Perrault syndrome: Clinical report and retrospective analysis

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Abstract

Background: Perrault syndrome (PRLTS4; OMIM# 615300) is a rare autosomal recessive disorder and only a few cases have been reported worldwide. We report a Chinese female characterized by sensorineural hearing loss and premature ovarian insufficiency.

Methods: We evaluated audiological, endocrine, and ultrasound examinations and examined the genetic causes using whole-exome sequencing. We reviewed the literature to discuss the pathogenesis, genotype–phenotype correlation, treatment, and prevention of PRLTS4.

Results: Bioinformatic analysis revealed compound heterozygous mutations in the LARS2 gene, c.880G>A (p.Glu294Lys), and c.2108T>C (p.Ile703Thr) which is a novel missense mutation, co-segregated in this family. Taken together, the patient was clinically diagnosed as PRLTS4. The literature review showed that the phenotype for PRLTS4 varies widely, but the sensorineural hearing loss, increased gonadotropin levels, and amenorrhea occurred frequently. All reported mutations are highly conserved in mammals based on conservation analysis, and there is a mutation hotspot for PRLTS4.

Conclusion: This study expanded the mutation spectrum of LARS2 and is the first report of PRLTS4 in a Chinese family. Genetic testing plays an important role in early diagnosis of syndromic deafness and clinical genetic evaluation is essential to guide prevention.

KEYWORDS
LARS2, Perrault syndrome, premature ovarian insufficiency, sensorineural hearing loss

Zhaoyu Pan and Hongen Xu contributed equally to this work.

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1 | INTRODUCTION

Perrault syndrome (PRLTS4; OMIM# 615300) is a rare autosomal recessive disorder characterized by premature ovarian insufficiency (POI) in females, and sensorineural hearing loss (SNHL) in both genders. Perrault, Klotz, and Housset (1951) first described the association of gonadal dysgenesis and SNHL in two sisters, and it has been referred to as Perrault syndrome afterward. Pierce et al. (2013) first identified homozygous and compound heterozygous mutations in the LARS2 gene (PRLTS4) in two Perrault syndrome families. There are six subtypes of Perrault syndrome, which comprise PRLTS1 (OMIM# 233400), PRLTS2 (OMIM# 614926), PRLTS3 (OMIM# 614129), PRLTS4 (OMIM# 615300), PRLTS5 (OMIM# 616138), and PRLTS6 (OMIM# 617565), with mutations identified in HSD17B4, HARS2, CLPP, LARS2, TWNK, and ERAL1 genes, respectively. However, in approximately 60% of patients with Perrault syndrome to date, a molecular diagnosis cannot be made (Roberts & Carnivale, 2019).

SNHL of PRLTS4 is bilateral and sometimes progressive, ranging in severity from moderate with early childhood onset to congenital profound. Ovarian dysfunction ranges from gonadal dysgenesis (absent or streak gonads) manifesting as primary amenorrhea to POI defined as amenorrhea or oligomenorrhea accompanied by follicle-stimulating hormone (FSH) more than 25 U/L before the age of 40 (Lerat et al., 2016). In addition, variable neurological symptoms have been present in patients with PRLTS1, PRLTS3, and PRLTS5. However, a Japanese family with PRLTS4 was first reported neurological symptoms as well (Kosaki, Horikawa, Fujii, & Kosaki, 2018). Characterized by the normal karyotype (46, XX), female patients with PRLTS4 can be differentiated from Turner syndrome by karyotype analysis, although nearly half of Turner patients have some degree of hearing loss (Roberts & Carnivale, 2019). Kiss et al. (1999) localized the cDNA encoding the precursor of mitochondrial leucyl-tRNA synthetase (mtLeuRS) to chromosome 3p21.3 region. Bonnefond et al. (2005) identified that the LARS2 gene contained 20 exons and coded for a 903-amino-acid-long mtLeuRS, which belongs to the class I aminoaicyl-tRNA synthetases. Aminoacyl-tRNA synthetases (aaRSs) are essential enzymes which can charge the tRNA with its cognate amino acid, thus, providing substrates for protein synthesis (Cusack, Yaremchuk, & Tukalo, 2000; Lue & Kelley, 2005; van der Knaap et al., 2019; Yao, Wang, Wu, & Wang, 2003).

PRLTS4 has been reported only a few times and there has been no report from China. In this study, we report a case from a Chinese family with clinical features of PRLTS4. Whole-exome sequencing (WES) revealed compound heterogeneous mutations in the LARS2 gene, one of which is novel. A literature review was performed to examine the natural history of PRLTS4.

2 | MATERIALS AND METHODS

2.1 | Subjects and clinical investigations

A 23-year-old female with deafness presented to the Department of Otorhinolaryngology, Head and Neck Surgery, the First Affiliated Hospital of Zhengzhou University. Audiological evaluation showed sensorineural hearing loss. The pedigree data were collected from the proband's parents. The clinical assessment included audiological, endocrine, and ultrasound examinations. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Zhengzhou University (reference number 2018008). Written informed consent was obtained from the proband, her parents, and younger brother. The phenotype and variant information was submitted to the LOVD database (https://datab ases.lovd.nl/shared/individuals/00295959).

2.2 | Whole-exome sequencing

Peripheral venous blood was collected from the proband, her parents, and younger brother. Genomic DNA was extracted using the GenMagBio Genomic DNA Purification kit (GenMagBio, Changzhou, China) per manufacturer’s protocol. After fragmentation and end-repair of genomic DNA from the proband, adapter ligation as well as PCR enrichment were performed following the manufacturer’s protocol for VAHTS TM Universal DNA Library Prep Kit for Illumina V3 (Vazyme Biotech Co., Ltd, Nanjing, China). Exons and the flanking regions of all known genes were captured using the SureSelect Human All Exon V7 (Agilent). The library was sequenced by an Illumina HiSeq 4000 sequencer with pair-end 150 mode at the Precision Medicine Center of Zhengzhou University, Zhengzhou, China.

2.3 | Bioinformatics analysis and variant classification

Bioinformatics analysis was performed in the framework of bcbio-nextgen (https://github.com/bcbio/bcbio-nextgen), which provides best-practice pipelines for variant calling, annotation, and validation. After trimming adapters and low-quality reads with Trimomatic, cleaned reads were aligned to the human reference genome (version GRCh37) using Burrow Wheeler Aligner (version 0.7.17-r1188). Single nucleotide variants (SNVs) and small indels were characterized using the Genome Analysis Toolkit version 4 (GATK4) HaplotypeCaller. Variant annotation was performed using snpeff and vcfanno with several databases for variant frequencies in the general population. We filtered out variants with minor allele frequency >0.05 and at least 2,000 alleles were observed in any general continental population in gnomAD
database. Pathogenicity was predicted using Polyphen2 and MutationTaster. The American College of Medical Genetics and Genomics (ACMG) guidelines were employed for sequence variation interpretation. Variant nomenclature was based on LARS2 canonical transcript NM_015340.3.

2.4 | Sanger sequencing

Sanger sequencing was used to verify the variants in the proband revealed by WES, and to test the co-segregation of variants in the kindred. Primer-Blast was employed to design primers covering these variants: c.880G>A (p.Glu294Lys) forward primer 5′-TGTTTGGGAATGAGGAGGGA-3′, reverse primer 5′-ATCCTACCACTGTACCCGTT-3′; c.2108T>C (p.Ile703Thr) forward primer 5′-CCATCAGGTTGAGCGAGG-3′, reverse primer 5′-GCAAAGACCAGGGAAAAGG-3′. Sequencing was done by SeqStudio Genetic Analyzer (Applied Biosystems/Life Technologies, Carlsbad, CA, USA) after PCR product purification.

2.5 | Amino acid conservation analysis and three-dimensional model prediction

Amino acid conservation was analyzed using the HomoloGene database among Homo sapiens, Pan troglodytes, Rattus norvegicus, Mus musculus, Bos taurus, Macaca mulatta, Gallus gallus, Danio rerio, and Pseudonaja textilis. The program PHYRE2 (http://www.sbg.bio.ic.ac.uk/phyre2/html/page.cgi?id=index) was used to construct three-dimensional models of LARS2 protein.

2.6 | Literature review

The literature was searched from 1950 to 2020 on PubMed with Perrault syndrome or LARS2 as the keyword. Then, the genotype-phenotype correlation and the natural history of PRLTS4 were summarized.

3 | RESULTS

3.1 | Case presentation

The proband (Il-1, Figure 1a) was the 23-year-old daughter of non-consanguineous Chinese parents. She was diagnosed with bilateral moderate SNHL at 2 years old, which was progressive to severe mixed hearing loss by age 22 (Figure 1c,d). The audiograms showed an uncommon pattern of low-frequency loss resulting in an upsloping audiogram. Electrocochleography evidenced the absence of cochlear microphonic (CM). Distortion product otoacoustic emission (DPOAE) was absent in total frequencies. Normal tympanic membranes and well-aerated middle ear clefts were shown by otological examination. Thin-section computed tomography of the temporal bone showed no abnormality. The proband presented with oligomenorrhea with a hormone profile indicative of increased gonadotropin levels (FSH; 38.29 U/L). Luteinizing hormone (LH; 6.11 U/L), estradiol level (E2; 52.51 pg/ml), and karyotype (46, XX) were normal. Serum anti-müllerian hormone concentrations showed 0.15 ng/ml, indicating diminished ovarian reserve and poor ovary response. The uterus and both ovaries appeared nearly normal size on transrectal ultrasound, but there were reduced ovarian follicles and multiple Naboth cysts on the cervix. No obvious neurological presentations were noted in the proband and she had a normal level of intelligence. She had normal speech development and used a hearing aid. Due to the uncommon pattern of low-frequency loss, the proband had very poor adaption to the hearing aid. The proband's parents (I-1, I-2, Figure 1a), and younger brother (II-2, Figure 1a) had normal hearing.

3.2 | Phenotypic diagnosis

By normal karyotype and the absence of CM, this case can be differentiated from Turner syndrome and auditory neuropathy (AN), respectively, although there is a similar upsloping audiogram to AN. Characterized by SNHL and POI, PRLTS4 fits the clinical diagnosis of this case well.

3.3 | Molecular diagnosis

The proband carried compound heterozygous missense variants in the LARS2 gene revealed by WES: c.880G>A (p.Glu294Lys), which was reported by Kosaki et al. (2018), and c.2108T>C (p.Ile703Thr), which was a novel missense variant (Figure 1b). These missense mutations were absent in a local database of 500 normal Chinese controls. The variants were validated in her family members by Sanger sequencing. Segregation was consistent with an autosomal recessive mode of inheritance: c.880G>A from the proband's mother and c.2108T>C from her father. Her younger brother carried neither of these two variants. The variants were predicted to be probably damaging by Polyphen2 and disease-causing by MutationTaster. According to the gnomAD population database, the allele frequency of the p.Glu294Lys was 0.00001592. It was considered as likely pathogenic according to the ACMG guidelines (Kosaki et al., 2018). The variant p.Ile703Thr was absent in the gnomAD population database and was classified as likely pathogenic based on the ACMG guidelines (PM2+PM3+PP1+PP4). Besides, both the proband and her father were heterozygous carriers of...
FIGURE 1  Pedigree, Sanger sequencing, and Audiograms of the PRLTS4 family. (a) Pedigree of the PRLTS4 family. (b) Sanger sequencing of the proband (II-1), parents (I-1, I-2), and younger brother (II-2). (c) Early audiograms of the proband. (d) Present audiograms of the proband.
c.5051C>T (p.Pro1684Leu) in the USH2A gene, a causative gene of Usher syndrome II inherited in an autosomal recessive manner. We took the LARS2 gene as the likely pathogenic gene based on the bioinformatic analysis.

We summarized reported LARS2 mutations in PRLTS4 (Table 1). Conservation analysis indicated that all reported mutations and p.Ile703 in this study were highly conserved across mammals, and 7 out of 11 of these mutations were highly conserved in non-mammals (Figure 2). Further, we conducted the three-dimensional structure modeling to infer the pathogenic effect of these two variants. In p.Glu294Lys, the Glu-to-Lys substitution replaced the carboxyl group with an amine group (Figure 3a,b). It was described as likely pathogenic based on functional prediction and segregation information by Kosaki et al. (2018). Another mutation p.Ile703Thr induced the increase of two hydrogen bonds, altering...
the interaction of residues p.Ile703, p.Thr699, p.Thr700, and p.Ala707 (Figure 3c,d). These results strongly indicated that the novel mutation c.2108T>C (p.Ile703Thr) was a disease-causing mutation.

4 | DISCUSSION

4.1 | Mechanism

The first essential step of protein translation is to covalently attach an amino acid to its cognate transfer RNA (tRNA), referred to as tRNA charging. This process is responsible for the fidelity of protein synthesis and catalyzed by aminoacyl-tRNA synthetases (aaRSs) specific for each particular tRNA (Antonellis & Green, 2008; Lee et al., 2003). The human mitochondrial genome is limited in size and contains genes encoding only 22 tRNAs, two rRNAs, and 13 polypeptides (all subunits of the inner mitochondrial membrane respiratory chain complexes). Thus, aaRSs family proteins are encoded in the nuclear genome, synthesized in the cytoplasm, and transported into the mitochondria, such as mitochondrial leucyl-tRNA synthetase (mtLeuRS) encoded by the nuclear gene LARS2 (Bullard, Cai, & Spremulli, 2000; Tiosano, Mears, & Buchner, 2019). Through the yeast complementation assay, Pierce et al. (2013) evidenced that homozygous
and compound heterozygous mutations in the LARS2 gene resulted in the reduced activity of mtLeuRS, leading to the inadequate mitochondrial function in the ovary and inner ear. The *C. elegans* strain with homozygous mutation in LARS2 produced no progeny at all, and the germ cell development was arrested. In mouse models, variants causing perturbations in mitochondrial protein translation had been shown to account for hearing loss because of tissue-specific apoptosis. Considering the role of apoptosis in ovarian development, accelerated or inappropriately timed apoptosis might explain ovarian features of Perrault syndrome (Pierce et al., 2013).

### 4.2 Molecular mapping

Mitochondrial leucyl-tRNA synthetase (mtLeuRS), encoded by the nuclear gene LARS2 at chromosome 3p21.3, is composed of 903-amino acids with a mitochondrial signal sequence (Li & Guan, 2010). The mtLeuRS belongs to the class I aminoacyl-tRNA synthetases which contains Rossmann fold defined as an adenylic-nucleotides recognition site (Bonnefond et al., 2005). And mtLeuRS consists of five major domains, namely catalytic, editing, leucine-specific, anticodon binding, and C-terminal domains (Figure 4), and two catalytically important motifs, called the HIGH sequence (p.Tyr92-p.Val102) and the KMSKS loop (p.Lys639-p.Ser643) which is responsible for the binding of the 3’ end of the tRNA during aminoacylation (Palencia et al., 2012; Soldà et al., 2015). The p.Thr522 is located in the catalytic domain and the residue sits at the N-terminal end of an α-helix which forms part of a pocket where the 3’ end of the tRNA strand binds. Therefore, the p.Thr522Asn substitution may change the position of the 3’ end of the tRNA, causing a reduction in aminoacylation efficiency. The mutation p.Thr629Met occurs in the leucine-specific domain, which is adjacent to the KMSKS loop, a critical catalytic loop. Replacing the small threonine side chain with a longer, more aliphatic methionine side chain might affect the ability of the KMSKS loop to take on an exposed position in the structure. The mutation p.Ile360fs is predicted to produce a truncated 373-amino-acid protein, causing the deletion of parts of the catalytic and editing domains, leucine-specific, and anticodon-binding domains, thus, it is unlikely that a functional protein would be yielded (Pierce et al., 2013). The mutation p.Thr300Met affects the pocket of the amino-acid binding in the editing domain, so that the substitution of threonine with methionine may either perturb the cleavage of the incorrectly paired aminoacyl-tRNA molecule or interfere with the discrimination of the cognate amino acid, probably resulting in the hydrolyzation of leucine from Leu-tRNALeu. Residue p.Glu638 is adjacent to the important KMSKS loop, and the p.Glu638 salt bridges with p.Lys644 at the other edge of KMSKS, possibly
TABLE 2  A review of physical features of PRLTS4

| Site       | Features                  | Frequency | Pierce et al. (2013) Family 1, proband | Pierce et al. (2013) Family 1, II-1 | Pierce et al. (2013) Family 2, proband | Pierce et al. (2013) Family 2, II-3 | Soldà et al. (2015) Proband | Soldà et al. (2016) Family 2, proband | Demain et al. (2016) Family 2, proband | Demain et al. (2016) Family 3, proband | Demain et al. (2016) III-1 | Lerat et al. (2017) Proband | Zerkaoui et al. (2017) Proband | Zerkaoui et al. (2017) III-5 | Kosaki et al. (2018) Proband | Kosaki et al. (2018) Patient 2 | This study Proband |
|------------|---------------------------|----------|----------------------------------------|--------------------------------------|----------------------------------------|-----------------------------------|---------------------------------|-----------------------------------|---------------------------------|---------------------------------|-----------------|-----------------|-----------------|----------------|-----------------|----------------|----------------|
| Ears       | Sensorineural hearing loss| 17/17    | +                                      | +                                    | +                                      | +                                  | +                               | +                                 | +                               | +                               | +               | +               | +               | +              | +               | +              |
|            | Upsloping audiograms     | 10/17    | +                                      | +                                    | -                                      | -                                  | +                               | +                                 | +                               | -                               | -               | -               | -               | -              | +               | -              |
| Ovaries    | Ovarian dysgenesis       | 6/11     | +                                      | M                                    | M                                      | +                                  | M                               | M                                 | -                               | +                               | M               | +               | +               | +              | -               | -              |
|            | Small ovaries            | 2/11     | -                                      | M                                    | M                                      | -                                  | M                               | M                                 | -                               | -                               | -               | -               | -               | -              | -               | -              |
| Uterus     | Small uterus             | 5/11     | +                                      | M                                    | M                                      | -                                  | M                               | M                                 | -                               | +                               | M               | -               | -               | -              | -               | -              |
|            | Bicornuate uterus        | 1/11     | -                                      | M                                    | M                                      | +                                  | M                               | M                                 | -                               | -                               | M               | -               | -               | -              | -               | -              |
|            | Hypotrophic uterus       | 2/11     | -                                      | M                                    | M                                      | -                                  | M                               | M                                 | -                               | -                               | M               | +               | -               | -              | -               | -              |
| Endocrine  | Increased gonadotropin   | 10/11    | +                                      | M                                    | M                                      | +                                  | M                               | M                                 | +                               | +                               | M               | +               | +               | +              | +               | +              |
|            | levels                   |          |                                        |                                        |                                        |                                    |                                 |                                    |                                 |                                 |                               |                 |                 |                 |                 |                 |                 |
|            | Low estradiol            | 3/11     | -                                      | M                                    | M                                      | +                                  | M                               | M                                 | -                               | M                               | -               | -               | +               | +              | -               | -              |
|            | Primary amenorrhea       | 6/10     | +                                      | M                                    | M                                      | -                                  | M                               | M                                 | +                               | +                               | M               | +               | U               | +              | -               | -              |
|            | Secondary amenorrhea     | 2/10     | -                                      | M                                    | M                                      | 19                                 | 28                               | M                                 | -                               | M                               | -               | -               | M               | U              | -               | -              |
|            | onset (years)            |          |                                        |                                        |                                        |                                    |                                 |                                    |                                 |                                 |                               |                 |                 |                 |                 |                 |                 |
|            | Oligomenorrhea           | 2/10     | -                                      | M                                    | M                                      | -                                  | M                               | M                                 | +                               | M                               | -               | M               | -               | U              | -               | -              |
| Neurology  | Delayed motor development| 2/17     | -                                      | -                                    | -                                      | -                                  | -                               | -                                 | -                               | -                               | -               | +               | +               | -              | -               | -              |
|            | Cognitive impairment     | 2/17     | -                                      | -                                    | -                                      | -                                  | -                               | -                                 | -                               | -                               | -               | +               | +               | -              | -               | -              |
|            | Ataxic gait              | 1/17     | -                                      | -                                    | -                                      | -                                  | -                               | -                                 | -                               | -                               | -               | +               | +               | -              | -               | -              |
|            | Tic                      | 1/17     | -                                      | -                                    | -                                      | -                                  | -                               | -                                 | -                               | -                               | -               | -               | -               | +              | -               | -              |
| Growth     | Marfanoid habitus        | 3/17     | -                                      | -                                    | -                                      | -                                  | -                               | -                                 | -                               | +                               | +               | -               | -               | +              | -               | -              |
|            | Hemidystrophy            | 1/17     | -                                      | -                                    | -                                      | -                                  | -                               | -                                 | -                               | -                               | -               | -               | -               | -              | -               | -              |
|            | Obesity                  | 1/17     | -                                      | -                                    | -                                      | -                                  | -                               | -                                 | -                               | -                               | -               | -               | -               | +              | -               | -              |

(Continues)
making for the full closure of KMSKS and the stabilization of the closed conformation (Soldà et al., 2015). All the variants p.Glu294Lys, p.Arg453Gln, and p.Thr519Met are within the editing domain of mtLeuRS which is responsible for the fidelity mechanisms of aaRSs (Kosaki et al., 2018). Moreover, both variants p.Met117Ile and p.Asn153His are in the catalytic domain. In our study, the novel mutation p.Ile703Thr is speculated to occur between the catalytic and anticodon-binding domains, inducing the increase of two hydrogen bonds which would alter the interaction of residues p.Ile703, p.Thr699, p.Thr700, and p.Ala707.

### 4.3 Natural history of PRLTS4

Pierce et al. (2013) first identified homozygous and compound heterozygous mutations in the *LARS2* gene in two families with Perrault syndrome. Soldà et al. (2015) described two novel disease-causing variants in *LARS2* in an Italian pedigree, providing the first independent replication of *LARS2* involved in the pathogenesis of Perrault syndrome. It was demonstrated that *HARS2*, *LARS2*, *CLPP*, and *TWNK* were nuclear genes encoding mitochondrial proteins, pointing to an important role for mitochondria in maintaining normal hearing and ovarian function. Demain et al. (2016) proposed that the variant p.Thr522Asn might be associated with the uncommon pattern of low-frequency hearing loss, and Perrault syndrome could be split into two classifications, type I with no additional neurological features and type II with neurological features. Lerat et al. (2016) illustrated that mutations in *HARS2* and *LARS2* are associated with Perrault syndrome type I, and the disruption of mitochondrial translation had previously been linked to progressive sensorineural hearing loss. Subsequently, Kosaki et al. (2018) reported two Perrault syndrome patients with biallelic mutations in *LARS2*, who exhibited neurological symptoms, and thus, should be classified as Perrault syndrome type II. Two siblings with marfanoid habitus reported by Zerkaoui et al. (2017) showed long faces, thin fingers, high-arched palates, and marfanoid body proportions. Al-Jaroudi, Enabi, and AlThagafi (2019) discussed a case of PRLT4 female with amenorrhea, infertility, Tarlov cyst, and degenerative disc, first reporting a case involving the spine.

Almost all reported cases have sensorineural hearing loss, increased gonadotropin levels, and amenorrhea (Table 2). Besides, all individuals with the variant p.Thr522Asn, whether homozygous or compound heterozygous, are associated with the uncommon pattern of low-frequency hearing loss manifested as upsloping audiograms. Therefore, it was believed that the variant p.Thr522Asn might be a hotspot and appeared to be a specific genotype–phenotype correlation linked to this unusual audiological pattern (Zerkaoui et al., 2017). The proband in our study who
carries compound heterozygous mutations p.Glu294Lys and p.Ile703Thr also shows upsloping audiograms, but patients with the mutation p.Glu294Lys was reported no upsloping audiogram by Kosaki et al. (2018). Therefore, we speculate that the novel mutation p.Ile703Thr could be linked to the uncommon pattern of low-frequency hearing loss. Patient 2 reported by Kosaki et al. (2018) was excluded from the comparison of amenorrhea due to receiving estrogen supplementation prior to menarche considering the family history. One patient reported by Demain et al. (2016) and the proband in this study have oligomenorrhea, which means they are in the early stage of POI and will later progress to secondary amenorrhea and the end-stage of ovarian failure named premature ovarian failure. The severity of ovarian dysfunction is variable in PRLTS4 and there seems to be no distinct genotype–phenotype correlations with \( LARS2 \) gene (Zerkaoui et al., 2017). Audiological and endocrine examinations should be performed regularly because PRLTS4 is characterized by SNHL and POI. More than half of patients in Table 2 perform the hypogenesis of ovaries and uterus, implying the important role of ultrasound. A few patients have neurological and skeletal features, hence, the magnetic resonance imaging and X-rays should be considered. The variants in \( LARS2 \) were also identified in patients with hydrops, lactic acidosis, sideroblastic anemia, leukodystrophy, and diabetes, indicating that the relevant examinations should be included (Riley et al., 2015). Owing to the variable phenotypes of PRLTS4, more patients are required before further defining genotype–phenotype correlations.

### 4.4 Treatment

In Table 3, the SNHL is bilateral and sometimes progressive, and the onset of PRLTS4 is mostly in early childhood or at birth. Apparently, the majority of interventions are cochlear implants. It is widely accepted that cochlear implants could be considered in patients with PRLTS4, who are cooperative enough to receive extensive training by speech therapists (Kosaki et al., 2018). However, only Soldà et al. (2015) described the postoperative effects of cochlear implants. Two siblings with congenital profound SNHL got normal speech development after receiving bilateral cochlear implants. Therefore, we believe that more long-term postoperative follow-up is in need to reach a clearer understanding of the effect of cochlear implantation in PRLTS4 patients. Because of the uncommon pattern of low-frequency hearing loss, patients most likely have difficulty adapting to the hearing aids. For the proband in our study, she copied poorly with hearing aids and SNHL has been progressive to severe, thus, cochlear implants seem to be a practical option next. Regarding ovarian insufficiency, patients who have primary amenorrhea in adolescence can use hormone replacement therapy to induce puberty. Female patients with gonadal dysgenesis can only choose the assisted reproduction through in vitro fertilization using donor eggs. In addition, females at risk for POI are

| Previous publications | SNHL degree | Age at SNHL onset (years) | Progression | Interventions |
|-----------------------|-------------|---------------------------|-------------|---------------|
| Pierce et al. (2013) Family 1, proband | L: mild R: severe | 3–5 | Y | No hearing aid used |
| Pierce et al. (2013) Family 1, II–1 | Severe | 3–5 | NA | NA |
| Pierce et al. (2013) Family 1, II–3 | Severe | 3–5 | NA | NA |
| Pierce et al. (2013) Family 2, proband | Severe | NA | NA | NA |
| Soldà et al. (2015) Proband | Profound | Congenital | NA | Bilateral cochlear implants |
| Soldà et al. (2015) II–1 | Profound | Congenital | NA | Bilateral cochlear implants |
| Demain et al. (2016) Family 2, proband | Moderate to severe | 8 | Y | Unilateral cochlear implant |
| Demain et al. (2016) Family 2, II–2 | NA | 26 | NA | NA |
| Demain et al. (2016) Family 3, proband | Severe to profound | 2.5 | Y | Unilateral cochlear implant |
| Demain et al. (2016) Family 3, II–2 | Severe to profound | 2.5 | Y | NA |
| Lerat et al. (2016) Patient III–1 | Moderate | <3 | N | NA |
| Zerkaoui et al. (2017) Proband | Moderate to profound | 6 | Y | Unilateral hearing aid |
| Zerkaoui et al. (2017) III–5 | Moderate to profound | 16 | Y | Unilateral hearing aid |
| Kosaki et al. (2018) Proband | Profound | 1.5 | NA | NA |
| Kosaki et al. (2018) Patient 2 | Profound | Congenital | NA | NA |
| Al-Jaroudi et al. (2019) Proband | NA | Congenital | NA | NA |

Abbreviations: L, left; N, no; NA, not available; PRLTS4, Perrault syndrome 4; R, right; SNHL, sensorineural hearing loss; Y, yes.
supported to consider the oocyte cryopreservation. Thus, the proband in this study is recommended oocyte cryopreservation as early as possible.

4.5 | Prevention

As a rare autosomal recessive disorder, if both parents are carriers of LARS2 mutations, their children have a 25% probability of being affected, a 50% probability of being an asymptomatic carrier, and a 25% probability of being unaffected and not a carrier. Each sibling of the proband’s parents has a 50% risk of being a carrier of a LARS2 pathogenic variant. The proband in our study and her future spouse are recommended to have genetic counseling. Preimplantation genetic diagnosis may help the proband’s parents to avoid the risk of having another PRLTS4 child. PRLTS4 can be easily misdiagnosed as nonsyndromic hearing loss, so that the vigilance on the diagnosis of such rare disorders ought to be encouraged. Genetic testing is of benefit to the early diagnosis of PRLTS4, and the clinical genetic evaluation is vital to guide prevention.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS APPROVAL

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Zhengzhou University (reference number 2018008).

AUTHOR CONTRIBUTIONS

Wei Lu and Wenxue Tang genetic counseling and study design. Zhaoyu Pan and Hongen Xu information collection, data analysis, draft and revision of the manuscript. Yongan Tian, Danhua Liu, Huafei Liu, and Ruijun Li whole-exome sequencing, Sanger sequencing, and variant classification. Qian Dou, Bin Zuo, and Ronggun Zhai phenotypic analysis. All authors have read and approved the final manuscript.

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