LETTER TO THE EDITOR

WILEY

A novel pathogenic variant of *CEP164* in an infant with Senior-Loken syndrome

To the editor:

A 4-month-old male patient was brought to our clinic due to an inability to pursue objects. He was born by cesarean section at term due to intrauterine hypoxia, with a birth weight of 4000 g. An ultrasound B-scan conducted at birth showed normal kidneys. The patient had light perception visual acuity, horizontal nystagmus, and intraocular pressures of 10 mmHg in both eyes. No abnormalities were observed in the anterior ocular segment except for a sluggish response to light. However, pigmented deposits were observed in the peripheral retina on fundus examination (Figure 1A). A full-field electroretinogram (ERG), recorded with the RETI-scan 21 system (Roland Company, Germany) showed completely extinguished a- and b-waveforms under both scotopic and photic conditions (Figure 1C, D). Refraction measurement using a hand-held autorefractor (Welch Allyn VS100, China) revealed hyperopia of +8.00D in the right eye and +7.50D in the left eye. The patient was first diagnosed with Leber congenital amaurosis.

The patient had normal hearing according to the result from the brainstem auditory evoked potentials. The B-scan showed that the heart and liver were normal, but the kidneys were enlarged with a volume of 8.30 cm × 3.81 cm on the right and 8.24 cm × 3.78 cm on the left (Figure 2A). The boundary between the renal cortex and medulla was blurred, with some diffuse lesions in the medulla and enhanced echoes in the renal cortex and pyramidal region. Color Doppler Flow Imaging also showed decreased renal blood flow signal. His urine specific gravity and blood urea nitrogen were also low, measuring less than 1.005 g/ml and 1.04 mmol/L, respectively. He also had motor and growth retardation as he was unable to roll over at 7 months and had limb weakness; however, MRI and electroencephalography of the brain appeared normal.

At the 12-month follow-up examination, the patient was found to have numerous bone spicule-like pigmented deposits in the retina (Figure 1B). MRI showed that the patient had a narrowed frontal lobe, a broadening of the subarachnoid space, and a relatively small cerebellum, indicating hypoplasia of both the cerebra and cerebellum (Figure 2C–E). Despite these, his BMI remained normal, but he was unable to sit by himself at 12 months of age. B-scan revealed that the patient had an enlarged kidney of 9.5 cm × 3.6 cm on the right and 8.7 cm × 4.5 cm on the left at the age of 14 months. These findings suggest that the patient may have a genetic disorder.

After getting approval from the Ethics Committee of Beijing Children's Hospital (2022-E-213-R) and obtaining written informed consent from the parents, panel-based next-generation sequencing was performed on the patient and the parents. A compound heterozygous variants of c.6_-3delGTCATGGCT and c.277C>T (p.R93W) was detected in the *CEP164* gene of the proband, where the novel variant of c.6_-3delGTCATGGCT inherited from his mother, and the known pathogenic variant of c.277C>T (p.R93W) from his father (Figure 2B). The variant of c.6_-3delGTCATGGCT is located in the 5'UTR, which would result in a frameshift of the coding region with 46 amino acid residues lost. This variant was classified as pathogenic following the American College of Medical Genetics and Genomics guideline (PVS1 + PM2 + PM3). Based on clinical findings and genetic testing, the patient was diagnosed with Senior-Loken syndrome.

A literature review was performed by searching the databases from "PubMed", "OMIM", "Google Scholar" and "Web of Science" to find out relevant publications about *CEP164* mutations. Previous reports have identified 13 pathogenic variants of *CEP164* in a total of 15 patients from 11 families (Table S1). Including the patient

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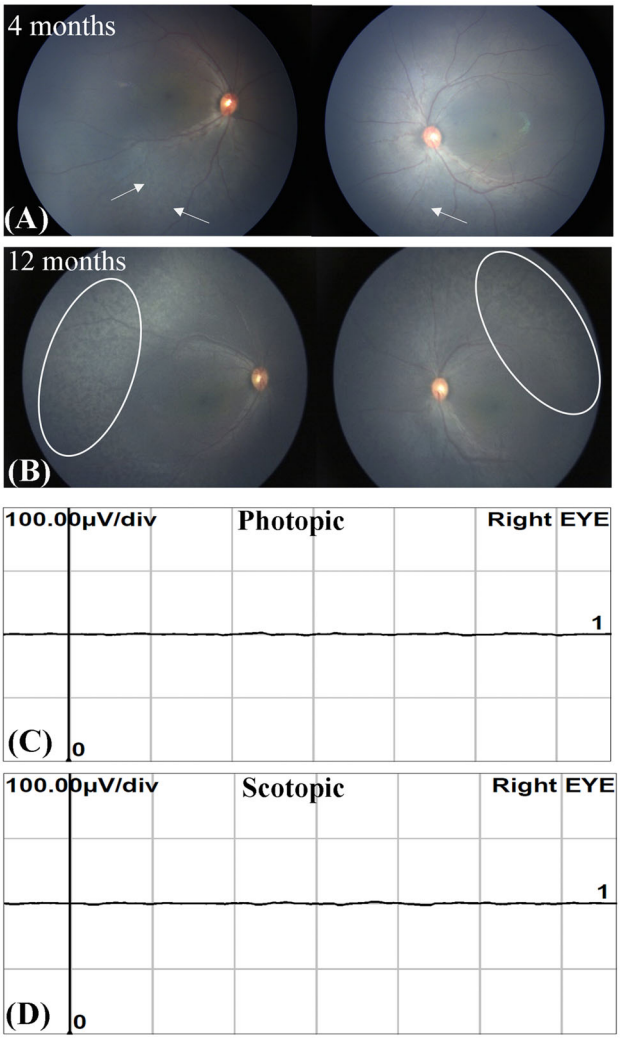

FIGURE 1 Fundus photographs and electroretinogram (ERG) recordings. (A) Fundus examination at postnatal 4 months revealed a few pigmented deposits (white arrows) in the periphery of the retina on both eyes. (B) At the age of 12 months, numerous pigmented deposits (white cycles) were visible. (C, D) The ERG recording showed extinguished a-and b-waveforms under photopic and scotopic conditions.

in this study, a total of 16 patients were identified. Of these patients, nine had compound heterozygous variants, six had homozygous variants, and only one had a single heterozygous variant. Most of these variants were missense and nonsense mutations, with only one splicing variant and one small insertion. The c.277C>T (p.R93W) variant was detected 9 times in 7 patients from 4 ethnically diverse families.[1–3]

The clinical phenotypes involved multiple systems and organs. Eye disease was the most frequent manifestation (12/16, 75%), followed by renal disease (11/16, 69%) and neurological disease (6/16, 37%). Other systemic disorders were less common. Obesity was found in 37% (6/16) of the patients, followed by polydactyly in 31% (5/16) and developmental delay in 27% (4/15). Other associated conditions include bronchiectasis (three patients), hypogonadism (two patients), and liver abnormalities (one patient). Notably, six patients had ocular-renal disorders, and two patients had ocular-brain-renal syndrome. Of the 11 patients with renal impairment, eight progressed to end-stage renal disease at a mean age of 9.6 ± 2.9 years.[1,3–5]

The *CEP164* gene encodes a centriolar protein that plays an important role in cilium growth and development.[6] Defects in ciliary structure or function can cause a group of inheritable disorders known as ciliopathies, which can affect numerous organs and tissues, including the eyes and kidneys.[7] Mutations in the *CEP164* gene can lead to a rare autosomal recessive disorder known as Nephronophthisis 15 (NPHP15), which is characterized by the early onset of kidney failure in children. During the first two years, the kidney may be moderately enlarged kidneys with cortical hyperechogenicity and no visible cysts. As time go by, the kidney volume decreases, and a few cortical macrocysts appear.[8] As the protein encoded by *CEP164* is involved in the growth and development of cilia, NPHP is often associated with extra-renal disorders, presenting as one of the syndromes of ciliopathies.[9] When NPHP is combined with retinitis pigmentosa, the disorder is referred to as Senior-Loken syndrome (SLSN1; 266900); when NPHP is combined with cerebellar vermis hypoplasia, the disorder is known as Joubert syndrome (JBTS1; 213300); and when it is combined with multiple developmental and neurological abnormalities, the disorder is known as Meckel-Gruber syndrome (MKS1; 249000).

This patient did not present with cystic kidneys at the follow-up but did present with structural changes, including enlarged kidneys with diffuse lesions internally and unclear boundaries between the renal cortex and medulla. The patient developed retinal degeneration at a very early age and was diagnosed with retinitis pigmentosa based on clinical findings of extinguished ERG recordings and typical fundus appearance of bone-spicule pigmentation deposited in the retina and narrowed retinal vessels. Although the patient had some structural brain changes, we diagnosed him with Senior-Loken syndrome rather than Joubert syndrome as the typical "molar tooth" appearance in the cerebella was absent.

To date, 9 disease-causing genes have been identified to be associated with the Senior-Loken syndrome, including *NPHP1*, *NPHP3*, *NPHP4*, *IQCB1*, *CEP290*, *SDCCAG8*, *WDR19*, *CEP164*, and *TRAF3IP1*.[10] The proteins encoded by these genes primarily participate in the structure and function of primary cilia and play important roles in various cell types, including retinal photoreceptor cells and renal tubular epithelial cells.[11] Recent studies suggested that CEP164 may also be involved in motile ciliogenesis.[12]

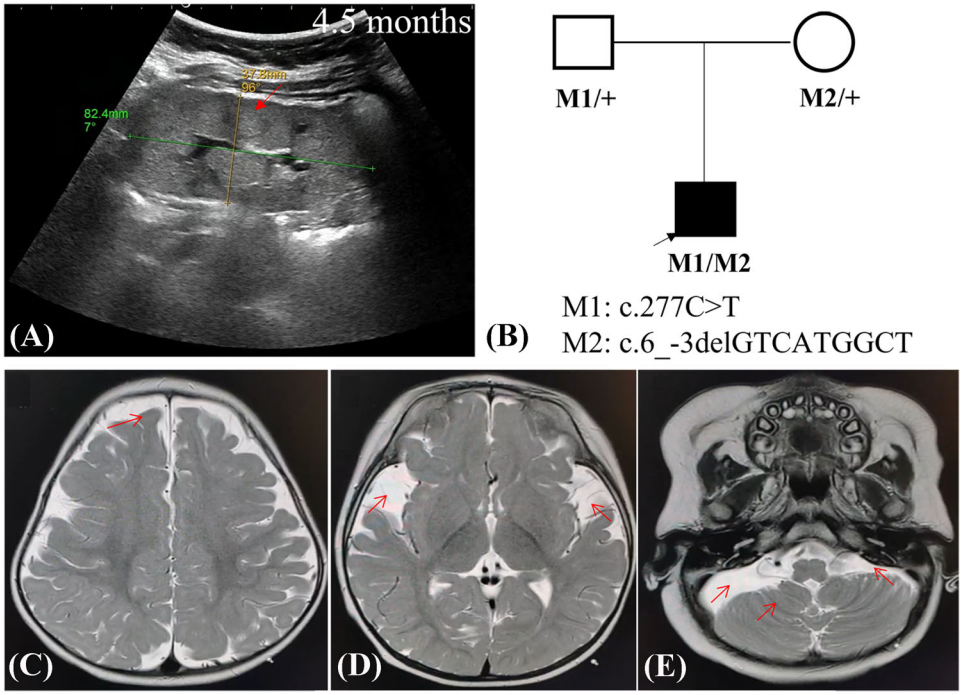

FIGURE 2 Imaging and genetic results of the patient. (A) Renal ultrasonography at 4.5 months of age showed an enlarged left kidney with an ill-defined boundary between the renal cortex and medulla (red arrow). The green line represents the longitudinal axis of the kidney and the yellow line represents the transverse axis. (B) Family pedigree showing carriers of the mutation in the *CEP164* gene. (C–E) T2-weighted MR image at 12 months of age revealed a narrowed frontal lobe, a broadening of the subarachnoid space, and a bilateral arachnoid cyst and cerebellum hypoplasia.

In summary, we presented a case of Senior-Loken syndrome in a Han Chinese boy with compound heterozygous variants in the *CEP164* gene. We identified a novel variant of c.6_-3delGTCATGGCT, which expands the spectrum of *CEP164* gene mutations and may provide insight into the molecular pathogenies of this ciliopathy.

Lili Liu[1], Yunyu Zhou[1], Yue Liu[2], Jiaojiao Ding[3], Yan Xie[1], Ningdong Li[1,4]

[1]Department of Ophthalmology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

[2]Department of Radiology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

[3]Department of Abdominal Ultrasound, First Affiliated Hospital of Xinjiang Medical University, Xinjiang, China

[4]Department of Ophthalmology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, National Clinical Research Center for Eye Diseases, Shanghai, China

Correspondence

Ningdong Li, Department of Ophthalmology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China.

Email: lnd30@163.com

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient's guardians.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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