neurological findings such as diminished visual acuity, hearing loss, and muscle weakness/atrophy were not confirmed. The MMSE score was 30 (out of 30). Cerebral MRI showed high signal intensity along the bilateral putaminal area on T2 images, low signal intensity on T1 images, and cystic changes on FLAIR images (Fig. 1E). The caudate nuclear volume was relatively preserved and the anterior horns were mildly enlarged.

3. Genetic analysis

3.1. DNA extraction from the patients

After obtaining written informed consent from all three patients, genomic DNA was extracted from peripheral blood leukocytes using the PAXgene Blood DNA Kit (QIAGEN, Hilden, Germany) according to the manufacturer's protocol.

3.2. Long-range PCR and next-generation sequencing

The following whole mtDNA genome primers were used: forward, mt16402F-5′-ACCATCCTCCGTGAAATC-3′ and reverse, mt16436R-5′-CTCTTGTGCGGGATATTGA-3′. All PCRs were performed in a 50-μl volume with approximately 50 ng of genomic DNA, 1 μl of KOD FX Neo polymerase (TOYOBO, Osaka, Japan), and 400 μM of dNTPs. Step-down PCR was performed as follows: a predenaturing step at 94 °C for 2 min, a denaturing step at 98 °C for 10 s, and an extension step at 74 °C for 9 min. The extension temperature was lowered by 2 °C (from 74 to 68 °C) every five cycles and was held at 68 °C for the last 30 cycles. PCR products were analyzed via 1% agarose gel electrophoresis and purified using the Minielute PCR Purification Kit (QIAGEN).

For the initial input, 50 ng of each DNA library were fragmented and tagged simultaneously with the Nextera transposome (Nextera DNA Sample Prep Kit; Illumina, San Diego, CA, USA), followed by index ligation (Nextera Index Kit; Illumina) and purification (Agencourt Bioscience, Beverly, MA, USA). Finally, the DNA libraries were pooled and sequenced on the MiSeq sequencing platform (Illumina) according to the manufacturer's instructions.

3.3. PCR of the ND6 coding region and direct DNA sequencing

The following primers were designed to amplify the entire coding region of the mitochondrial NADH dehydrogenase subunit 6 gene (*ND6*): forward, 5′-GCGTATTGGGGTCATTGGTG-3′ and reverse, 5′-TCCTCTCTTTCTTCTTCCCACT-3′. PCRs were performed in a 50-μl volume containing approximately 50 ng of genomic DNA, 0.25 μl of TaKaRa Taq (Takara Bio Inc., Shiga, Japan), 2.5 mM $MgCl_2$, and 200 μM dNTPs. A three-step PCR was performed as follows: a predenaturing step at 98 °C for 2 min, denaturion at 98 °C for 10 s, annealing at 65 °C for 30 s, and extension at 72 °C for 1 min. This process was repeated for 30 cycles. PCR products were analyzed via 2% agarose gel electrophoresis, excised, and purified using the QIAquick Gel Extraction Kit (QIAGEN). The purified PCR products were directly sequenced on a 3730xl DNA Analyzer (Applied Biosystems, Waltham, MA, USA) according to the manufacturer's instructions.

3.4. TA cloning and plasmid sequencing of the ND6 coding region

PCR fragments from the *ND6* coding region were subcloned using a TA-vector (pCR4-TOPO; Invitrogen, Waltham, MA, USA) according to the manufacturer's instructions. DNA was purified from four independent clones per patient using the QIAprep Spin Miniprep Kit (QIAGEN). DNA sequences of the cloned inserts were analyzed on a 3730xl DNA Analyzer according to the manufacturer's instructions.

3.5. PCR-RFLP analysis

ND6 region PCR products were subjected to a restriction fragment length polymorphism (RFLP) analysis with the restriction enzyme *Tsp*RI (New England Biolabs, Ipswich, MA, USA). The *ND6* coding region PCR fragment measured 633 base pairs (bp) in length and *Tsp*RI digestion of a mutant PCR fragment would yield 362-bp and 301-bp products. Each restriction digestion was performed overnight at 65 °C in a 20-μl volume containing 1 μg of PCR product and 10 units of *Tsp*RI. A 10-μl aliquot of each reaction product was analyzed via 2% agarose gel electrophoresis.

4. Results

The mtDNA *ND6* coding region from Patient A-1 was initially examined by long-range PCR and next-generation sequencing, leading to the identification of the 14459G > A mutation (alanine to valine substitution), which was previously reported to be pathogenic and causative of BSN [14]. This mutation was further examined by PCR-based direct DNA sequencing in Patients A-1 and A-2, and an electropherogram of the PCR products indicated that all contained the 14459G > A mutation, indicating homoplasmy in both Patients (Fig. 2A**, lower**; data not shown). To confirm the homoplasmy of the 14459G > A mutation, the PCR products were further subjected to PCR-RFLP with the restriction enzyme *Tsp*RI, as described above. The results of this analysis revealed complete digestion into two fragments, thus confirming a homoplasmic mutation in Patients A-1 and A-2 (Fig. 2C**, left and middle**).

In addition to the 14459G > A mutation, the single nucleotide polymorphism (SNP) 14605A > G, which was previously reported as a synonymous SNP (rs386829222), was identified in Patients A-1 (Fig. 2A**, lower**) and A-2 (data not shown). Plasmid sequencing of the PCR product was performed to confirm a genetic linkage of the 14459G > A mutation with the 14605A > G SNP and revealed that both *ND6* coding region DNA substitutions were located on the same mtDNA in both patients (Fig. 2A**, upper**; data not shown).

Regarding the mtDNA analysis of Patient B-1, PCR-direct sequencing identified the same 14459G > A mutation. However, the electropherogram indicated the co-occurrence of G and A nucleotides at this position (Fig. 2B**, lower**), indicating heteroplasmy. In contrast to Patients A-1 and A-2, the PCR-RFLP analysis of the *ND6* coding region of Patient B-1 was incompletely digested, thus confirming heteroplasmy (Fig. 2C**, right**). Notably, Patient B-1 also harbored the 14605A > G SNP (Fig. 2B**, lower**) and the plasmid sequencing of the PCR product confirmed the linkage of this SNP with the 14459G > A mutation (Fig. 2B**, upper**).

5. Discussion

Mitochondrial disorders comprise a heterogeneous group of genetic diseases with a range of clinical manifestations [15,16] and may be induced by either mtDNA or nuclear DNA mutations [17]. For example, mitochondrial BSN may be caused by mutations in genes involved in mitochondrial function maintenance, which are located on both mitochondrial and nuclear DNA [2–13]. In addition to mitochondrial disorders, various acquired and hereditary conditions have been reported as the pathogenesis of BSN. In hereditary conditions, organic acidurias such as glutaric, methylmalonic, and propionic acidurias are known to cause BNS [1].

Herein, we reported three BSN cases from two independent Japanese families harboring the mtDNA 14459G > A mutation. This *ND6* mutation was initially identified as a cause of maternally inherited LHON and dystonia in a Hispanic family [14]. Subsequently, the same mutation was reported in patients from Caucasian [18–21], African-American [18], and Asian [5,22] families. Although the maternally inherited 14459G > A mutation is distributed among many races worldwide, it has been associated with various clinical phenotypes such as LHON, LHON plus dystonia, pediatric onset dystonia, and Leigh syndrome [5,14,18–21,23].

Regarding the present cases, the main clinical phenotype of Patients A-1 and A-2 was infantile-onset dystonia, whereas that of Patient B-1 was juvenile-onset mild truncal ataxia with parkinsonism. None of the patients exhibited optic neuropathy, based on ophthalmological examinations. All patients exhibited the characteristic cerebral MRI findings of abnormal signal intensity along the bilateral putaminal area, although this was more prominent in Patient B-1 than in Patients A-1 and A-2. In contrast, atrophy of the caudate nuclei and enlargement of the lateral ventricle anterior horns were more severe in Patients A-1 and A-2, and might reflect the increased disease severity and disability of these patients.

Genetic analyses of the three patients revealed homoplasmic 14459G > A mutations in Patients A-1 and A-2, and a heteroplasmic mutation in Patient B-1. The pathogenicity of the 14459G > A mutation was previously confirmed biochemically using transmitochondrial cybrids. Cybrids harboring the homoplasmic 14459G > A mutation exhibited a 39% reduction in complex-I-specific activity relative to wild-type cybrid lines but normal activity for other complexes [24]. Although our mtDNA

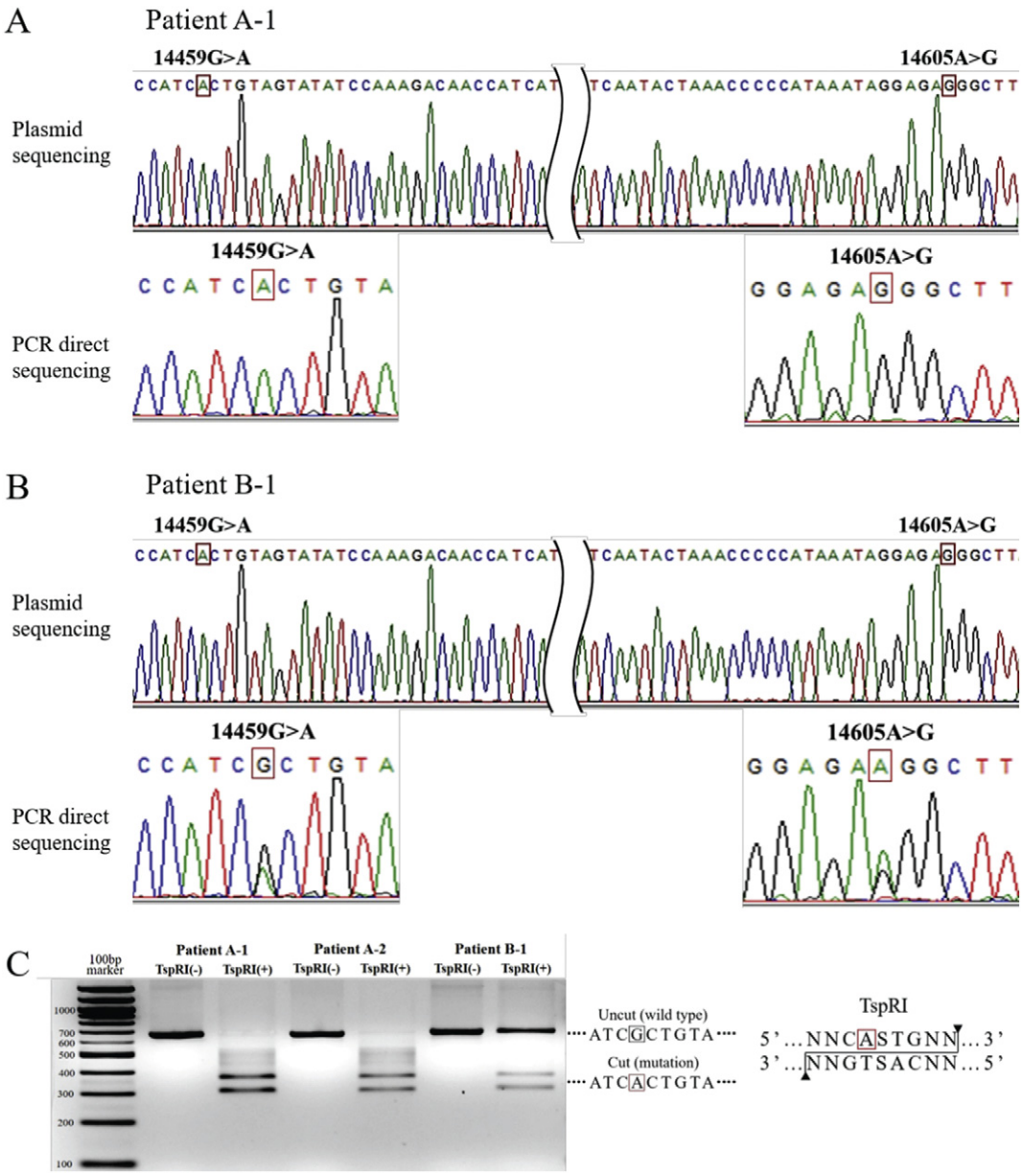

Fig. 2. Genetic analyses of three patients with bilateral striatal necrosis In a mitochondrial DNA (mtDNA) analysis, PCR-based direct DNA sequencing of the *ND6* coding region of Patient A-1 revealed a homoplasmic 14459G > A mutation and 14605A > G single nucleotide polymorphism (SNP) (**A, lower**). Plasmid sequencing of the PCR product from Patient A-1 revealed that the two DNA substitutions in *ND6* were located on the same mtDNA (**A, upper**). A PCR-based direct DNA sequencing analysis of mtDNA from Patient B-1 identified the same 14459G > A mutation and 14605A > G SNP; however, an electropherogram indicated that these changes were heteroplasmic (**B, lower**). Plasmid sequencing of the PCR product from Patient B-1 confirmed the linkage of the 14459G > A mutation with the 14605A > G SNP on the same mtDNA (**B, upper**). In a PCR-restriction fragment length polymorphism (RFLP) analysis of Patients A-1, A-2, and B-1, the restriction enzyme *Tsp*RI yielded complete digestion into two fragments in Patients A-1 and A-2, indicating a homoplasmic 14459G > A mutation (**C, left and middle**), but incomplete digestion in Patient B-1, indicating heteroplasmy of the same mutation (**C, right**).

analysis was only accessible using leukocytes, the differences in clinical severity between patients from Families A and B might be attributable to the respective presence of homoplasmy or heteroplasmy. However, previous reports have described asymptomatic homoplasmic 14459G > A mutation carriers, in contrast to our findings [14,20,22]. Gropman et al. [20] and Kim et al. [22] speculated that the varied pathogenesis of the 14459G > A mutation might involve other nuclear modifier genes. Because the previous studies of asymptomatic homoplasmic 14459G > A mutation carriers extracted DNA from peripheral blood leukocytes, the heteroplasmic mutation rates of affected tissues such as the optic nerve or striatum could not be determined. It is also necessary to consider that tissue heteroplasmy might affect the penetrance of the 14459G > A mutation and the diversity of clinical phenotypes.

In Japan, the 14459G > A mutation was initially reported by Watanabe et al. [5] as a pathogenic cause of LHON with dystonia; as in our cases, patients in that family also harbored the 14605A > G SNP. The frequency of this SNP (rs386829222) was reported to be 4.3% in a population of 672 Japanese subjects based on the GiiB-JST mtSNP database (http://mtsnp.tmig.or.jp/mtsnp/index.shtml) [25]. All three cases in the present study harbored both the 14605A > G SNP and the 14459G > A mutation, and plasmid sequencing of the *ND6* coding region confirmed the linkage of both substitutions on the same mtDNA. In contrast, in the previous report describing familial LHON with dystonia, the mutations were detected in a different area and the cases exhibited distinct clinical phenotypes [5].

In conclusion, our finding of a link between the pathogenic mutation and rare SNP on the same mtDNA suggests that the families in the

present case and the previously reported family share a genetic founder. Given the inconsistent penetrance of the mtDNA mutation, an mtDNA analysis should be considered for all BSN cases, even in the absence of familial occurrence.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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