

CLINICAL REPORT

Novel homozygous nonsynonymous variant of *CNNM4* gene in a Chinese family with Jalili syndrome

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Abstract

Background: Jalili syndrome (JS) is a rare autosomal-recessive inherited disorder characterized by cone-rod dystrophy and amelogenesis imperfecta. It is often misdiagnosed in clinical practice due to its heterogeneity and rarity.

Methods: Two JS patients from a consanguineous family were included in this study. Detailed ophthalmic examinations were performed. Oral photography was taken. The DNA sample of the proband was sequenced using the customized capture panel, which includes 338 retinal disease genes. Sanger sequencing was performed for validation and segregation.

Results: The patients had poor vision, photophobia, and nystagmus from childhood. Fundus examination revealed diffused chorioretinal atrophy with a prominent macular coloboma. OCT showed a deep staphyloma, severely reduced retinal thickness, retinoschisis, loss of photoreceptor layer, and retinal pigment epithelium in the macular region. Amelogenesis imperfecta, dental decay, staining, irregular shapes, and loss of teeth were present. Next-generation sequencing combined with Sanger validation identified a novel homozygous nonsynonymous variant c.598T>C (p.S200P) in *CNNM4* gene (NM_020184.3).

Conclusions: We described the clinical features of a Chinese family with JS and identified a novel disease-causing mutation. Our findings broadened the phenotypes and mutation spectrums of JS in Chinese population, as well as are helpful in the diagnosis of this rare disease.

KEYWORDS

amelogenesis imperfecta, *CNNM4* gene, cone-rod dystrophy, Jalili syndrome

1 | INTRODUCTION

Jalili syndrome (JS) (OMIM # 217080), first described by Jalili and Smith in 1988 in a large Arab consanguineous family in Gaza strip, is a rare autosomal-recessive inherited disease (Jalili & Smith, 1988). It has also been reported in

Moroccan, Iranian, Polish, Kosovan, American, Turkish, Scotland, Lebanon, Guatemalan, Brazilian, Indian, and Chinese populations (Maia et al., 2018; Parry et al., 2009; Polok et al., 2009; Prasov et al., 2020; Purwar et al., 2015; Wang et al., 2015; Xu et al., 2015). The characteristic features of Jalili syndrome are Cone-rod dystrophy (CRD) and

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amelogenesis imperfecta (AI) (Daneshmandpour et al., 2019). CRD is characterized by severely reduced visual acuity, photophobia, loss of color vision, and nystagmus from childhood or early adulthood, due to the predominant dysfunction of cones (Hamel, 2007). Patients with Jalili syndrome may experience night blindness as rods are gradually involved (Michaelides et al., 2004). Progressive chorioretinal atrophy and prominent maculopathy are main ophthalmic findings. AI comprises a group of heterogeneous developmental dental conditions, including hypoplastic and/or hypomineralized tooth enamels, structural, and morphological abnormalities of tooth enamels, staining, and loss of teeth (Aldred et al., 2003).

Jalili syndrome is caused by pathogenic variants of *CNNM4* gene, which is located at 2q11.2 (Polok et al., 2009). *CNNM4* was predominantly expressed in various ocular tissues and teeth, with the highest level in retina and ameloblasts (Parry et al., 2009; Polok et al., 2009). The protein encoded by *CNNM4* is hypothesized to be involved in metal ions transport and homeostasis, particularly magnesium, which is crucial for the proper function of photoreceptors and teeth (Guo et al., 2005; Parry et al., 2009). To date, a total of 34 pathogenic variants in *CNNM4* have been identified (Human Gene Mutation Database, HGMD <http://www.hgmd.cf.ac.uk/ac/index.php>), consisting of 21 missense mutations (61.8%), 6 small deletions (17.6%), 3 small inserts (8.8%), 3 gross variants (8.8%), and 1 splice-site variant (2.9%).

So far, Jalili syndrome has been reported in approximately 34 families around the world, among which only one case was with Chinese ethnicity (Maia et al., 2018; Prasov et al., 2020; Wang et al., 2015). In the present study, we described the detailed clinical manifestations of a Chinese family with Jalili syndrome and investigated the underlying genetic defect.

2 | MATERIALS AND METHODS

2.1 | Clinical evaluation and DNA preparation

A consanguineous family initially diagnosed as Leber congenital amaurosis (LCA) was identified at the ophthalmic clinic at the First Affiliated Hospital of Fujian Medical University, Fuzhou, China. Detailed medical and family histories were taken. The two affected subjects underwent ophthalmic evaluations, including best corrected visual acuity (BCVA) according to the decimal Snellen E chart, slit-lamp biomicroscopy, dilated funduscopy, optical coherent tomography (OCT; Carl Zeiss), and ocular B-ultrasonography. The study protocol was approved by the Institutional Review Board of the First Affiliated Hospital

of Fujian Medical University and adhered to the tenets of the Declaration of Helsinki. Informed consents were obtained from all subjects. Genomic DNA was isolated from peripheral blood with the QIAamp DNA Blood Midi Kit (Qiagen) according to the manufacturer's protocol.

2.2 | Capture sequencing, data analysis, and Sanger verification

Pre-capture Illumina libraries were generated as in previous literature (Fu et al., 2013). Illumina adapters were ligated to the repaired ends and DNA fragments were polymerase chain reaction (PCR) amplified for eight cycles after ligation. The targeted DNA was captured by a customized panel including 338 retinal disease genes. Captured libraries were sequenced on Illumina HiSeq 2000 (Illumina) according to the manufacturer's protocol. Paired-end sequencing reads were mapped to human reference genome hg19 using Burrows-Wheeler Aligner. Base quality recalibration, local realignment, and variant calling were performed as previously described (Fu et al., 2013). We obtained the variant frequencies from a series of public and internal control databases as well as the Exome Aggregation Consortium (ExAC) database. Variant frequencies >0.5% were filtered out. After frequency-based filtering, we filtered out synonymous variants, identified known retinal disease-causing variants according to HGMD professional database (version 2021/02) and predicted the pathogenicity of variants using sorting intolerant from tolerant (SIFT), Polyphen2, likelihood ratio test, and Mutation Taster as previously described (Fu et al., 2013; Xu et al., 2015).

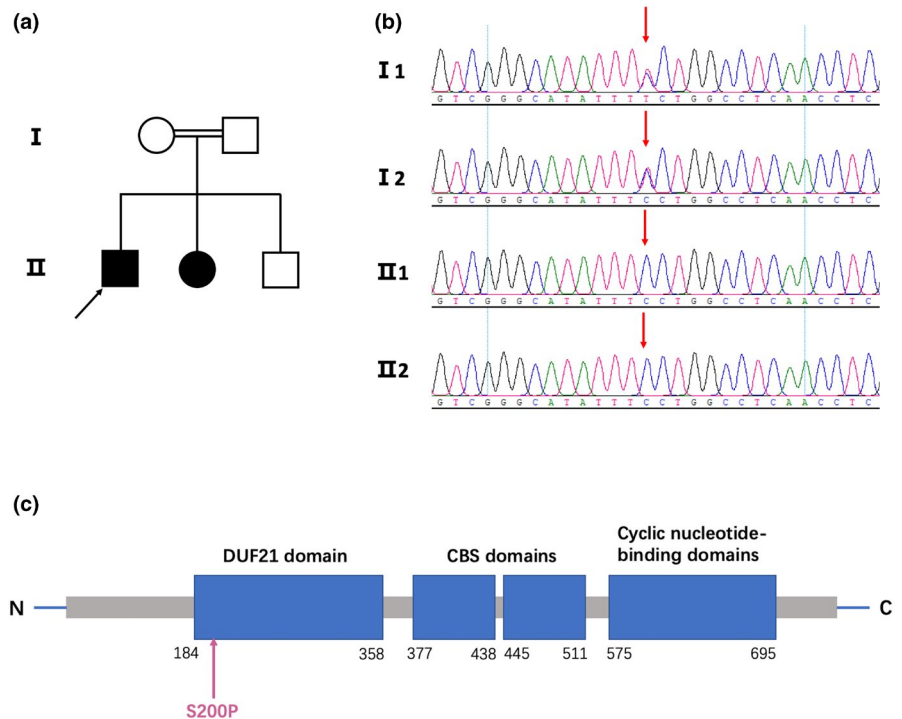
The causative pathogenic variants were validated and co-segregated by Sanger sequencing. Primers were designed by Primer 3 (<https://bioinfo.ut.ee/primer3-0.4.0/>). The PCR amplicons were sequenced using forward and reverse primers on an ABI 3730 Genetic Analyzer (ABI). The sequences were assembled and analyzed using Lasergene SeqMan software (DNASTAR). The results were compared with the *CNNM4* transcript (GenBank Accession No. NM_020184.3).

3 | RESULTS

3.1 | Clinical evaluation

The proband was a 45-year-old male from a consanguineous family (Figure 1a). He had poor vision and nystagmus from childhood, with no obvious difference between day and night. He experienced photophobia since 8 years old. On examination, his visual acuity was light perception, both eyes. Refractive error was undetectable due to

FIGURE 1 Pedigree and *CNNM4* variant of the JS family. (a) The pedigree of the JS family. Squares indicate men; circles indicate women; black indicates affected subjects; black arrow indicates proband. (b) The electropherograms of the JS family. Two patients (II1 and II2) carried the same homozygous c.598T>C variant, their parents (I1 and I2) both carried the heterozygous c.598T>C variant. Red arrow indicates the variant. (c) THE schema of *CNNM4* showing protein domains and the location of the variant. The purple arrow indicates the variant; the three-digit numbers indicate the numbers of residues



the opaque lens. Cataracts were observed in both eyes, with severe posterior capsular opacification. Dilated funduscopy revealed diffused chorioretinal atrophy with a prominent macular coloboma. Pigment clumps were scattered around mid-peripheral retina (Figure 2a,b). OCT showed a coloboma, severely reduced retinal thickness, retinoschisis, loss of photoreceptor layer, and retinal pigment epithelium in the macular region (Figure 2c). B-ultrasonography demonstrated a deep staphyloma in the posterior pole, both eyes (Figure 2d,e). The proband complained of dental decay and teeth loss from childhood, and underwent full dental implant when he was 20 years old.

The proband's affected sister (II2) was a 40-year-old female. She had poor vision, photophobia, and nystagmus from childhood. Her visual acuity was light perception in both eyes when she was referred to our clinic. The ocular manifestations and severity were similar to the proband, as shown in Figure 2f-i. Oral photography showed amelogenesis imperfecta, dental decay, staining, irregular shapes, and loss of teeth (Figure 3).

The ocular axial length by A-scan ultrasonography was unable to perform due to nystagmus and poor cooperation. No other systemic abnormalities such as polydactyly, hearing loss, and mental retardation were identified in the two patients.

3.2 | Genetic analysis

Next-generation sequencing (NGS) together with Sanger sequencing identified a novel homozygous

nonsynonymous variant c.598T>C (p.S200P) in *CNNM4* (NM_020184.3), which was co-segregated in this pedigree (Figure 1b). This nonsynonymous variant was classified as “likely pathogenic” according to the criteria of ACMG standards (Richards et al., 2015) (PM2, PM5, PP1, PP3, and PP4). It was not found in 1000 Genomes, gnomAD, and ExAC database, and predicted as “damaging” by SIFT (score 0.006), “probably damaging” by Polyphen2 (score 0.993), and “disease-causing” by Mutation Taster (score 1.00). The conservation score is 6.843, which was predicted as “conserved” by PhyloP. The variant is located in DUF21 domain of *CNNM4* protein, as shown in Figure 1c.

4 | DISCUSSION

Cone-rod dystrophy is a heterogeneous group of inherited retinal degenerations characterized by predominant loss of cone function, followed by progressive loss of rod function. CRD could be an independent ocular disease, or a syndromic disorder involving multiple tissues and organs, such as Alström syndrome, and some forms of Bardet-Biedl syndrome (Hamel, 2007; Khan et al., 2016; Liang et al., 2013). Jalili syndrome is a rare oculo-dental disorder characterized by CRD and AI. The patients in our study presented these two typical features of Jalili syndrome. The ocular manifestations of the proband and his 5-year younger sister shared a similar severity. They both had poor vision and photophobia from childhood. None of them experienced night blindness. Their visual acuities were both light perception. Ophthalmic examinations

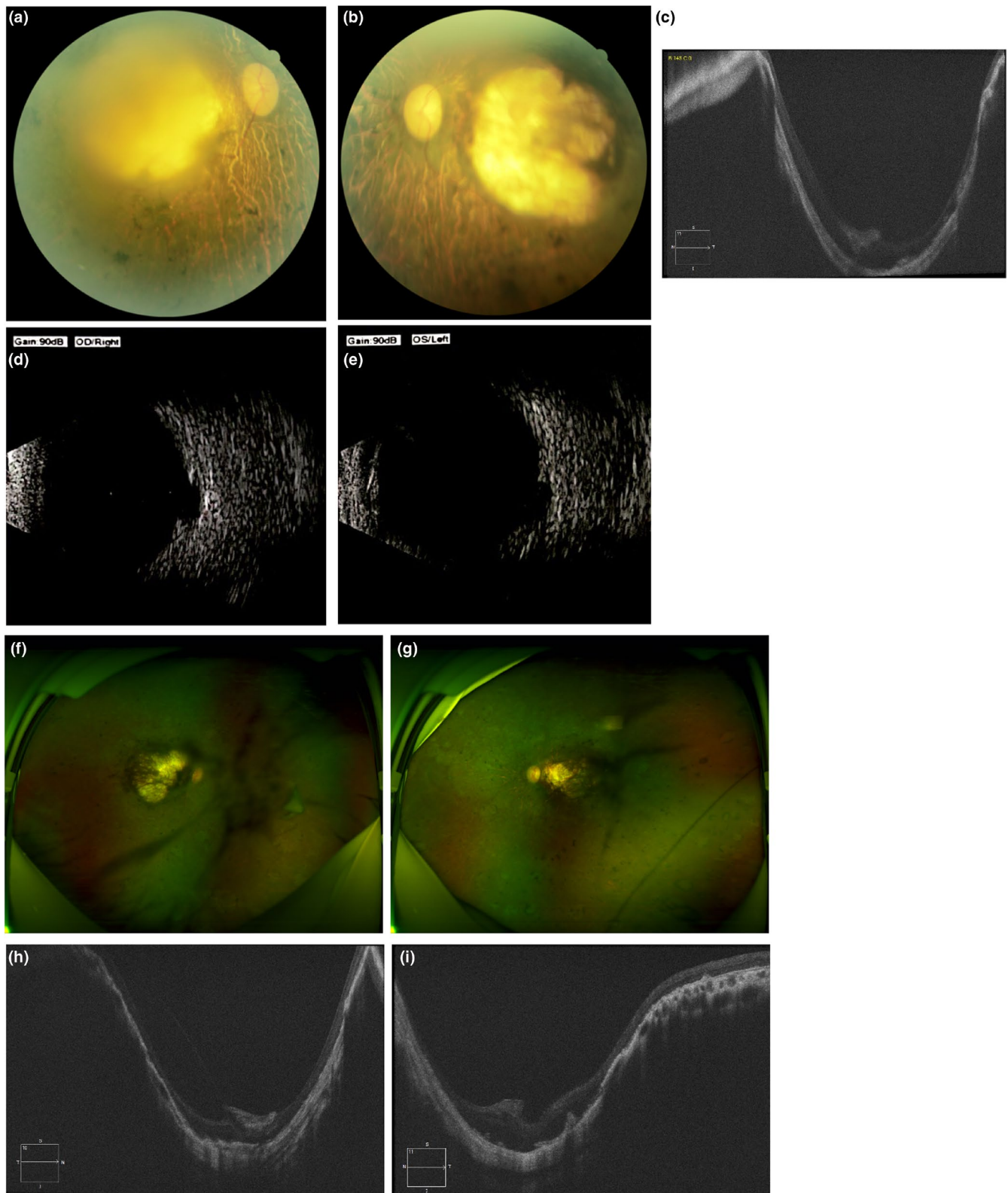
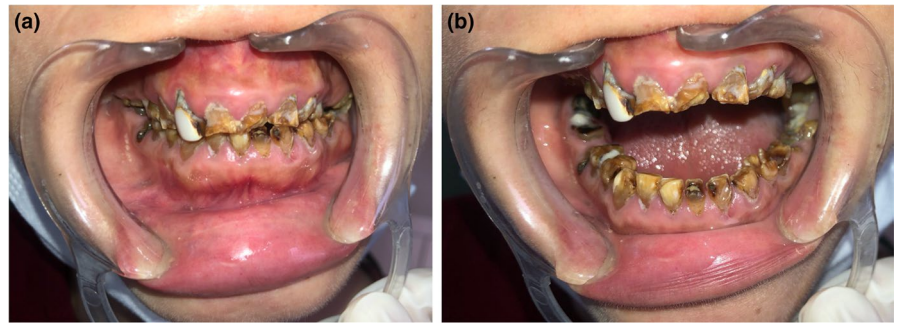


FIGURE 2 Fundus photographs, OCT, and B-scan ultrasonography of the JS family. Fundus photographs of II1 (a–b) and II2 (f–g): Diffused chorioretinal atrophy with a prominent macular coloboma. Pigment clumps were scattered around mid-peripheral retina. The images are opaque due to posterior capsular cataracts. OCT images of II1 (c) and II2 (h,i): OCT showed a coloboma, severely reduced retinal thickness, retinoschisis, loss of photoreceptor layer, and retinal pigment epithelium in the macular region, both eyes. B-scan images of II1 (d, e): B-ultrasonography demonstrated a deep staphyloma in the posterior pole, both eyes

FIGURE 3 Oral photography of II2: Amelogenesis imperfecta, dental decay, staining, irregular shapes, and loss of teeth



revealed nystagmus, posterior capsular cataracts, extensive chorioretinal atrophy with a distinct macular coloboma. According to previous literatures, visual acuity of the patients with JS was poor, ranging from no light perception to 20/100, generally no more than 20/200 (Jalili & Smith, 1988; Parry et al., 2009; Polok et al., 2009). Refractive error was unavailable due to the opaque lens of the two patients in this study. In other literatures, mild to moderate hyperopia, and posterior capsular cataracts were common among JS patients (Rahimi-Aliabadi et al., 2016; Wawrocka et al., 2017). In addition, strabismus and keratoconus were reported in a few cases (Maia et al., 2018; Purwar et al., 2015).

Another remarkable feature of JS is AI, which is marked by abnormal formation of the enamel. It composes of a spectrum of structural and morphological abnormalities, including hypoplastic and/or hypomineralized enamels, irregular dentition, staining, cavities, and eventual loss of teeth. II2 displayed typical dental abnormalities of JS. Her affected brother shared similar dental conditions and he underwent full teeth implant at the age of 20. No other systemic abnormalities have been found in these two patients. Besides dental abnormalities, mild myopathy with muscular overgrowth in legs and situs inversus were reported in one family, respectively (Purwar et al., 2015; Wawrocka et al., 2017). Whether they are novel manifestations of JS remain to be further investigated.

JS is a disorder with high phenotypic and genotypic heterogeneity between families. Based on phenotypic features, JS was proposed to be classified into two clinical types (Jalili, 2010). Type A was characterized by an infancy onset form with progressive macular lesion and Peripheral pigmentary clumping. Type B was characterized by an early childhood-onset form with normal fundus. As recorded by electroretinograms (ERGs), photopic responses were more severely impaired in type-A patients, while rod functions were more preserved in early stage of the disease. Macular lesions in type-A JS varied from atrophic macular degeneration to coloboma (Gerth-Kahlert et al., 2015; Hirji et al., 2018; Purwar et al., 2015). Based on the fundus appearance, it is obvious that the patients in our study belonged to type-A JS. Furthermore,

the atrophic macula and macular coloboma seemed more severe compared with other type-A JS patients reported in previous literatures (Cherkaoui Jaouad et al., 2017; Jalili, 2010; Li et al., 2018). Currently, no genotypic correlations have been identified between these two distinct clinical types (Hirji et al., 2018; Jalili, 2010). Notably, intra-familial phenotypic variability exists even with the same variant in the same family (Gerth-Kahlert et al., 2015). It is speculated that there might be modifier factors regulating the phenotypic expression of JS.

Due to its heterogeneity and rarity, JS is often misdiagnosed as other hereditary retinal degenerations in clinical practice, such as LCA, CRD, and achromatopsia (Doucette et al., 2013; Wawrocka et al., 2018). Notably, the majority of which was initially clinically diagnosed as LCA, as well as our case (Wang et al., 2015; K. Xu et al., 2020). The ocular findings of type-A JS mimic some forms of LCA, such as *RDH12* and *CRB*-related LCA (Huang et al., 2021). Patients of these two genotypes of LCA are featured by atrophic maculopathy. But few patients complain of photophobia, and their teeth are normal. *GUCY2D*-related LCA or CRD shared some similarities with type-B JS (Liu et al., 2020). Most of them had impaired vision, photophobia, and a normal-looking fundus, but the dental conditions are normal. It is worth noting that when checking patients with hereditary retinal degenerations, systemic abnormalities should not be ignored. Careful history-taking and a basic assessment of facial, dental, skeletal, genitourinary, and neurological systems are helpful for accurate diagnosis.

Genetic testing is vital for the final diagnosis of hereditary retinal degenerations. NGS plus Sanger validation revealed a novel homozygous deleterious variant c.598T>C in *CNNM4* gene in this pedigree. The nucleotide change is located in exon 1 of *CNNM4*, causing the replacement of serine with proline (p.S200P) in the DUF21 domain. It is hypothesized to generate the damaged *CNNM4* protein which would cause abnormal metal ions transport, particularly magnesium, and destruct the proper function of photoreceptors and enamel mineralization (Guo et al., 2005; Luder et al., 2013). Parry et al reported a Gaza JS family carried a pathogenic

variant affecting the same amino acid (c.599C>A, p.S200Y), but with a milder ocular phenotype (Parry et al., 2009). To date, only one Chinese JS patient was reported (Wang et al., 2015). She was an 8-year-old girl who had poor vision from childhood, with BCVA of 20/200. Fundus examination showed severe macular atrophy and scattered bone spicule pigmentation, belonging to type-A JS. Molecular screening identified a homozygous frameshift variant in *CNNM4* gene (c.897dupT, p.A300Cfs*22). Amelogenesis imperfecta and irregular teeth shapes were present, but much milder than our patients, probably due to her young age. Long-term follow-up is needed to investigate the natural course of JS.

In summary, we described the detailed clinical manifestations of a Chinese family associated with JS and identified a novel homozygous nonsynonymous pathogenic variant in *CNNM4* gene. Our findings broadened the phenotypes and mutation spectrum of JS in Chinese population, as well as are helpful in the diagnosis of this rare disorder.

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CONFLICT OF INTEREST

The authors have no disclosures or other conflicts of interest to report.

AUTHOR CONTRIBUTIONS

HL and MX conceived and designed the study; JL and YH conducted the experiments; HL collected and analyzed the data; HL wrote the manuscript; All authors reviewed and approved the manuscript.

ETHIC STATEMENT

This study was approved by the Institutional Review Board of the First Affiliated Hospital of Fujian Medical University. All the participants signed informed consent allowing the publication of the relevant information.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author upon request.

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