• Letter to the Editor •

The first Chinese case with LCAEOD syndrome caused by mutation of *TUBB4B* gene

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Dear Editor,

Leber congenital amaurosis with early-onset deafness syndrome (LCAEOD, OMIM 617879) is a rare autosomal dominant syndromic disease that was first described in 2017. The *TUBB4B* gene, encoding the beta-tubulin 4B isotype, has been identified as the primary genetic cause of the disease[1]. LCAEOD is characterized by night blindness, nystagmus, strabismus, hypermetropia, serious vision loss, pigmentary retinopathy, minimal or no detectable electroretinogram responses and inner-ear cell dysfunction in the first decade of life[1-3]. In short, this disease combines Leber congenital amaurosis (LCA, OMIM 204000) and sensorineural hearing loss (SHL). To date, only three studies have reported cases of LCAEOD with *TUBB4B* mutations[1-3]. Here, we present the first Chinese case of LCAEOD syndrome caused by a mutation in *TUBB4B* gene.

CASE PRESENTATION

Ethical Approval This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and approved by the local ethics committee of Southwest Hospital, Army Medical University, Chongqing, China (reference number: KY2023007). Informed consent was obtained from participant and her relatives involved in the study.

A 5-year-old female presented our clinic with complaints of night blindness and poor vision after birth told by her parents. Nystagmus, strabismus and astigmatism were found after examination. Best-corrected logMAR visual acuity in the right and left eyes was 0.7 [+7.25 diopter sphere (DS)/-2.50 diopter cylinder (DC)×175] and 0.8 (+8.00 DS/-2.50 DC×175), respectively. Fundus photography of both eyes showed signs of retinal degeneration, including depigmentation, pale optic disc, narrowed retinal vessel, and a coin-like atrophic fundus in the right eye (Figure 1A-1D). Spectral-domain optical coherence tomography images revealed abnormal fovea, disappeared ellipsoid zone, and reserved retinal epiretinal membrane at the macula (Figure 1E-1H). Visual electrophysiological examination, conducted in accordance with guidelines of International Society for Clinical Electrophysiology of Vision, showed delayed P100 latencies and decreased amplitudes of the P100 components in pattern visual evoked Potentials (Figure 2). Additionally, the pattern electroretinography displayed moderately reduced amplitudes of P50 and N95, while no response was detected in the full-field electroretinogram.

Hearing impairment was detected at age of 5y when her parents noticed that she frequently didn't react to their calls. A recent result of pure tone audiogram was 46 dB (right ear) and 45 dB (left ear) which confirmed she had moderate bilateral sensorineural hearing loss, particularly affecting higher frequencies (2000-8000 Hz; Figure 3). Subsequently, she started using hearing aids at the age of 6y.

The patient and her healthy parents (confirmed through kinship analysis), underwent the whole exome sequencing and mitochondrial genome sequencing. Combined with the clinical information, a *de novo* single-nucleotide mutation was identified in *TUBB4B* gene: c.1171C>T (p.Arg391Cys), which was absent from her parents, sister (Figure 4A-4B) and the controls in the Genome Aggregation Database. Referring to the American College of Medical Genetics and Genomics, c.1171C>T (p.Arg391Cys) is assessed to be "pathogenic (PS2, PS3, PS4, PM2, PP2, PP3, PP4)". The Combined Annotation Dependent Depletion score (Chromosome 9, Position

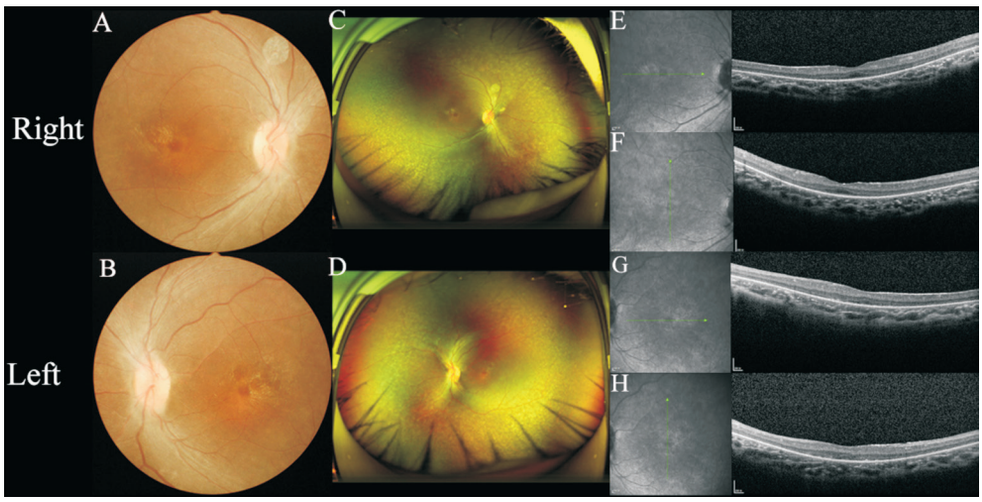

Figure 1 Clinical information of patient A-D: Fundus photography; E-H: Spectral-domain optical coherence tomography.

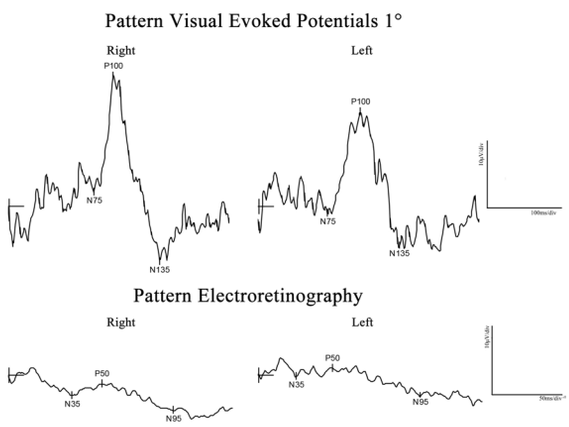

Figure 2 Visual electrophysiological examination of patient.

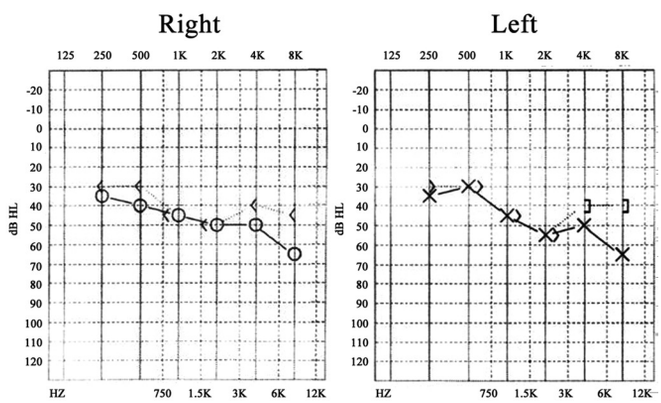

Figure 3 Pure tone audiometry Air conduction (right: ○, left: ×) and bone conduction (right: <, left: >).

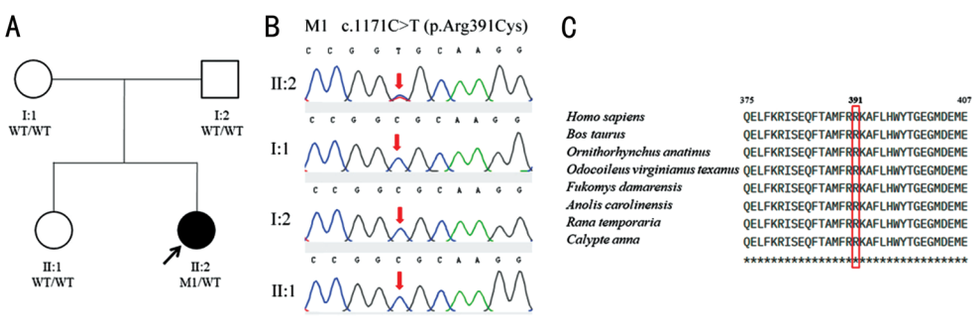

Figure 4 *TUBB4B* mutation in a Chinese patient with LCAEOD A: Pedigrees of LCAEOD in a Chinese family. M1: c.1171C>T (p.Arg391Cys); WT: Wild-type alleles; B: Sanger sequencing validation and segregation analysis of the *TUBB4B* mutation in the family. The transcripts of the *TUBB4B* we used in this study for sequencing and reference was NM_006088.6; C: Multiple alignment of eight species of TUBB4B protein. *Completely conserved residue in evolution. The position of the mutated residue is highlighted by a red frame. LCAEOD: Leber congenital amaurosis with early-onset deafness syndrome.

140137841, GRCh37-v1.7) for the mutation is 23.9. Moreover, comprehensive data filtering of whole exome sequencing did not show any suspicious variants in the reported genes for independently LCA, SHL and Usher syndrome.

DISCUSSION

This report delineates the detailed phenotype–genotype of a young female diagnosed with LCAEOD, who has molecularly confirmed to harbor heterozygous *TUBB4B* mutation. To our knowledge, only three studies have reported similar cases, encompassing 11 patients from 7 unrelated families from diverse ethnic backgrounds, as summarized in Table 1. Two specific mutations: c.1171C>T (p.Arg391Cys) and c.1172G>A (p.Arg391His) in *TUBB4B* were implicated in the disease. About 10 out of 11 patients exhibited various degrees of early-onset retinitis pigmentosa and bilateral sensorineural hearing loss. Additionally, all patients exhibited hypermetropia, with

Table 1 Clinical features of patients with *TUBB4B*-induced LCAEOD from the published literatures

Study	Family No.	Patient (gender)	Origin	Age (y)		Nucleotide alteration	Visual acuity, hypermetropia		Nystagmus	Fundus	Full-field electroretinogram	Audiograms
				Onset	Examination in study		RE	LE				
Luscan *et al*[1]	1	II2 (F)	France	30	61	c.1171C>T (p.Arg391Cys)	20/20, +6	20/29, 9	NM	NRV, PDPR, PRA	Normal	Severe-bilateral SHL
		III2 (F)		Birth	34		NLP, +6	NLP, +6	Yes	NRV, PDM, PDPR, MA	Flat	Severe-bilateral SHL
		IV1 (M)		Birth	5.5		20/63, +10	20/63, +10	NM	NRV, PDPR	Flat	Moderate bilateral SHL
	2	II1 (M)	Algeria	2.5	31	c.1172G>A (p.Arg391His)	LP, +8	LP, +8	Yes	NRV, PD	NM	Moderately severe-bilateral SHL
	3	II2 (F)	France	3	6	c.1172G>A (p.Arg391His)	20/40, +7	20/40, +7	NM	NRV (No figure)	NM	Mild-bilateral SHL
	4	II3 (M)	Denmark	Birth	8	c.1171C>T (p.Arg391Cys)	20/50, +8.25	20/63, +8.75	NM	NRV, PDPR	Flat	Moderately severe-bilateral SHL
Medina *et al*[2]	5	F	America	2	6	c.1172G>A (p.Arg391His)	20/500, +7.50	20/200, +5.75	Yes	NM	NM	Mild bilateral SHL
	6	M	America	Birth	8	c.1171C>T (p.Arg391Cys)	20/250, +7.50	20/300, +7.50	NM	NM	NM	Moderate bilateral SHL
Maasz *et al*[3]	7	II1 (F)	Hungary	1	41	c.1171C>T (p.Arg391Cys)	NM, Yes	NM, Yes	NM	PDPR (blurry figure)	NM	Have bilateral hearing aid
		III1 (M)		NM	2.8				Yes	NRV, PDM, PDPR (blurry figure)		
		III2 (F)		NM	0.7				Yes			
This study	8	III2 (F)	China	Birth	6	c.1171C>T (p.Arg391Cys)	20/100, +7.25	20/100, +8.00	Yes	NRV, depigmentation	Flat	Moderate bilateral SHL

LCAEOD: Leber congenital amaurosis with early-onset deafness syndrome; F: Female; M: Male; LE: Left eye; LP: Light perception; MA: Macular atrophy; NLP: No light perception; NM: Not mentioned; NRV: Narrowed retinal vessel; PD: Pigment disorder; PDM: Pigmentary deposits in macula; PDPR: Pigmentary deposits in peripheral retina; PRA: Peripheral retina atrophy; RE: Right eye; SHL: Sensorineural hearing loss.

6 displaying nystagmus. Moreover, night blindness and strabismus were also noted, as reported by Medina *et al*[2] and Maasz *et al*[3]. Narrowed retinal vessel was a prevalent feature, whereas pigmentary deposits were observed in some cases, and others showed only disorders of pigment. In addition, Spectral-domain optical coherence tomography results showed the absence of ellipsoid zone in all but one patient (F1-II2). Only one patient (F7-III1) and our patient exhibited the presence of retinal epiretinal membrane. Thus, although patients had mutations at the same amino acid site in the same gene, the clinical manifestations were not identical, suggesting heterogeneity in the clinical phenotype and severity among patients.

TUBB4B gene is located on chromosome 9q34.3 and contains 11 exons. It encodes a 445-amino acid protein (tubulin beta-4B chain) which belonging to *TUBB* gene family. In humans, *TUBB* gene family encodes eight α- and nine β-tubulin isotypes, majoring components of microtubules that play key roles in a variety of cellular functions[4-6]. In our study, we found a heterozygous missense alteration c.1171C>T in *TUBB4B* gene, which causes arginine to cysteine amino acid change at position 391. The mutant residue and neighboring residues show completely conserved residues in evolution (Figure 4C). Functional analysis showed c.1171C>T (p.Arg391Cys) and c.1172G>A (p.Arg391His) affect microtubules polymerization dynamics as well as a significant inhibition of normal microtubules growth[1]. Furthermore, the specific residue has been identified in all cases of LCAEOD related to *TUBB4B* mutations, suggesting it may be a potential hotspot. However, a larger cohort is necessary to confirm this observation. Moreover, the latest research showed that the changes of methylation levels of *TUBB4B* and other core genes may disturb the function of cytoskeleton and intercellular junctions, eventually leading to sporadic congenital cataract[6].

Without genetic testing, doctors would often mistake LCAEOD, characterized by pigmentary retinopathy and hearing loss for Usher syndrome or other multisystem syndromes. Other genes, such as *RPGR*[7] and *CEP78*[8] are also associated with pigmentary retinopathy and hearing loss. Thus, it is crucial to conduct both molecular and clinical examinations to establish the accurate diagnosis of the disease.

In conclusion, we report the first study of LCAEOD caused by *TUBB4B* gene mutation in Chinese population. We will continue to follow up on patients' clinical updates to facilitate appropriate prognostic information and clinical management of patients.

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G and Liu B: data analysis and revision and final approval of manuscript, Liu Y and Meng XH: revision and final approval of manuscript.

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