

First Chinese patient with mental retardation-40 due to a *de novo* CHAMP1 frameshift mutation: Case report and literature review

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Abstract. Mental retardation-40 (MRD40) is a rare autosomal dominant neurodevelopmental disorder with a poor prognosis that is caused by a heterozygous mutation in chromosome alignment maintaining phosphoprotein 1 (CHAMP1). It was previously considered a non-syndromic disease due to the lack of specific external features. Only limited international reports describing CHAMP1 mutations are currently available. The present case study was the first to report on a Chinese patient with MRD40. The patient presented with severe global development delay with significant craniofacial dysmorphism. Using trio whole-exome sequencing, a novel *de novo* frameshift mutation in CHAMP1, NM_032436.2: c.530delCinsTTT, was identified, which expands the spectrum of the known pathogenic variants. The present case report helps to improve the syndromic profile of the rare MRD40 disorder and provides an example for the clinical diagnosis of MRD40.

Introduction

Autosomal dominant intellectual disability (ID), previously known as mental retardation, is a series of Mendelian neurodevelopmental disorders that result in ID (1), and most of the cases are caused by *de novo* heterozygous mutations in >50 genes [one gene per case; Mendelian Inheritance in Man (MIM) phenotypic series no. PS156200] and have a sporadic epidemiology. In general, patients with a global development delay (GDD), which is defined as failure to achieve developmental milestones within the expected age range in at least two realms of development (2), have an increased risk

of developing ID, with an incidence of 1-3%, as they have altered development of cognitive and adaptive functions (3). In addition, ID has been classified into syndromic intellectual disability (S-ID) and non-S-ID (NS-ID), and NS-ID has been traditionally defined by the presence of ID as the sole clinical feature. Thus, the diagnosis of a dominant NS-ID is much more difficult in clinical practice.

The Deciphering Developmental Disorders (DDD) Study (4) first identified heterozygous mutations in the chromosome alignment maintaining phosphoprotein 1 (CHAMP1) gene that caused a type of GDD/ID named autosomal dominant mental retardation-40 (MRD40; MIM no. 616579), and the disorder was previously known as NS-ID (Orphanet no. 178469) due to the lack of more subtle neurological anomalies and psychiatric disorders shared by the patients. As more MRD40 cases have been described (5), a better understanding of the disease is on the horizon; however, genetic testing is now the only method to diagnose MRD40.

The present study reported on a Chinese pediatric patient diagnosed with MRD40 due to a CHAMP1 truncating mutation identified by whole-exome sequencing (WES). A practical online workflow of a comprehensive trio WES analysis was used in the present study, as recommended by the DDD study (6).

Case study

The patient was a four-month-old male admitted to the Third Affiliated Hospital of Zhengzhou University (Zhengzhou, China) due to delayed development. His anomalies in appearance included a tented upper lip, a high-arched palate and open-mouth appearance (Fig. 1A), hypertelorism, low-set ears (Fig. 1B) at the age of 4 months. At 9 months these included sparse hair in general and microcephaly [occipitofrontal circumference (OFC), 42.5 cm which was between -3 and -2 standard deviation (SD) compared with a normal population] (7) (Fig. 1C). The neurological examination (8) revealed hypotonia, poor attention and no active grasping consciousness. According to the Griffiths Development Scales-Chinese (8), all developmental parameters of the patient were equal to infants aged 1.5 months, indicating severe GDD.

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The patient was the first-born child and delivered by full-term, natural labor, and a family history of diseases in the neurological system was not present.

Laboratory tests indicated slightly elevated urine oxalic acid, succinic acid and glyceric acid levels; brain MRI revealed symmetric enlargement in the bilateral lateral ventricle (Fig. 2), and an 8-h video electroencephalography test was unremarkable.

The patient was provided with proper rehabilitation training, but at the age of 1 year and 3 months, the patient still had difficulties acquiring language skills and was not able to stand up by himself. In addition, the patient was monitored continuously. The patient displayed a severe developmental delay at the age of 9 months with microcephaly (Fig. 1C). The reexamination of organic acid levels in urine provided normal results. At the time writing of the present study, the patient was 1 year and 3 months old with an OFC of 45 cm (-2 SD~-1 SD) and a body length of 67 cm (<-3 SD). The average body length of a child of this age was 79.1±5 cm (7) but the weight of the patient was within the normal range (11 kg). The patient was unable to communicate with his family, in contrast to other children of the same age; he still had difficulty acquiring language skills and was not able to stand by himself.

Materials and methods

Methods. EDTA-treated peripheral blood samples for the trio-WES analysis were collected from the patient and the patient's parents to detect germline variation. Genomic DNA was extracted from blood samples using the Blood Genome Column Medium Extraction Kit (Kangweishiji). Protein-coding exome enrichment was performed using xGen Exome Research Panel v1.0 (Integrated DNA Technologies), which consists of 429,826 individually synthesized and quality-controlled probes that target a 39-Mb protein-coding region (19,396 genes) of the human genome and cover 51 Mb of end-to-end tiled probe space. High-throughput sequencing was performed using an Illumina NovaSeq 6000 series sequencer (PE150; Illumina, Inc.). The sequencing process was performed by the Beijing Chigene Translational Medicine Research Center Co., Ltd. Variants were called and files in binary alignment map format were screened for insertions/deletions and recalibrated using The Genome Analysis Toolkit (9). Sequenced data were aligned to the reference human genome (hg19; <http://genome.ucsc.edu/index.html>) and no control sample was used.

After sequencing, the data were processed using the Illumina DNA sequencing data analysis pipeline (<https://www.illumina.com/informatics/sequencing-data-analysis/dna.html>) and sequencing data and phenotypes were normalized. Human Phenotype Ontology terms were uploaded to the cloud platform for the genetic disease analysis system (<http://www.chigene.org>). The data, including pathogenicity of variants, inheritance type and phenotypes, were determined using a protocol similar to that in the DDD study (10) with the Chigene® system, followed by manual screening by physicians.

Literature review. For the literature review, the PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Online MIM (OMIM; <https://omim.org/>), Orphanet (<https://www.orpha.net/consor/>

cgi-bin/index.php), The Genetic and Rare Diseases Information Center (<https://rarediseases.info.nih.gov/>), Genetics Home Reference (<https://ghr.nlm.nih.gov/>), GeneReviews (<https://www.ncbi.nlm.nih.gov/books/NBK1116>) and Wanfang (Chinese, <http://www.wanfangdata.com.cn/>) databases were searched using the key words 'CHAMP1' or 'autosomal dominant mental retardation'. Eligible studies were included if they fulfilled the following criteria: A case report about autosomal dominant mental retardation causing by CHAMP1 mutation. Exclusion criteria were shown as follow: i) Publications not diagnosed as CHAMP1 mutation associated autosomal dominant mental retardation; ii) studies published in the format of meetings or as only an abstract.; or iii) the cases had syndromic intellectual disability. All 17 cases were included in the article ranging from the year 2015-2017 (Table I).

Results

Molecular evaluation. A novel *de novo* mutation, NM_032436.2 (CHAMP1): c.530delCinsTTT p.Ser177Phefs*2, was identified in the patient and it was confirmed using Sanger sequencing (Fig. 3). This CHAMP1 variation is a loss-of-function mutation, and it is a *de novo* variation verified by the patients parents who did not have this variation. It has not been reported in the Single Nucleotide Polymorphism Database (dbSNP; <http://www.ncbi.nlm.nih.gov/SNP>), the Exome Aggregation Consortium (ExAC; <http://exac.broadinstitute.org>) or the 1,000 Genomes Project (<http://browser.1000genomes.org/index.html>) database (Minimum allele frequency <0.005), so it is a pathogenic mutation according to the American College of Medical Genetics and Genomics (ACMG) guidelines (PVS1+PS2+PM2) (11).

According to the results, the patient was diagnosed with MRD40. Of note, the pediatric patient of the present study was the first Chinese case to be reported to have a CHAMP1 mutation.

Literature review. At the time the present study was submitted, 18 cases of MRD40 had been reported, including the present case, and this patient was the first known affected individual in China. As a result, GDD/ID with speech delay, motor developmental delay and facial anomalies were observed in all patients, as well as hypotonia (17/18), abnormal muscular tone (16/18), vision damage (15/18), abnormal behaviors (14/18) and reproductive issues (13/18) were quite common in patients with MRD40, while seizures (4/18), abnormal hearing (3/18) and spasticity (4/18) were less prevalent phenotypes. The clinical features of the above-mentioned patients are listed in Table I (6,12-14). In addition, all identified mutations in the CHAMP1 gene in patients diagnosed with MRD40 are truncating (nonsense or frameshift) mutations (Table II).

Discussion

NS-ID refers to a rare, hereditary, neurological disease characterized by early-onset cognitive impairment as the sole disability (14); however, patients with NS-ID may also be diagnosed with autism, epilepsy, neuromuscular deficits or external deformity, which may explain why MRD40 was previously considered an NS-ID (Orpha no. 178469). In addition to GDD or

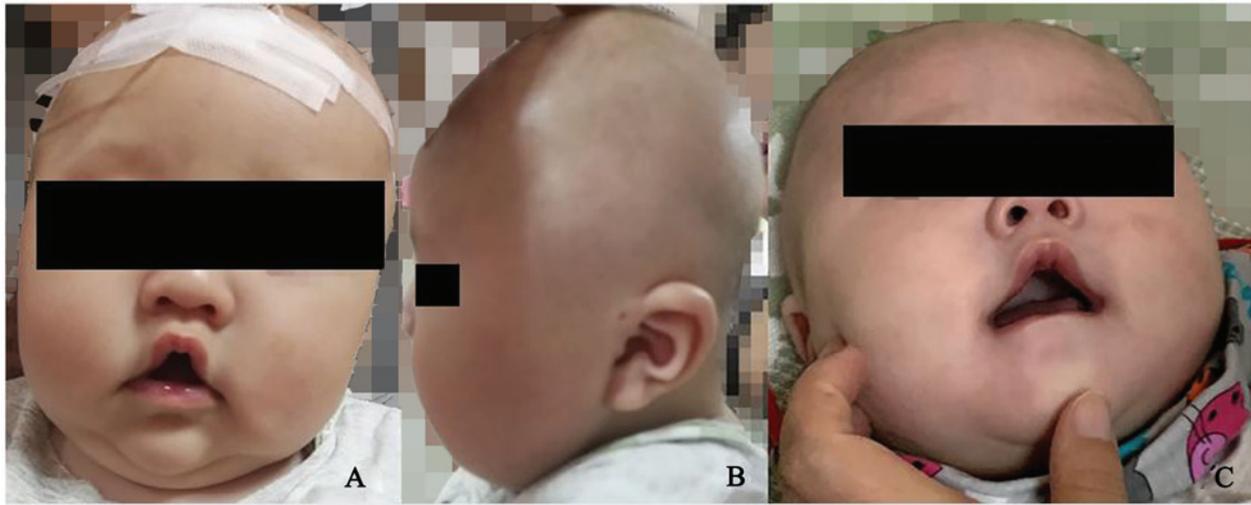


Figure 1. Images displaying dysmorphic features at different ages. Features included a tented upper lip, open-mouth appearance, low-set ears, sparse hair in general and microcephaly at the age of (A and B) 4 months and (C) 9 months.

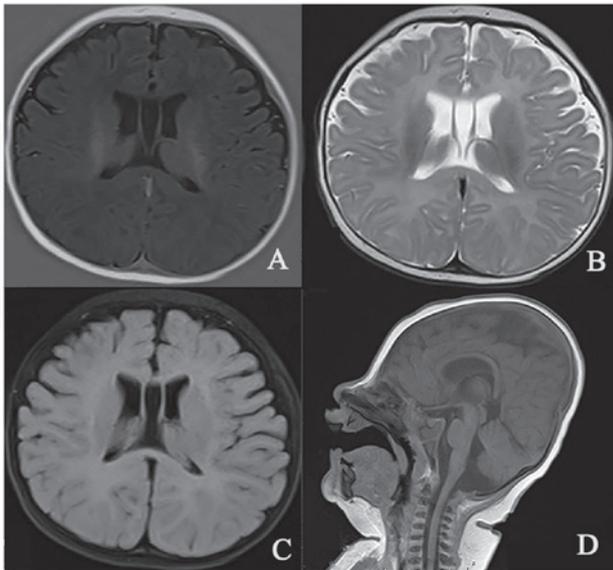


Figure 2. Brain MRI at the age of 4 months: Bilateral lateral ventricle fullness is presented in (A) T1-weighted, (B) T2-weighted and (C) T2 fluid-attenuated inversion recovery images. (D) Sagittal imaging revealed the features of the lip and high-arched palate.

ID, specific craniofacial dysmorphia, including microcephaly, a long and hypotonic face, pointed chin, upslanting palpebral fissures, short philtrum, high arched palate, tented upper lip, everted lower lip and open mouth, facilitates the diagnosis of MRD40 (5). In addition, previously reported epicanthal folds may be unspecific in Chinese or East Asian patients, and eye dysfunction, such as strabismus and hyperopia, are difficult to assess in infants (5). The abnormal behaviors mainly manifest as hyperactivity that results in attention deficit hyperactivity disorder or even self-injury; therefore, the abnormal behavior and mental impairment of the patients should be taken seriously during rehabilitation to care for patients. The patient of the present study displayed dysmorphic features, severe motor and cognitive developmental delays, as well as microcephaly.

Most patients have normal or nonspecific radiographs, while others exhibit slightly delayed myelination, cerebral atrophy and a decreased white matter volume (6,12-14). For the patient of the present study, the bilateral lateral ventricular enlargement appeared to be nonspecific, and no abnormalities in the brain parenchyma were identified.

The human CHAMP1 protein is an 812-amino-acid zinc-finger protein that is located on chromosome 13q34 and is expressed in the fetal brain during development and in all adult tissues (14). The protein contains 5 C-terminal C2H2 zinc-finger domains that were indicated to regulate the binding of CHAMP1 to chromosomes on the mitotic spindle *in vitro*, which has a key role in proper chromosome alignment (10). All 18 individuals with ID carrying CHAMP1 mutations reported to date had *de novo* mutations, and 17 mutation sites were identified [two patients carried the same mutation, namely c.1192C>T (p.Arg398*)]. The CHAMP1 mutation identified in the patient of the present study, c.530delCinsTTT (p.Ser177Phefs*2), has not been reported previously, and it is a pathogenic mutation according to ACMG guidelines (11). The reported gene mutation types are nonsense and frameshift mutations, all of which induced the synthesis of truncated proteins (Table II).

Thus, based on these findings, all of the truncating mutations (Table II) would result in loss of function of the CHAMP1 protein, which indicates the requirement for the function of the lost C-terminal domains or protein regions. Two regions, aa451-590 (FPE motifs, the region localized to the spindle and kinetochores) and aa591-812 [containing zinc-finger (ZNF) domains], localize to the spindle and both the chromosomes and the spindle, respectively (15), which are essential for proper chromosome alignment. In addition to the disruption of microtubule-kinetochore attachment, another functional study indicated that truncated CHAMP1 proteins are unable to bind to two of the direct binding partners of normal CHAMP1 protein, pogo transposable element derived with ZNF domain and heterochromatin protein 1, suggesting a pathogenic mechanism mediated by direct interacting proteins

Table I. Summary of patients with mutations in chromosome alignment maintaining phosphoprotein 1.

Case no. ^a	Author (year)	Nationality of the case	Age	Sex	GDD/ ID	Feeding difficulty	Seizures	Delay in				Spasticity	Abnormal vision	Abnormal hearing	Dysmorphic features	(Refs.)
								motor development	Speech delay	Abnormal behavior	Muscular hypotonia					
1	Okamoto (2017)	Japanese	6 y	M	+	+	+	+	+	+	+	-	+	+	(14)	
2	Isidor (2016) #1	French	NA	M	+	+	-	+	-	+	+	-	+	+	(13)	
3	Isidor (2016) #2	UK	NA	M	+	-	-	+	-	+	+	-	-	-	(13)	
4	Isidor (2016) #3	USA	NA	F	+	NA	+	+	-	+	+	-	-	+	(13)	
5	Isidor (2016) #4	USA	NA	M	+	+	-	+	-	+	+	-	-	+	(13)	
6	Isidor (2016) #5	UK	NA	F	+	+	-	+	-	+	+	-	-	+	(13)	
7	Isidor (2016) #6	UK	NA	F	+	NA	NA	+	-	+	+	-	-	+	(13)	
8	Hempel (2015) #1	NA	4 y	M	+	+	-	+	-	+	+	-	-	+	(6)	
9	Hempel (2015) #2	Dutch	3 y	M	+	+	+	+	-	+	+	-	-	+	(6)	
10	Hempel (2015) #3	Dutch	18 y	M	+	+	-	+	-	+	+	-	-	+	(6)	
11	Hempel (2015) #4	Dutch	3 y	F	+	+	-	+	-	+	+	-	-	+	(6)	
12	Hempel (2015) #5	German	9 y	F	+	-	-	+	-	+	+	-	-	+	(6)	
13	Tanaka (2016) #1	NA	23 y	F	+	+	-	+	-	+	+	+	+	+	(12)	
14	Tanaka (2016) #2	NA	7 y	F	+	+	+	+	-	+	+	-	-	+	(12)	
15	Tanaka (2016) #3	NA	4 y	F	+	+	-	+	-	+	+	+	+	+	(12)	
16	Tanaka (2016) #4	NA	12 y	F	+	+	+	+	-	+	+	-	-	+	(12)	
17	Tanaka (2016) #5	NA	6 y	F	+	+	-	+	-	+	+	+	+	+	(12)	
18	Dong (2020)	Chinese	4 m	M	+	-	-	+	-	+	+	-	-	+	Current study	

^aCase number is the same with that in Table II. NA, not available; y, years; m, months; M, male; F, female; GDD, global development delay; ID, intellectual disability.

Table II. Mutations in CHAMP1 and brain MRI features of patients with *de novo* CHAMP1 mutations.

Case no.	DNA change	Protein change	Mutation types	Brain MRI features
1	c.2068_2069delGA	p.Glu690Serfs*5	Frameshift	Cavum septum pellucidum, cavum vergae, cerebral atrophy, and decreased white matter volume
2	c.1880C>G	p.Ser627*	Nonsense	Normal or unremarkable findings
3	c.1002G>A	p.Trp334*	Nonsense	Normal or unremarkable findings
4	c.1876_1877delAG	p.Ser626Leufs*4	Frameshift	Normal or unremarkable findings
5	c.1043G>A	p.Trp348*	Nonsense	Normal or unremarkable findings
6	c.958_959delCC	p.Pro320*	Frameshift	Normal or unremarkable findings
7	c.1489C>T	p.Arg497*	Nonsense	Normal or unremarkable findings
8	c.1866_1867delCA	p.Asp622Glufs*8	Frameshift	Mild brain atrophy and cerebellar cortical dysplasia
9	c.1768C>T	p.Gln590*	Nonsense	Slightly delayed myelination
10	c.1192C>T	p.Arg398*	Nonsense	Normal
11	c.635delC	p.Pro212Leufs*7	Frameshift	Normal
12	c.1192C>T	p.Arg398*	Nonsense	Normal
13	c.1044delG	p.Trp348*	Frameshift	Hypoplastic corpus callosum
14	c.542_543delCT	p.Ser181CysfsX5	Frameshift	NA
15	c.1945C>T	p.Gln649*	Nonsense	Normal
16	c.1969C>T	p.Gln657*	Nonsense	Slightly decreased white matter volume, possible hypopituitarism
17	c.2029G>T	p.Glu677*	Nonsense	Mild cerebellar atrophy with mild inferior vermian hypogenesis
18	c.530delCinsTTT	p.Ser177Phefs*2	Frameshift	Bilateral lateral ventricle fullness

CHAMP1, chromosome alignment maintaining phosphoprotein 1; NA, not available.

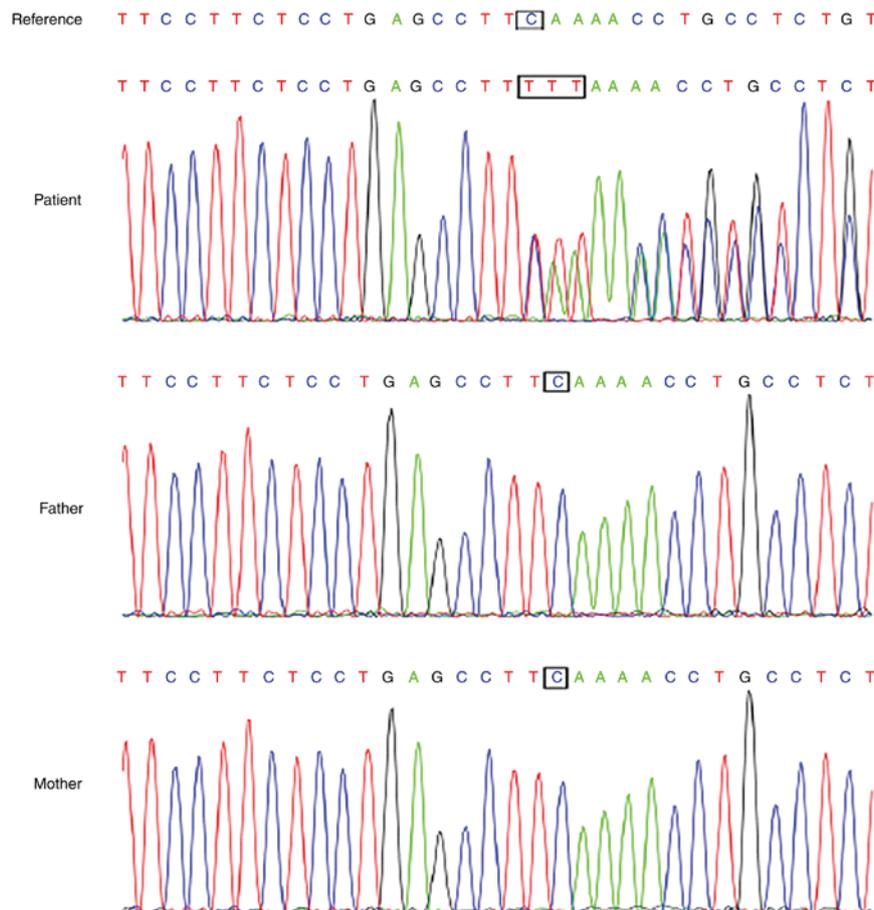


Figure 3. Mutation in the chromosome alignment maintaining phosphoprotein 1 gene: A frameshift mutation (c.530delCinsTTT, p.Ser177Phefs*2) was detected in the proband using Sanger sequencing, while the proband's parents did not carry the mutation. Sequenced data were aligned to the reference human genome (hg19; <http://genome.ucsc.edu/index.html>) and no control sample was used.

of CHAMP1, several of which are involved in syndromic ID (12). In summary, functional loss of the C-terminus of CHAMP1 alters the localization to chromosomes and spindles and disrupts the microtubule attachment complex, which results in kinetochore-microtubule-related syndromic ID.

WES is a powerful tool for the diagnosis of neurodevelopmental disorders; however, the analysis of massive amounts of data has been a major challenge (16). MRD40 was first described and the phenotype was linked to CHAMP1 in the DDD study (4). The DDD project recommended a comprehensive and highly efficient workflow for diagnosing Mendelian diseases (6). The workflow includes 3 main steps: i) Obtaining sequencing data from the patient and the parents (trio) were preferred to determine the inheritance of the candidate genetic variants; ii) assessment of the pathogenicity of variants; and iii) matching the phenotype. Using this approach, thousands of yield variant data may be narrowed to 1-3 candidate genes. In the present study, the 3-step screen was automatically performed using an online analysis system (<http://www.chigene.org>), and in addition to integrating genetic variations and disease databases which have been anonymized to preserve confidentiality and references in the pipeline, the system is online, which provides unlimited access only for the treating physicians of the patients to participate in the process and generate the final report. The limitation of the present study was that sequenced data were aligned to hg19 (<http://genome.ucsc.edu/index.html>) and no control sample was used. According to the Abstract, the present study expands the spectrum of the known pathogenic variants. The present case report and literature review also help to improve the syndromic profile of the rare MRD40 disorder and provides an example for the clinical diagnosis of MRD40. In summary, a comprehensive, highly efficient workflow is key to diagnosing rare genetic diseases.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request. The sequencing data have been uploaded to a curated repository (<https://www.ncbi.nlm.nih.gov/clinvar/submitters/507898>).

Authors' contributions

YD made substantial contributions to conception and design, agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. XS participated in drafting the manuscript acquired, analyzing and interpreting the data. KD, TJ and JW participated in

acquisition and interpretation of data, revising the manuscript critically for important intellectual content. RX, LW and RH participated in analyzing and interpreting the data. YD and KD confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Ethical approval for the present study was obtained from the Ethics Committee of the Third Affiliated Hospital of Zhengzhou University (Zhengzhou, China; no. 2019116).

Patient consent for publication

Informed consent was obtained from the parents of the patient included in the study for genetic testing and publication of data and images.

Competing interests

The authors declare that they have no competing interests.

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