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Confirmation of the mitochondrial *ND1* gene mutation G3635A as a primary LHON mutation

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ABSTRACT

We report the clinical and genetic characterization of two Chinese LHON families who do not carry the primary LHON-mutations. Mitochondrial genome sequence analysis revealed the presence of a homoplasmic *ND1* G3635A mutation in both families. In Family LHON-001, 31 other variants belonging to the East Asian haplogroup R11a were identified and in Family LHON-019, 37 other variants belonging to the East Asian haplogroup D4g were determined. The *ND1* G3635A mutation changes the conversed serine^{110} residue to asparagine. This mutation has been previously described in a single Russian LHON family and has been suggested to contribute to increased LHON expressivity. In addition, a mutation in cytochrome c oxidase subunit II at C7868T (COII/L95F) may act in synergy with G3635A, increasing LHON expressivity in Family LHON-001, which had a higher level of LHON penetrance than Family LHON-019. In summary, the G3635A mutation is confirmed as a rare primary pathogenic mutation for LHON.

Introduction

Leber's hereditary optic neuropathy (LHON, OMIM#535000) is a maternally inherited disorder characterized by acute or subacute central vision loss leading to central scotoma and blindness. Point mutations in mitochondrial DNA (mtDNA), affecting the function of complex I in the mitochondrial respiratory chain, are pathogenic for LHON [1–3]. To date, more than 30 mtDNA mutations have been associated with this disease (http://www.mitomap.org). Of these, 10 variants (3460A, 3733A, 4171A, 10663C, 11778A, 14459A, 14482A/G, 14484C, 14495G, and 14568T) represent confirmed "primary" LHON mutations. Primary LHON mutations share certain genetic features, such as alteration of complex I (NADH dehydrogenase) genes, absence in control individuals, occurrence in at least two independent LHON families, and a very rare incidence of co-occurrence within families [4,5]. Twenty further putative LHON mutations fulfill the above criteria, except that they have been found in only a single patient/family and hence await confirmation as primary LHON mutations [4,5]. Other mutations, most of which are common polymorphic variants, have been associated with LHON as weak genetic determinants [4–7].

The majority of worldwide LHON cases (over 95%) are caused by one of the three primary mtDNA point mutations (G3460A, G11778A, and T14484C) [8]. Usually, these three mutations are screened in suspected LHON patients. However, there are a significant number of patients who received a clinical diagnosis compatible with LHON and presented with maternal inheritance, but lacked any of the three prevalent pathogenic mutations [7,9]. Herein, we report two Chinese LHON families without the three most common primary mutations. To elucidate the molecular genetics underlying LHON in these families, we sequenced and analyzed the mitochondrial genome in matrilineal relatives.

Abbreviations: LHON, leber's hereditary optic neuropathy; mtDNA, mitochondrial DNA; MAS-PCR, multiplex allele-specific polymerase chain reaction; nps, nucleotide positions.

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2. Materials and methods

Patients and subjects. As the part of a genetic screening program for genetic eye disorders, two Chinese families with clinically diagnosed LHON, LHON-001 from Tianjin city and LHON-019 from Fuzhou City, Fujian province (Fig. 1), were investigated. A total of 13 individuals, including 10 individuals (five affected individuals II:1, II:3, II:5, II:7, III:7 and five normal individuals I:1, II:4, III:4, III:6, IV:2) in Family LHON-001, and three individuals (one affected individual IV:1 and two normal individuals III:3 and III:7) in Family LHON-019 participated in this study. The family members were evaluated according to their medical records, the history of eye symptoms or visual disturbances, and detailed clinical examinations, including tests for visual acuity, color vision, visual evoked potentials (VEPs), and fundus photography. The case histories and clinical details are summarized in Table 1. The degree of visual impairment was defined according to visual acuity as follows: normal > 0.3, mild = 0.3–0.1; moderate < 0.1–0.05; severe < 0.05–0.02; and profound < 0.02 [10]. After informed consent was obtained, peripheral blood was collected from participants.

The proband, III:7, from Family LHON-001 suffered a rapid (within 2 weeks) bilateral loss of vision at the age of 14. His visual acuity was restricted to hand motion (HM/30 cm right eye and HM/20 cm left eye) and his visual fields showed central scotomas in both eyes. Funduscopic examination showed that both his optic disks were abnormal: the right optic nerve was hyperemic, with telangiectasias, and the left optic nerve was pale. VEPs showed bilaterally decreased amplitudes with delayed latencies. Therefore, he exhibited typical clinical features of LHON. Note that the affected individual, II:5, from Family LHON-001 had a sudden visual loss at 17 and his visual acuity was only 0.01–0.02. According to the patient's testimony, his visual function started to recover one year later, but no medical documentation of this event is available. However, his current visual acuity at age 43 years is 1.0 in the right eye and 0.6 in the left eye. The overall penetrance of LHON in LHON-001 family members reached 60% (6/10), and the average age at onset of the initial visual loss was 21.8 years, ranging from 14 to 34 years. No other abnormality was found on radiological and neurological examination in this family.

The proband, IV:1, from Family LHON-019 suffered a rapid bilateral loss of vision at the age of 21. His visual loss occurred within 20 days, first in the right eye and then in the left eye. Ophthalmological evaluation showed that his visual acuity was 0.1 and 0.07 in his right and left eyes, respectively. Visual field testing demonstrated centrocaecal scotoma in both eyes. Fundus examination showed atrophy of both his optic disks. Flash VEP showed bilaterally considered amplitudes of P100 to be decreased with delayed latencies. Further examination of familial history and clinical evaluation revealed that none of the other seven matrilineal relatives in this family exhibited a visual deficit.

Mutational analysis. Total genomic DNA was extracted from whole blood using the Wizard Genomic DNA Purification Kit (Pro-

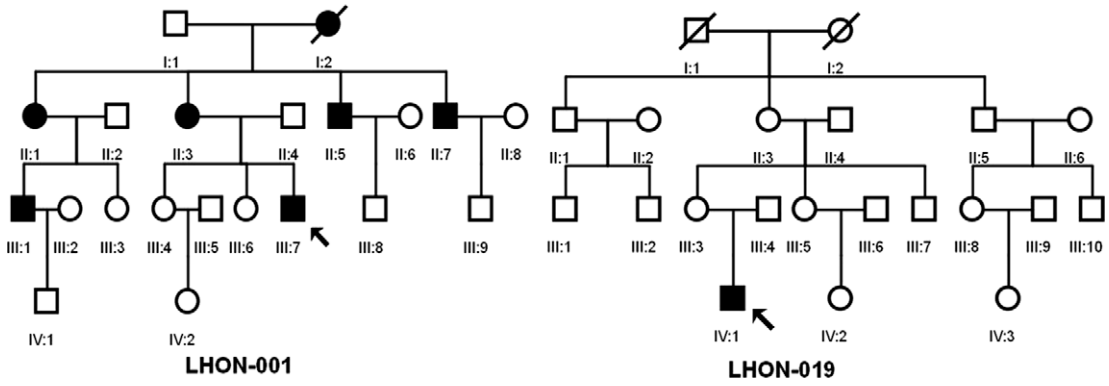

Fig. 1. Pedigree of two Chinese LHON families (Family-001 and Family-019) that carry the G3635A mutation. Affected individuals are marked by filled squares (males) or circles (females), and unaffected individuals are marked by empty symbols. The proband is indicated by an arrow.

Table 1
The clinical data of some matrilineal members from two Chinese LHON families with G3635A mutation.

Subject	Sex	Age of onset			Age of test			Level of visual impairment [10]
		Yrs	Visual acuity		Yrs	Current visual acuity		
			OD	OS		OD	OS	
Family-LHON-001								
II:1	F	27	—	—	53	0.1	0.2	Moderate
II:3	F	34	—	—	50	Count fingers		Profound
II:5	M	19	—	—	43	0.5	0.1	Normal/Moderate
II:7	M	17	0.02	0.01	43	1.0	0.6	Normal
III:1	M	20	—	—	31	0.1	0.3	Mild
III:4	F	—	—	—	27	1.0	1.0	Normal
III:6	F	—	—	—	24	1.2	0.8	Normal
III:7	M	14	—	—	15	HM/30 cm	HM/20 cm	Profound
IV:2	F	—	—	—	4	1.5	1.5	Normal
Family-LHON-019								
III:3	F	—	—	—	43	0.8	1.0	Normal
III:7	M	—	—	—	37	1.0	1.2	Normal
IV:2	M	21	0.1	0.07	21	0.1	0.07	Mild/moderate

mega, Beijing, China) according to manufacturer's instructions. We screened for the three primary LHON-mutations (G3460A, G11778A, and T14484C) by multiplex allele-specific polymerase chain reaction (MAS-PCR) as previously described [11,12]. The complete mtDNA was PCR-amplified in overlapping fragments [13–15]. To avoid sequencing errors, we sequenced two maternally related individuals in each family using different two-set PCR primers, as previously described [13,14]. PCR products were purified and sequenced on an ABI 3730XL Automated Sequencer (PE Biosystems, Foster City, CA, USA) using the corresponding primers, as previously described [13–15]. The sequence results were compared with the updated consensus Cambridge sequence (GenBank Accession No. AC_000021.2) [16]. The two complete mtDNA sequences determined in this study were deposited in GenBank under Accession Nos. FJ969382 and FJ969383.

3. Results and discussion

To elucidate the molecular basis of visual impairment, we first examined three primary LHON mtDNA mutations (G3460A, G11778A, and T14484C) by MAS-PCR [11,12]. We failed to detect these mutations in our patients (data not shown), which suggests that other pathogenic mtDNA mutations may exist in these two LHON families. Analysis of the entire mtDNA genome of both families showed the presence of a homoplasmic G3635A mutation (Fig. 1A), which was regarded as a candidate LHON mutation, because it was previously identified in a single Russian LHON family [17]. The G3635A mutation substitutes an asparagine for a highly conserved serine at *ND1* amino acid 110. A role for the *ND1* 3635A mutation in the etiology of LHON was confirmed by cybrid transfer of mtDNA, which caused a strong complex-I-linked respiration defect. However, this mutation did not cause a defect in the complex I enzyme itself [17].

For Family LHON-001, we found 31 other variants relative to the standard Cambridge sequence [16], 29 of which were known polymorphisms (Table 2) [18,19]. Of the remaining two variants, one was a novel silent mutation at nucleotide position (np) 5033 (G to A), and the other was a missense mutation at np 7868 (C to T) (Fig. 1B). Among the polymorphisms were those at np 16189, 185, 189, 709, 8277, 8278insC, 10031, 10398, 11061, 12950, 13681, 16311, and 10978, which, in part, define the East Asian haplogroup R11a [20]. The mtDNAs from the proband and his mother of Family LHON-019 harbored 37 other variants (Table 2), all of which were known polymorphisms. Among the polymorphisms were those at np 15043, 16362, 4883, 5178A, 3010, 8414, 14668, and 13104, which define the East Asian haplogroup D4g [20]. The mtDNA from the previously reported Russian LHON Family E with the G3635A mutation belonged to the European haplogroup J [17]. Therefore, although these three families carry the same G3635A mutation, there are obvious mtDNA polymorphism differences among the three LHON families. This excludes the possibility that the families are related, indicating that the mutation in each family must have arisen independently. Overall, our cases confirm the pathogenicity of this mutation, and further suggest that the G3635A mutation is a primary, but rare, LHON mtDNA mutation, according to the evaluation criteria of primary LHON mutations [4,5].

Despite sharing the identical G3635A mutation, these two families presented an obvious difference in the penetrance of LHON: the overall penetrance of LHON reached 60% (6/10) in Family LHON-001, while in Family LHON-019, only 12.5% (1/8) of individuals had the clinical presentation of LHON (Fig. 1). However, maybe due to the small sample size, the difference of LHON penetrance between the two families was not statistically significant (Fisher's exact test, two-tailed test, $P = 0.06561$; Chi-square with Yates' correction, 2.4575, $P = 0.1170$). We compared the mitochondrial genomes of Families LHON-001 and LHON-019 and we identified the mutation C7868T in Family LHON-001 only. We believe, for the following reasons, that mutation C7868T may contribute, as a secondary mutation, to the expressivity of LHON and account for the difference in penetrance between the families. First, except for the G3635A and C7868T mutations, all the other missense variants that we identified are previously characterized mtDNA polymorphisms. Second, the C7868T mutation substituted a phenylalanine for a moderately conserved leucine at amino acid 95 of cytochrome c oxidase subunit II (COII); the leucine residue is found in 48 of 61 mammalian species (http://mtsnp.tmig.or.jp). Third, this mutation was not a mtDNA polymorphism archived in the Mitomap [18] or in the Human Mitochondrial Genome Database, which comprises 1865 complete mtDNA sequences and 839 coding region sequences [19]. In addition, to date, there is no evidence to show that haplogroups R11a and D4g have an influence on the expression and penetrance of LHON with primary or other LHON-associated mutations, although some haplotypes have been shown to increase the penetrance of LHON, in particular the J haplotype, which is associated with T14484C and G11778A mutations [21]. Thus, the C7868T mutation may affect the expressivity of LHON in Family LHON-001. This is consistent with other secondary point mutations that contribute to the phenotypic expression of the primary LHON mutations 11778, 14484, and 3460 [10,15,22,23] (Fig. 2).

As shown in Table 3, the penetrance of visual impairment was 60%, 12.5%, and 40%, and the ratios between affected male and female matrilineal relatives was 2:1, 3:1, and 1:0 in Family LHON-001, LHON-019 and Russian Family E [17], respectively (these fam-

Table 2
mtDNA mutations in two Chinese LHON families: LHON-001 and LHON-019.

Gene	Position	LHON-001	Gene	Position	LHON-019
D-Loop	73	A>G	D-Loop	73	A>G
	185	G>A		152	T>C
	189	A>G		263	A>G
	263	A>G		298	C>T
	16183	A>C		310	T>CCTC
	16189	T>C		489	T>C
	16304	T>C		16140	T>C
	16311	T>C		16223	C>T
	16365	C>T		16362	T>C
	16519	T>C		16519	T>C
12S rRNA	709	G>A	12S rRNA	750	A>G
	750	A>G		1438	A>G
16S rRNA	2706	A>G	16S rRNA	2706	A>G
ND1	3635	G>A (S110 N)		3010	G>A
ND2	4706	A>G	ND1	3421	G>A (V39I)
	4769	A>G		3635	G>A (S110 N)
	5033	A>G		4131	A>G
CO1	7028	C>T	ND2	4769	A>G
CO2	7868	C>T (L95F)		4883	C>T
NC7	8277	T>C		5178	C>A (L237 M)
	8278+3c	Ins3C		5231	G>A
ATP6	8860	A>G (T112A)	CO1	7028	C>T
	9071	C>T (S182L)	ATP8	8414	C>T (L17F)
$tRNA^{GLY}$	10031	T>C	ATP6	8701	A>G (T59A)
ND3	10398	A>G (T114A)		8860	A>G (T112A)
ND4	10978	A>G	CO3	9540	T>C
	11061	C>T (S101F)	ND3	10398	A>G (T114A)
	11719	G>A		10400	C>T
ND5	12358	A>G (T8A)	ND4	10873	T>C
	12950	A>G (N205S)		11719	G>A
	13681	A>G (T449A)	ND5	12705	C>T
CYB	14766	C>T (T7I)		13104	A>G
			ND6	14668	C>T
			CYB	14766	C>T (T7I)
				14783	T>C
				15043	G>A
				15301	G>A
				15326	A>G (T194A)

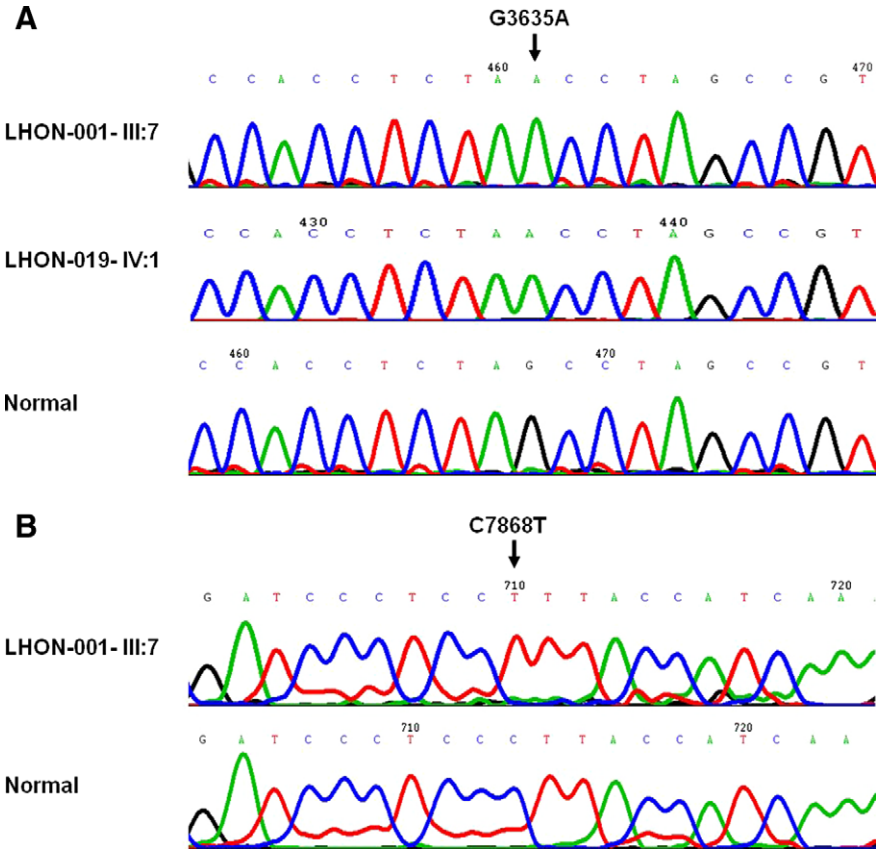

Fig. 2. Partial sequence chromatograms of ND1/3635 (A) and COII/7868 (B). LHON-001-III:7 represents the affected individual III:7 and Normal is his father in Family LHON-001, and LHON-019-IV:1 represents the affected individual IV:1 in Family LHON-019. An arrow indicates the location of the base changes at position 3635 and 7868.

Table 3
Summary of clinical characteristics for three independent LHON families with G3635A mutation.

Family	Affected:unaffected ratio (among maternal relatives)	LHON male: female	Age of onset range (mean)	Recovery	Abnormal neurological
Family E[17]	8:20	3:1	15–33 (22.1)	Yes	Yes
LHON-001	7:4	2:1	14–34 (21.8)	Yes	No
LHON-019	1:8	1:0	21	No	No

ilies have the same G3635A mutation). A variable severity of visual impairment in the maternal relatives of these families, ranging from profound visual impairment to normal vision is also shown in Table 3. Unlike the previously reported Russian Family E [17], there was no other neurological abnormality in Family LHON-001 or LHON-019; however, the average age at onset of the initial visual loss was similar (about 20 years). These data indicated that these three families have the common features of LHON, consistent with the features of other LHON families with the primary mutations, 11778A, 14484C, and 3460A [24–26]. These data also suggest that other modifying factors, including nuclear background, mitochondrial haplotypes and environmental factors account for the phenotypic variability of visual impairment in these LHON families with the G3635A mutation.

In summary, we identified two Chinese LHON families carrying the G3635A mutation in the mitochondrial *ND1* gene, and further confirmed that this mutation is a primary, but rare, LHON mtDNA mutation. The C7868T mutation may act in synergy with the G3635A mutation, increasing the expressivity of LHON in Family LHON-001, which had a higher level of LHON penetrance compared to that in Family LHON-019. However, analysis of the complete mtDNA sequence failed to yield a molecular genetic explanation for all the clinical features, such as incomplete penetrance, phenotypic variability of visual impairment and sex bias, in these three independent LHON families with the same G3635A mutation. Thus, further studies on the involvement of unknown nuclear modifier genes and/or other factors may provide valuable information to account for the complex clinical manifestations of LHON in these families.

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