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Research article

Clinical and genetic analysis of trichohepatoneurodevelopmental syndrome caused by a *CCDC47* variant

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ABSTRACT

Trichohepatoneurodevelopmental syndrome is an extremely uncommon autosomal recessive disorder resulting from variants in the *CCDC47* gene, which encodes a $Ca2^{+}$-binding endoplasmic reticulum (ER) transmembrane protein. To date, only four patients with CCDC47 deficiency have been reported, all of them with homozygous truncating *CCDC47* variants. For this study, a Chinese family was recruited, which included a patient diagnosed with trichohepatoneurodevelopmental syndrome. Whole exome sequencing (WES) identified the proband's novel homozygous *CCDC47* variation (NM_020198: c.634C > T(p.Arg212*). The variant was confirmed to be segregating in the proband and her unaffected relatives through Sanger sequencing. The patient described exhibited a clinical phenotype similar to that of patients with the *CCDC47* variant. Compared to reported cases with *CCDC47* pathogenic variants, our patients showed a novel complication of hearing impairment. In addition, brain abnormalities, small feet, bilateral hip dislocation, hip dysplasia, overlapping toes, pectus excavatum, scoliosis and narrow chest were not observed in our patient. We also examined five different variations and their corresponding phenotypes from five patients, both in current and previous research. Although some clinical manifestations of trichohepatoneurodevelopmental syndrome were highly variable, the most common phenotypes observed in these patients include microcephaly, profound intellectual disability, severe global development delay, pronounced growth restriction, hypotonia, woolly hair, facial dysmorphism, respiratory and visual abnormalities, gastrointestinal abnormalities, liver dysfunction, pruritus, skeletal and limb abnormalities, congenital heart defects and immunodeficiency. The present report is the first of a Chinese infant with homozygous variant in the *CCDC47* gene. We expanded the genetic and phenotypic spectrum associated with trichohepatoneurodevelopmental syndrome.

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1. Introduction

Trichohepatoneurodevelopmental syndrome (THNS, OMIM 618268) is an extremely uncommon autosomal recessive disorder characterized by global developmental delay, woolly hair, hepatic dysfunction, pruritus, dysmorphic features and hypotonia [1]. The disease is caused by homozygous or compound heterozygous variants in the coiled-coil domain containing the 47 (*CCDC47*, NM_020198, MIM 618260) gene sitting on 17q23.3. This 13-exon gene encodes the Ca^{2+}-binding endoplasmic reticulum (ER) transmembrane protein [2]. It is extensively present in various human tissues such as the brain, heart, stomach, lung, liver, kidney, spleen, testis and muscle [2]. Knockout mice models of Ccdc47 presented delayed embryonic development, heart defects, atrophic neural tubes, and a paucity of blood cells in the dorsal aorta, ultimately resulting in embryonic lethality [3]. Loss of *CCDC47* resulted in impaired Ca^{2+} signaling in mouse embryonic fibroblasts.

To date, only one study has been conducted on trichohepatoneurodevelopmental syndrome, which included four patients with four variants, to describe its clinical features [1]. All variants identified were null variants predicted to interfere with CCDC47 binding to Ca^{2} + . It will be crucial to the understanding of this disease to have further reports on *CCDC47* variants and their phenotypes. Here we investigated a homozygous nonsense variant (c.634C > T(p.Arg212*)), not previously reported, in a Chinese infant diagnosed with trichohepatoneurodevelopmental syndrome. Furthermore, we describe the patient's relevant clinical characteristics.

2. Materials and methods

2.1. Patients and ethics approval

This study involving human participants underwent review and approval by the Institutional Review Board and Ethics Committee of Guangxi Maternal and Child Health Hospital. The patient's parents gave informed signed consents. Peripheral blood specimens were

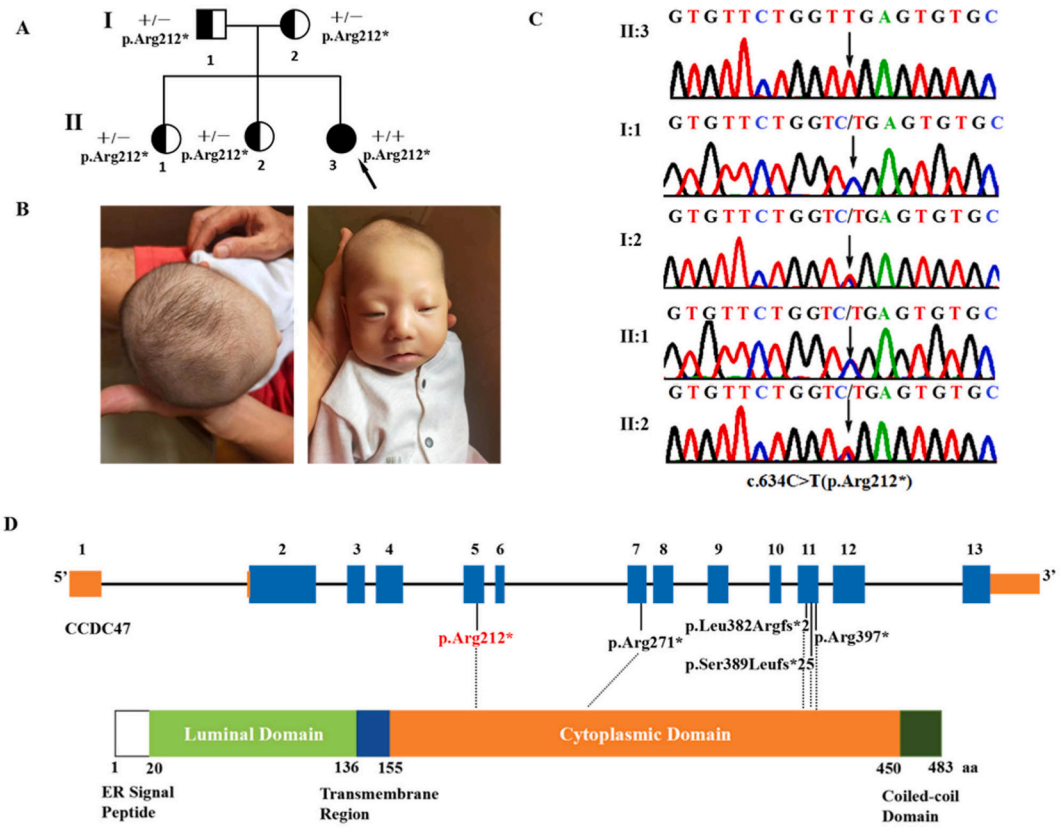

Fig. 1. Figure 1. Pedigree, phenotype, DNA sequencing of the patient and the spectrum of *CCDC47* variants. **A** Pedigree chart of the family of the patient with trichohepatoneurodevelopmental syndrome. The proband was the third child of healthy non-consanguineous Chinese parents and indicated by a black arrow. **B** The patient showed microcephaly, plagiocephaly, Hypertelorism, Sparse hair, Long eyelashes, Sparse and thin blonde eyebrow, Synophrys,Wide nasal bridge, thick lips, High palate and micrognathia. **C**DNA sequence chromatograms by Sanger sequencing of *CCDC47* showing a homozygous nonsense variant c.634C>T(p.Arg212*) in the proband and heterozygous variant in the proband's parents and sisters. **D**The spectrum of *CCDC47* variants. The variants are shown below the schematic representation of the CCDC47 genome structure and above the schematic representation of the CCDC47 protein structural domain structure. The novel variant (p.Arg212*) in our patient is highlighted in red.

obtained from the proband and her parents. The proband underwent a thorough examination in our hospital, including laboratory examinations, physical examination, echocardiography, electroencephalography, brain magnetic resonance imaging (MRI), audiological tests, routine eye examination, and gene detection analyses.

2.2. Whole-exome and Sanger sequencing

Genomic DNA was extracted from lymphocytes in 2 mL peripheral blood collected from the proband and her family members using the Lab-Aid DNA kit (Zeesan Biotech Co., Ltd., Xiamen, China). The proband underwent whole-exome sequencing (WES) to elucidate the etiology of Trichohepatoneurodevelopmental syndrome. The Agilent SureSelect Human All Exon V5 Kit (Agilent Technologies, Santa Clara, CA, USA) was used for whole-exome capture, following the manufacturer's instructions. The library was enriched and then subjected to paired-end sequencing on the HiSeq 2500 platform (Illumina, San Diego, CA, USA). Sequencing reads were aligned to the human genome reference (hg19 assembly) employing the Burrows–Wheeler Aligner. Sequencing data analysis and variant calling were performed with the Genome Analysis Tool Kit (version 3.3), and the variants were annotated and classified with TGex software (LifeMap Sciences, Alameda, CA, USA). Next, the variants were filtered based on the following rules: (i) exonic variants and intronic variants within 10-bp exon-flanking regions; (ii) a frequency less than 0.1% in public databases such as the 1000 Genomes Project, Exome Sequencing Project, and ExAC, as well as our in-house databases; (iii) identification of loss-of-function alleles or damaging missense variants using prediction tools such as MutationTaster, CADD, SIFT, or PolyPhen2. The final interpretation and classification of variants were conducted in accordance with the American College of Medical Genetics (ACMG)/Association of Molecular Pathology (AMP) guidelines [4].

3. Results

3.1. Clinical description

Proband (II:3), a 2-month-old female infant, was the third child of healthy unrelated Chinese parents. (Fig. 1A). She was delivered at 38 weeks and 6 days of gestation through unassisted vaginal delivery at a hospital, exhibiting a normal cry at birth. Her birth weight was 2.86 kg, which was appropriate for her gestational age. At 1 month and 20 days of age, she was admitted to our hospital because of laryngeal stridor and dyspnea. A physical examination showed that she suffered from severe malnutrition with all anthropometric measurements below the 3rd percentile (height: 52 cm, head circumference: 33.5 cm, weight: 3090 g). Her dysmorphic features included microcephaly, plagiocephaly, hypertelorism, sparse hair, long eyelashes, sparse and thin blonde eyebrow, synophrys, wide nasal bridge, thick lips, high palate and micrognathia (Fig. 1B). In the first two months of life, she exhibited infantile hypotonia with a poor suck, laryngomalacia, feeding difficulties, failure to thrive, weak cry and decreased spontaneous movement. Laboratory investigations on day 3 of admission showed she had high total bile acids (214.9 μmol/L; normal range 0–20 μmol/L). Her complete blood count showed moderate anemia with a hemoglobin level of 72 g/L (reference range 140–180 g/L). The patient's interictal EEGs

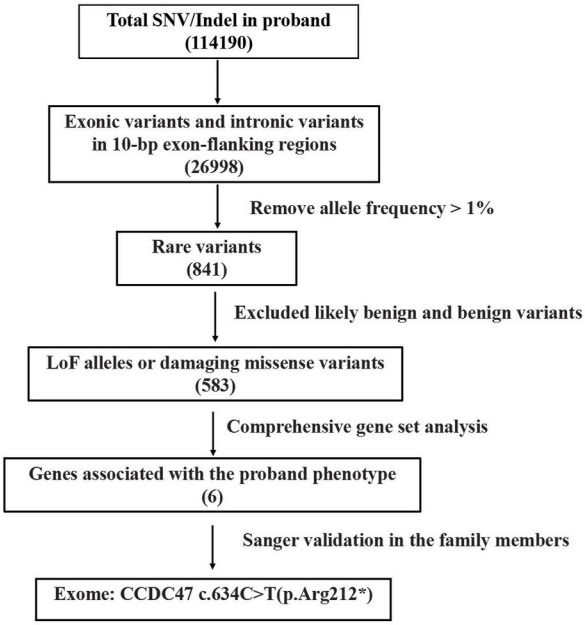

Fig. 2. Figure 2. Whole-exome sequencing (WES) and bioinformatics analysis. The schematic illustrates the main steps of WES analysis. WES = whole-exome sequencing.

Table 1
Summary of the clinical features of the patients.

Patients clinical data	Our patient	Machol et al. [10]				Total
	Patient1	Patient2	Patient3	Patient4	Patient5	N = 5
Variants in CCDC47 (NM_020198)	c.634C > T (p. Arg212*)	c.811C > T (p. Arg271*)	c.1145delT (p. Leu382Argfs*2)	c.1165delT (p. Ser389Leufs*25)	c.1189C > T (p.Arg397*)	Frameshift = 2 nonsense = 3
Affected exon/intron	5	8	1	11	11	
Gender	Female	Female	Male	Female	Female	Male = 1; female = 4
Age at last examination	Two months	5 years	8 years	8 years	6 years and 6 months	
Facial dysmorphism						
Coarse facies	–	+	+	+	+	4/5
Midface hypoplasia	–	+	+	+	–	3/5
Hypertelorism	+	+	+	+	–	4/5
Almond-shaped palpebral fissure	–	+	+	–	–	2/5
Epicanthal folds	–	–	–	+	–	1/5
Ptosis	–	+	+	+	+	4/5
Long eyelashes	+	+	+	–	–	3/5
Synophrys	–	+	–	+	+	3/5
Ectropion	–	+	+	–	–	2/5
Unusual nose	+	+	+	+	+	5/5
Downturned mouth	–	+	+	+	+	4/5
Macrostomia	–	–	+	Wide mouth	–	2/5
Macroglossia	–	–	+	+	+	3/5
Full or thick lips	–	+	+	+	+	4/5
Dental abnormalities	NA	+	–	+	+	3/4
High arched palate	+	+	+	+	+	5/5
Ear abnormalities	–	+	+	+	+	4/5
Bilateral otitis media	–	+	+	+	+	4/5
Bitemporal narrowing	–	–	+	+	+	3/5
Brachycephaly	–	+	+	+	+	4/5
Plagiocephaly	+	+	+	+	–	5/5
Pruritus	––	+	+	+	+	4/5
Unusual hair	+	+	+	+	+	5/5
Thoracic hypertrichosis	+	+	+	+	+	5/5
Visual abnormalities						
Hyperopia	–	+	NA	–	+	2/4
Astigmatism	–	+	NA	–	+	2/4
Cortical visual impairment	–	+	NA	+	+	3/4
Immunodeficiency	–	–	+	+	+	3/4
Hearing impairment	+	–	–	–	–	1/5
Endocrine Findings						
Hypothyroidism	–	–	NA	+	–	1/4
Rickets	–	–	+	+	–	2/5
Respiratory Findings						
Obstructive sleep apnea	–	+	+	+	–	3/5
Central sleep apnea	–	+	NA	+	–	2/5
Ocular anomalies						
Ventricular septal defect	–	–	+	–	–	1/5
Patent ductus arteriosus	+	+	+	–	–	3/5
Growth delay						
Decreased body weight	+	+	+	+	+	5/5
Microcephaly	+	+	+	+	+	5/5
Short stature	+	NA	+	+	+	4/4
Neurological abnormality						
ID	NA	+ + +	+ + +	+ + +	+ + +	4/4
DD	+ + +	+ + +	+ + +	+ + +	+ + +	5/5
Speech impairment	NA	+	+	+	+	4/4
Brain radiologic features	––	Cerebral atrophy, slight posterior thinning of the corpus callosum	Cerebral atrophy	Cerebral atrophy	Cerebral atrophy, white matter abnormalities, thinning of the corpus callosum, White matter abnormalities	4/4
Behavioral abnormalities	–	–	–	+	+	2/5
Hypotonia	+	+	+	+	+	5/5

(*continued on next page*)

Table 1 (*continued*)

Patients clinical data	Our patient	Machol et al. [10]				Total
	Patient1	Patient2	Patient3	Patient4	Patient5	N = 5
Variants in CCDC47 (NM_020198)	c.634C > T (p. Arg212*)	c.811C > T (p. Arg271*)	c.1145delT (p. Leu382Argfs*2)	c.1165delT (p. Ser389Leufs*25)	c.1189C > T (p.Arg397*)	Frameshift = 2 nonsense = 3
Seizures	–	–	–	+	–	1/5
EEG abnormalities	+	+	NA	+	+	4/4
Skeletal and limb abnormalities						
Bilateral hip dislocation	–	+	+	ND	–	2/4
hip dysplasia	–	+	+	+	+	4/4
bilateral coxa valga	–	+	–	ND	+	2/4
abnormal bone density	ND	+	+	ND	ND	2/2
narrow chest	–	+	+	–	–	2/5
fibular bowing	–	+	+	–	–	2/5
genu valgum	–	–	–	+	–	1/5
bilateral clubfoot	+	+	+	–	+	4/5
small feet	–	+	+	+	+	4/5
pectus excavatum	–	+	–	–	+	2/4
fifth digit hypoplasia and/or clinodactyly	–	+	+	+	+	4/5
dystrophic nails	–	–	–	+	–	1/4
overlapping toes	–	+	+	+	+	4/5
distal arthrogryposis/ joint laxity	–	+	+	+	+	4/5
cubitus varus	+	–	–	–	–	1/5
Genital anomaly	–	+	+	–	–	2/5
Gastrointestinal Findings						
Hepatosplenomegaly	–	+	–	+	–	2/5
Liver dysfunction	–	+	ND	+	+	3/4
Recurrent pancreatitis	–	+	NA	–	–	1/4
Exocrine pancreatic insufficiency	–	+	NA	–	–	1/4
Gastresophageal reflux	+	+	NA	+	+	4/4
Steatorrhea	–	–	+	–	–	1/5
Chronic diarrhea	–	–	+	–	+	2/4
Gallstones	–	+	–	–	+	2/4
Gastrostomy tube	–	+	–	+	+	3/5

The following abbreviations are used: NA, not assessed or not available; ID intellectual disability, DD, Development delay.

on admission showed diffuse slow waves (predominantly posterior) during wakefulness and multifocal spike-waves during sleep. An echocardiogram showed a patent ductus arteriosus (PDA). Ophthalmological examination revealed that she had cortical visual impairment. Her skeletal survey revealed bilateral talipes equinovarus, cubitus varus and abnormal posturing. She also had moderate hearing impairment. The initial brain MRI, at 1 month and 23 days of age, was normal.

3.2. Genetic analysis

The WES was performed to identify the potential gene variant in the proband. WES generated 11.55 Gb of data with an appropriately 98.8% coverage of target region, and 97.6% of the target covered at a depth of 20 fold. There were 26998 SNV or indel variants in coding regions and splice sites (splicing junction, 10 bp). Data filtering excluded the variants with a minor allele frequency (MAF) > 1% in gnomAD, dbSNP132, ESP, 1000G and our internal database, 841 unique SNPs were identified. After excluding likely benign and benign variants, which included synonymous and harmless missense variants predicted by *in silico* prediction tools, 531 variants remained (Fig. 2). After data analysis using TGex analysis software (https://tgex.genecards.cn/), we extracted six variants in six genes (*CCDC47*, *ASXL3*, *SLC6A9*, *PPFIBP1*, *KDM4B*, and *LAMA5*) that matched with known phenotypes. The variants in the *SLC6A9*, *PPFIBP1,* and *LAMA5* genes were heterozygous. The disorders resulting from these genetic mutations are autosomal recessive and, as such, have been ruled out. The mutations in the *ASXL3* and *KDM4B* genes were transmitted from the unaffected parent, yet they were determined not to be causative of the observed phenotype (Supplementary Table S1). Then, a homozygous *CCDC47* nonsense variant, c.634C > T(p.Arg212*), was identified in the proband. Further Sanger sequencing revealed that her parents and her sisters were heterozygous for the same variant (Fig. 1C).

4. Discussion

CCDC47, known as caluminis, is an endoplasmic reticulum (ER) transmembrane protein that binds calcium ions and plays a pivotal role in embryogenesis and development. In 2014, Yamamoto et al. found that Ccdc47 knockout mice exhibited developmental delay, neural tube atrophy, cardiac malformations, scarcity of dorsal aortic blood cells, and embryonic death [3]. Moreover, they observed

that embryonic fibroblasts (MEFs) derived from these mice displayed compromised Ca^{2+} signaling, involving a versatile intracellular signaling network that is crucial for various cellular processes such as including synaptic vesicle exocytosis, muscle contraction, regulation of secretion, transcription, and cellular proliferation [3,5,6]. In 2018, Morimoto et al. reported that loss-of-function variants in *CCDC47* were associated with a distinct developmental phenotype [1]. These findings indicated that the absence of CCDC47 was accountable for the multisystem anomalies observed in individuals affected by trichohepatoneurodevelopmental syndrome. In the present study, a homozygous pathogenic variant c.634C > T(p.Arg212*), was identified in the coding region of the *CCDC47* gene in a Chinese infant with trichohepatoneurodevelopmental syndrome. The variant, c.634C > T(p.Arg212*), was not reported in the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/ac/), 1000 genome database, HPSD (http://liweilab.genetics.ac.cn/HPSD/), dbSNP (http://www.ncbi.nlm.nih.gov/SNP/), ExAC (https://exac.broadinstitute.org/), and gnomAD (https://gnomad.broad.institute.org/). The novel nonsense variant is predicted to be disease-causing by MutationTaster. c.634C > T(p.Arg212*) and is a loss-of-function variant that introduces a premature termination codon in exon 5, resulting in nonsense-mediated mRNA decay that reduces the overall level of *CCDC47* mRNA. According to the ACMG/AMP standards and guidelines, the nonsense variant identified in this family was likely pathogenic with evidence justified PVS1+PM2_supporting. This finding confirmed that CCDC47 defects were likely to be the cause of the developmental abnormalities in our patient.

To date, only five affected individuals (including our patient) from five different families have been reported with variants in *CCDC47* [1]. The variants included three nonsense variants and two frameshift variants (Fig. 1D). The list of reported variants of *CCDC47* and the clinical available phenotypes of all cases are summarized in Table 1. Phenotypic analysis of affected individuals revealed a high degree of phenotypic homogeneity in patients with *CCDC47* loss-of-function variants. All patients had severe neurological abnormalities, including microcephaly, profound intellectual disability, severe global development delay, hypotonia, brain and ophthalmologic abnormalities. All affected individuals presented with severe global developmental delay, both in growth motor skills (only patient 4 has learned to sit, but has not been reported to have the ability to walk independently to date) and in language acquisitions (all patients had no spoken language). Brain imaging showed abnormalities in most patients, with cerebral atrophy(4/5), corpus callosum abnormalities (2/5), white matter abnormalities(1/4), cerebellar hypoplasia (1/4). Notably, no brain abnormality was observed in our patient, however, EEG abnormalities were observed in four patients, including our patient. In addition, two patients had behavior issues and one patient had seizures. Dysmorphic traits, which became increasingly distinctive with age, were observed in all affected individuals. These included unusual hair (5/5), brachycephaly (4/5), plagiocephaly (4/5), bitemporal narrowing (3/5), coarse facies(4/5), midface hypoplasia (3/5), hypertelorism (4/5), almond-shaped palpebral fissure (2/5), epicanthal folds (1/5), ptosis (5/5), long eyelashes(3/5), synophrys(3/5), ectropion (2/5), unusual nose (5/5), downturned mouth (4/5), macrostomia (2/5), macroglossia (3/5), full or thick lips(5/5), dental abnormalities (3/4), high arched palate (5/5), and ear abnormalities (4/5). Skeletal and limb abnormalities were seen in all patients, with bilateral hip dislocation (2/4), hip dysplasia (3/4), bilateral coxa valga (2/4), abnormal bone density (2/3), narrow chest (2/5), fibular bowing (2/5), genu valgum (1/5), bilateral clubfoot (4/5), small feet (3/4), pectus excavatum (2/5), scoliosis (2/5), fifth digit hypoplasia and/or clinodactyly (4/5), dystrophic nails (1/5), overlapping toes (4/5) and distal arthrogryposis/joint laxity (4/5). Compared with reported patients, our patient exhibited a milder phenotype of limb abnormalities with bilateral talipes equinovarus, cubitus varus and abnormal posturing. A pronounced growth restriction was observed in all affected patients on all growth variables with increasing deviation from reference values with age. Our patient also exhibited severe malnutrition with all anthropometric values below the 3rd percentile. Gastrointestinal abnormalities and liver dysfunction should be considered an important cause of growth restriction in these patients. In these patients, we observed hepatosplenomegaly (2/5), liver dysfunction (4/4), recurrent pancreatitis (1/5), gastresophageal reflux (4/4), steatorrhea (2/5), chronic diarrhea (2/5), gallstones (2/5) and gastrostomy tube (3/5). Respiratory and visual abnormalities were also common. Sleep apnea occurred in at least 60% of CCDC47-deficieny patients. Three had cortical visual impairment, two had hyperopia and one had astigmatism. A subset had congenital heart defects (3/5) and immunodeficiency was common (3/5). Our case presented with a severe infection reminiscent of patients 3 and 4, who were hospitalized for recurrent infections. Based on this observation, we hypothesized that CCDC47 deficiency caused recurrent infections due to defects in the conduction of multiple signaling pathways such as Toll-like receptor signaling. In addition, other dysmorphic features, such as hypothyroidism, rickets and hearing impairment, were also observed. Notably, the hearing impairment observed in the patient we described has not been documented in previous cases with *CCDC47* pathogenic variants.

There were several limitations in the present study. First, long-term follow-up studies on patients are necessary to assess disease progression. Second, due to the insufficient number of patients, our results should be considered provisional, and as the number of reported patients continues to increase, it is expected that the phenotypes will further be refined, providing greater clarity on genotype effects and other determinants of phenotypes. Third, this study did not include a direct evaluation of the functional implications of the variants, therefore, additional functional investigations will enhance our comprehension of CCDC47-related disorders and their mechanisms of action.

The mechanism by which these variants lead to woolly hair, facial dysmorphism, microcephaly, severe global developmental delay, hypotonia, liver dysfunction, pruritus, skeletal and limb abnormalities, and other clinical symptoms remains unclear. Multiple mechanisms can be hypothesized to explain CCDC47-related disorder. The CCDC47 protein, which comprises 483 amino acids, includes an ER signaling peptide localized at the N-terminus, a calcium-binding domain, a transmembrane domain, and a cytosolic domain localized at the C-terminus. A previous study reported that CCDC47 played a key role in ER-regulated calcium control and homeostasis [7]. Indeed, CCDC47-deficiency leads to a decrease in stored Ca^{2+} and impairs signaling in the ER [1]. CCDC47 is also involved in the modulation of Ca^{2+} release-activated Ca^{2+} (CRAC) channels that play a role in endoplasmic reticulum (ER) refilling, and it interacts with STIM1 and ORAI1, which are involved in calcium entry [2,8]. Furthermore, CCDC47 is involved in a variety of membrane-associated processes [1,2,8,9]. CCDC47 engages early transmembrane domains of multipass proteins to promote their

biogenesis by forming a PAT complex with Asterix, and functionally impaired CCDC47 may lead to reduced biogenesis of numerous multi-spanning membrane proteins [10]. Additional functional studies will enhance our comprehension of CCDC47-related disorders and their mechanisms of action.

5. Conclusion

In summary, we identified a novel homozygous likely pathogenic variant in *CCDC47* in a female Chinese infant with trichohepatoneurodevelopmental syndrome. This is the first description of the *CCDC47* variant in a Chinese patient. The variant associated with severe global development delay, intellectual disability woolly hair, facial dysmorphism, microcephaly, hypotonia, feeding difficulties, failure to thrive, severe malnutrition, severe anemia, elevated bile acids, skeletal and limb abnormalities and hearing impairment. The data further extended the phenotype spectrum of *CCDC47* variations.

Ethics statement

The protocol of the current study received approval from the Department of Genetic Metabolic Central Laboratory of Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region (GXMC20230504). The study was carried out in strict adherence to Good Clinical Practice and the principles outlined in the Declaration of Helsinki. Comprehensive written informed consent was obtained all family members who participated, as well as from the parents of participants under the age of 16, for the use of their related images and information for scientific purposes.

Data availability statement

Data will be made available on request.

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CRediT authorship contribution statement

Qi Yang: Writing – review & editing, Writing – original draft, Funding acquisition, Data curation, Conceptualization. **Xunzhao Zhou:** Validation, Software, Methodology, Data curation. **Yeying Ling:** Resources, Data curation. **Qiang Zhang:** Software, Methodology, Data curation. **Shang Yi:** Validation, Software, Data curation. **Qiuli Chen:** Validation. **Shujie Zhang:** Validation. **Zailong Qin:** Formal analysis, Data curation. **Jingsi Luo:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27955.

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