Identification of a novel idiopathic congenital nystagmus-causing missense mutation, p.G296C, in the FRMD7 gene

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Abstract. Exploring the genetic basis for idiopathic congenital nystagmus is critical for improving our understanding of its molecular pathogenesis. In the present study, direct sequencing using gene specific primers was performed in order to identify the causative mutations in two brothers from a Chinese family who had been diagnosed with idiopathic congenital nystagmus. A comprehensive ophthalmological examination, including eye movement recordings, fundus examination, and retinal optical coherence tomography imaging was also conducted, to characterize the disease phenotype. The results revealed that the two brothers exhibited clear signs of nystagmus without any other ocular anomalies. Direct sequencing revealed a G to T transition (c.886G>T) in exon 9 of the four-point-one, ezrin, radixin, moesin domain-containing 7 (FRMD7) gene, which resulted in a conservative substitution of glycine to cysteine at codon 296 (p.G296C), leading to idiopathic congenital nystagmus in the two affected brothers. c.886G>T is a novel idiopathic congenital nystagmus-inducing mutation in the FRMD7 gene. This finding expands the spectrum of known gene mutations in idiopathic congenital nystagmus, and may be useful for faster gene diagnosis, prenatal testing, the development of potential gene therapies, and for improving the understanding of the molecular pathogenesis of idiopathic congenital nystagmus.

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Introduction

Idiopathic congenital nystagmus is one of the most common oculomotor disorders, characterized by involuntary, periodic, and predominantly horizontal oscillations of both eyes (1). The symptoms usually appear at birth or during the first few months of life. To date, the pathogenesis of idiopathic congenital nystagmus remains unclear. Abnormal brain control of the ocular motor system possibly contributes to this disease. At present, there is no effective treatment for idiopathic congenital nystagmus, and only very limited surgical, optical and pharmaceutical therapies are available improve the symptoms (2,3). Idiopathic congenital nystagmus exhibits extreme genetic and clinical heterogeneity. There are three different inheritance patterns that have been reported, including X-linked idiopathic congenital nystagmus [Online Mendelian Inheritance in Man (OMIM) nos: 300628, 300589], autosomal recessive (OMIM no: 257400) and autosomal dominant (OMIM nos: 164100, 608345 and 193003) (4,5). Although the inheritance mode is heterogeneous, X-linked idiopathic congenital nystagmus is the most commonly reported. Three disease loci for X-linked idiopathic congenital nystagmus have been mapped to Xp11.4-p11.3 [Nystagmus (NYS)5, OMIM no. 300589] (6), Xp22.3 (NYS6, OMIM no. 300814) (7) and Xq26-q27 (NYS1, OMIM no. 310700) (8). The four-point-one, ezrin, radixin, moesin (FERM) domain-containing 7 gene (FRMD7; OMIM no. 300628), containing 12 exons and encoding a member of the protein 4.1 superfamily, is credited for the disease loci at Xq26-q27, which is the main cause of X-linked idiopathic congenital nystagmus in Asian populations (1,9). As demonstrated in Table I, >73 mutations responsible for idiopathic

congenital nystagmus have been identified to date. In the present study, two brothers from a Chinese family who had been diagnosed with idiopathic congenital nystagmus were evaluated. To identify the causative gene mutations, the affected patients were first genotyped with microsatellite markers flanking the FRMD7 locus. Direct sequencing using gene specific primers then identified the mutations. The aim of this study was to identify a causative mutation responsible for idiopathic congenital nystagmus in a Chinese family, which may be important for the future genetic diagnosis and treatment of idiopathic congenital nystagmus.

Materials and methods

Clinical evaluation and DNA sampling. The present study was approved by the ethics committee of Xiamen Eye Center Affiliated Xiamen University (Xiamen, China) and adhered to the guidelines of the Declaration of Helsinki. The study participants included the two affected brothers and their parents, as well as 100 unaffected control subjects (45 male, 55 female; age range 18-56, recruited from 1st January-29th February 2016); written informed consent was received from all participants prior to enrolment. All subjects underwent comprehensive ophthalmologic evaluation, including eye movement recording using the Metrovision MonPack 3 vision monitoring system (Metrovision, Lille, France), fundus examination, and retinal optical coherence tomography (OCT) imaging. Peripheral venous blood samples (2 ml) were obtained from the affected brothers, their unaffected parents, and the 100 controls.

Mutational analysis and multiple-sequence alignment. The coding exons and splice junctions of the FRMD7 gene were amplified via polymerase chain reaction (PCR) using PCR primers (Table III) that have been previously published (14). PCR products were purified and directly sequenced using an ABI A3730 Automated Sequencer (Applied Biosystems; Thermo Fisher Scientific, Inc., Waltham, MA, USA). The suspected mutation identified in the two affected brothers was further confirmed as a mutation by sequencing of other family members and control males from the same ethnic background. Mutation descriptions followed the nomenclature recommended by the Human Genomic Variation Society (www.hgvs.org/). The amino acid sequences of the FRMD7 protein from various species were obtained from the National Center for Biotechnology Information website (www.ncbi.nlm.nih.gov/). The amino acid sequences of the FRMD7 gene from different species were aligned by the CLC Sequence Viewer 6 (CLC bio A/S; www.clcbio.com). The potential impact of amino acid substitution on the function of the FRMD7 protein was predicted using online tools, including the PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) and SIFT (http://sift.jcvi.org/) programs.

Protein structural modeling. The secondary structure of the human wild type was predicted by the Phyre2 program (www.sbg.bio.ic.ac.uk/~phyre2/html/page.cgi?id=index, 2.0) and 3D structures of the human wild type and mutant FRMD7 proteins were predicted using Iterative Threading ASSEmbly Refinement (I-TASSER; zhanglab.ccmb.med.umich.edu/I-TASSER), and the results saved in a Protein Data Bank (PDB) file format. The PDB files obtained for the two proteins were then analyzed using PyMOL1.7.0.0 (pymol.org/2/) to visualize the structural variations.

Results

Phenotypic characterization of the affected brothers. There were two affected individuals in this two-generation family. The probands (II:1 and II:2) presented with nystagmus as the first symptom. The clinical findings are summarized in Table II. Mental retardation, night blindness and photophobia were not observed in either of the two affected individuals. No head nodding was observed in the two affected patients, although one exhibited a clear head tilt. As demonstrated in Fig. 1, a representative ophthalmological examination results of both probands suggested that there was no indication of other ocular anomalies. OCT imaging demonstrated that the retinal nerve fiber layer thickness was within the normal range. Eye movement recordings revealed that nystagmus of the proband 1 was predominantly a horizontal waveform (Fig. 2). The ocular oscillation could be slightly slowed at a right gaze of 5˚. Patients in this family were confirmed to have X-linked congenital nystagmus based on the comprehensive ophthalmologic examination and family history.

Mutation analysis and protein structure modeling. A pedigree analysis of the patients is presented in Fig. 3A. Sequencing the FRMD7 gene revealed a G to T transition (c.886G>T) in exon 9 (Fig. 3B), which caused a conservative substitution of a glycine to a cysteine at codon 296 (p.G296C). This mutation was identified in both affected individuals and was present in the mother, but was absent in the father and in all control subjects. The FRMD7 p.G296C mutation is not present in any single nucleotide polymorphism database. In addition, this mutation was predicted with high confidence to be 'probably damaging' and 'damaging' by Polyphen-2 (score, 0) and SIFT (score, 2.54), respectively. Furthermore, multiple sequence alignment of the FRMD7 gene from different species was performed. The results demonstrated that codon 296, where the mutation (p.G296C) occurred, was located within a phylogenetically conserved region (Fig. 3C). Considering the above, it is reasonable to conclude that the p.G296C substitution is a causative mutation with the disease.

Using the Phyre2 program (www.sbg.bio.ic.ac.uk/~phyre2/html/page.cgi?id=index, 2.0), the secondary structure of the wild type FRMD7 protein was predicted, the three-dimensional structure of the wild type FRMD7 protein (1-336) was modeled, and p.G296C was mapped within the structure (Fig. 4). The results demonstrated that, with the p.G296C mutation, the amino acid residues at 296 were largely surrounded by hydrophilic polar amino acid residues. Substitution of glycine to cysteine at codon 296 increased the regional polarity of the amino acids. Furthermore, the thiol group of cysteine is a reducing group, able to change the local electron density. Changes in hydrophobicity and electron density may cause structural instability of the FRMD7 protein leading to protein dysfunction, thus causing idiopathic congenital nystagmus, but this requires further investigation.

Table I. Genetic mutations in the FRMD7 gene responsible for X-idiopathic congenital nystagmus, identified since 2008.

Author, year	Origin	Mutation type	Nucleotide change	Protein change	(Refs.)
Bai *et al*, 2017	China	Missense	c.284G>T	p.R95M	(10)
Jia *et al*, 2017	China	Missense	c.473T>A	p.I158N	(11)
Bai *et al*, 2017	China	Missense	c.521A>T	p.D174V	(10)
Gupta *et al*, 2015	India	Missense	c.556A>G	p.M186V	(12)
Jia *et al*, 2017	China	Missense	c.580G>T	p.A194S	(11)
Bai *et al*, 2017	China	Missense	c.586G>A	p.D196N	(10)
Jia *et al*, 2017	China	Missense	c.605T>A	p.I202N	(11)
Li *et al*, 2011	China	Missense	c. 623A>G	p. H208R	(13)
Liu *et al*, 2013	China	Missense	c.635T>C	-	(14)
Bai *et al*, 2017	China	Missense	c.T766A	p.F2561	(10)
Al-Moallem *et al*, 2015	Belgium	Missense	c.801C>A	-	(15)
Thomas *et al*, 2008	China	Missense	c.811T>C	p.C271R	(16)
Jia *et al*, 2017	China	Missense	c.811T>A	p.C271S	(11)
Al-Moallem *et al* and Kohmoto *et al*, 2015	Belgium, Japan	Missense	c.875T>C	p.L292P	(15,17)
Radhakrishna *et al*, 2012	India	Missense	c.A917G	Q305R	(18)
Bai *et al*, 2017	China	Missense	c.A973G	p.R325G	(10)
Choi *et al*, 2015	Korean	Missense	c.A>G	p.M1>V	(19)
Zhao *et al*, 2016	China	Nonsense	c.1090C>T	p.Q364X	(20)
AlMoallem *et al*, 2015	Belgium	Frameshift	c.2036del	-	(15)
He *et al*, 2008	China	Frameshift	c.1274-1275delTG	-	(21)
Bai *et al*, 2017	China	Frameshift	c.999delT	p.H333fs	(10)
Jia *et al*, 2017	China	Slice mutation	c.57+1G>A	-	(11)
Hu *et al*, 2012	China	Splicing mutation	c.163-1G>T	-	(22)
AlMoallem *et al*, 2015	Belgium	Splice site mutation	c.497þ5G>A	-	(15)
Hu *et al*, 2011	China	Splicing mutation	c.658+1g>t	-	(23)
Al-Moallem *et al*, 2015	Belgium	Copy number variation	1.4 Mb deletion	-	(15)
Jia *et al*, 2017	China	Deletion	c.41_43delAG	-	(11)
Al-Moallem *et al*, 2015	Belgium	Deletion	c.660del	-	(15)
Jia *et al*, 2017	China	Deletion	c.689-690delAG	p.Ser232del	(11)
Du *et al*, 2011	China	Deletion	c.1486-1489delTTTT	p.F497fs26X	(24)
Bai *et al*, 2017	China	Shear mutation	c.162+2T>C	-	(10)
Bai *et al*, 2017	China	Shear mutation	c.206-1G>A	-	(10)
Jia *et al*, 2017	China	Insert	c.1492-1493insA	p.Y498X	(11)
Schorderet *et al*, 2007	Switzerland	Variant	c.383-11G>A	-	(25)
Schorderet *et al*, 2007	Switzerland	Variant	c.206-20T>C	-	(25)

A total of 38 mutations identified before 2007 summarized in a previous review (21), were not included in this table. FRMD, four-point-one, ezrin, radixin, moesin domain-containing.

Discussion

Idiopathic congenital nystagmus is an inherited ocular disorder that develops at birth or shortly after and persists throughout the patient's life (26). Nystagmus has an estimated prevalence of 6.72 per 100,000 for individuals younger than 19 years (27). Idiopathic congenital nystagmus is associated with significant negative psychosocial and functional consequences, including negative social stigma and poor visual function scores (28,29). There is a great interest in the treatment and early diagnosis of idiopathic congenital nystagmus. However, there is currently no effective treatment for idiopathic congenital nystagmus, and only limited surgical, optical and pharmaceutical therapies have been tested for the improvement of nystagmus waveforms and visual acuity (2,3). The early diagnosis of congenital nystagmus is critical for facilitating habilitation, providing genetic counseling, and potential gene therapies in the future (30). The diagnosis of idiopathic congenital nystagmus remains being a challenge and potential patients are usually required to undergo numerous examinations (31). Nystagmus is currently clinically described in terms of its peak-to peak amplitude, frequency, mean velocity and waveform (32). In the present study, idiopathic congenital nystagmus in two brothers from

Table II. Clinical features of individuals with idiopathic congenital nystagmus in the present study.

Phenotype	I:1	II:2
Sex	Male	Male
Age (years)	7	6
Age at diagnosis (years)	4	3
Visual activity at presentation	OD20/100 OS20/80	OD20/50 OS20/50
Nystagmus	Horizontal	Horizontal
Abnormal head movement	Negative	Clear head tilt
Neurological findings	Normal	Normal

OD, oculus dextrus (right); OS, oculus sinister (left).

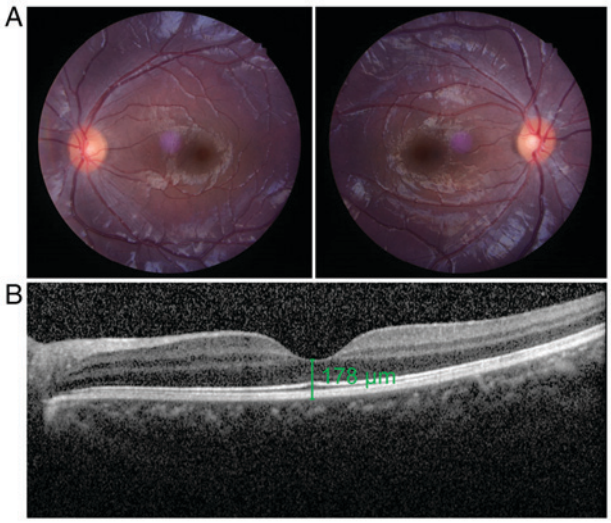

Figure 1. Ophthalmological examination suggested no other ocular anomalies in the two patients from the Chinese family. Representative (A) fundus and (B) optical coherence tomography images from proband 1.

a Chinese family was first diagnosed using eye movement recordings and a comprehensive ophthalmologic examination.

Recently, a next-generation sequencing panel has been used for the early diagnosis of idiopathic congenital nystagmus (31). Comprehensive understanding of the mutation spectrum is the foundation for efficient early genetic diagnosis. To identify the causative mutations in the two affected brothers, direct sequencing of genomic DNA samples from the affected brothers was conducted. The results revealed a G to T transition (c.886G>T) in exon 9 of the FRMD7 gene, which resulted in a conservative substitution of a glycine to a cysteine at codon 296 (p.G296C), leading to idiopathic congenital nystagmus. So far, >40 mutations causing idiopathic congenital nystagmus have been identified in the FRMD7 gene, predominantly concentrated in two key regions: The FERM and FERM adjacent domains (9). Identification of the mutations is not only critical for early diagnosis, but also for understanding the pathogenesis of idiopathic congenital nystagmus. The genetic

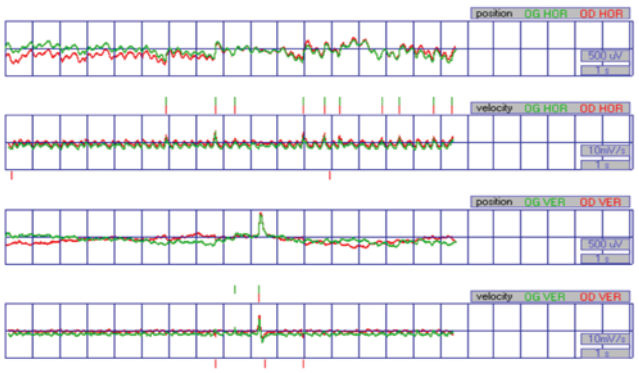

Figure 2. Eye movement recordings from proband 1. Typical nystagmus waveforms recorded by Metrovision MonPack 3 vision monitor system, which revealed that nystagmus of the probands were predominantly a horizontal waveform. OS (Green), oculus sinister/left eye; OD (red), oculus dextrus/right eye; HOR, horizontal; VER, vertical.

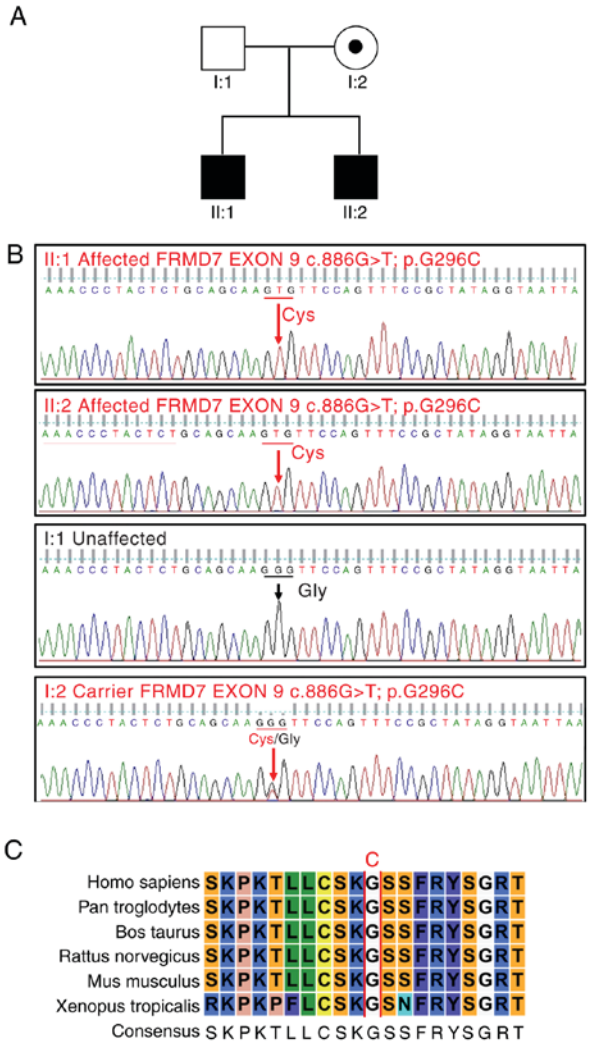

Figure 3. Determination of the p.G296C mutation in the FRMD7 gene causing idiopathic congenital nystagmus. (A) Pedigree analysis. (B) DNA sequence chromatograms of the two affected probands, one unaffected family member and one carrier family member. A single base G to T transition in exon 9 of the FRMD7 gene that causes a conservative substitution of glycine to a cysteine at codon 296 (p.G296C) was detected. (C) Multiple-sequence alignment of the FRMD7 gene from different species revealed that codon 296, where the mutation (p.G296C) occurred, was located within a highly conserved region. The red box indicates the location of the mutation. FRMD, four-point-one, ezrin, radixin, moesin domain-containing.

Table III. Primers and PCR conditions for FRMD7.

Exon	Sequence (5'>3')	Annealing temp	Length
FRMD7 E1	CCCTTGGGTGTGCATTACTT TTGCTCTCTAATGGGCTGTTC	58˚C	308 bp
FRMD7 E2	CAGAGAGTCTTGTGGCTTCTAC TGGCCAAGGTGACTGTTAAT	58˚C	380 bp
FRMD7 E3	CCACCTATTTGACATTGCTGTTT CCAGCAGCATGATTTCTTTCATC	58˚C	399 bp
FRMD7 E4	AGTCTGTAGGAGGGAGTGATG TCCTGTAGTCTCCACCCTTT	58˚C	418 bp
FRMD7 E5	GCCTGCCAAAGTGTTCAATC GCCATGCTGTTTCTCTCTATCT	58˚C	455 bp
FRMD7 E6+7	TTTGATGGAGGACAAGGGTATG CCCTTTCTGGCTGGTGATAAT	58˚C	660 bp
FRMD7 E8	CATCCTTGTATCCCACCTGAAATG CTGGTCACTCCCATTTGACTTA	58˚C	590 bp
FRMD7 E9	GTTTCTGGCAGAGAAGAGTGAGT CATCTTCCTCCCTCCTAGTTAG	58˚C	638 bp
FRMD7 E10+11	CTCTGCCTGGTCCTTGAATAAG CCAGGAAGCTAACCTACTCAAA	58˚C	562 bp
FRMD7 E12a	CTGGAAGTAGGATGGCATTGAG TTGGAGTACTTGCAGGTCTTG	58˚C	845 bp
FRMD7 E12b	CAGGTCAGCAGGTTGGTATTAT GAGGAGAGGGCATGTTCTAAAG	58˚C	916 bp

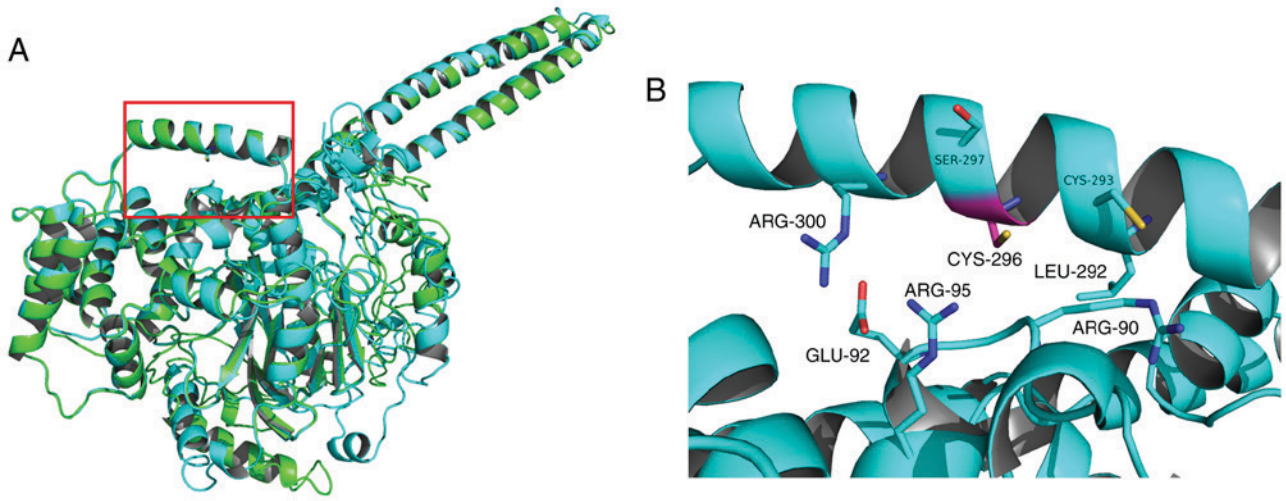

Figure 4. Structural model of the FRMD7 protein. (A) Structural modeling and structure alignment indicated that the wild type (green) and p.G296C (cyan) proteins share a similar structure overall, with the exception of the loop region. (B) Structural analysis of the amino acid sequences where the mutation p.G296C is localized. FRMD, four-point-one, ezrin, radixin, moesin domain-containing.

etiology of idiopathic congenital nystagmus is not yet fully understood, especially regarding sporadic cases. Identifying previously unknown genetic mutations involved in idiopathic congenital nystagmus will allow the development of cell and animal-based models to help classify idiopathic congenital nystagmus and guide future therapies. The present findings provide further insight into the genetic spectrum for idiopathic congenital nystagmus, which is useful for the earlier genetic diagnosis, genetic counseling, and potential future gene therapy of patients with idiopathic congenital nystagmus.

In summary, a novel mutation in the FRMD7 gene causing idiopathic congenital nystagmus was identified using direct sequencing. G to T transition (c.886G>T) in exon 9 that resulted in the conservative substitution of a glycine to a cysteine at codon 296 (p.G296C) was identified in two affected brothers from a Chinese family. The present study expanded the already known gene mutation spectrum for idiopathic congenital nystagmus, providing more evidence for the genetic heterogeneity associated with idiopathic congenital nystagmus. This novel finding is important for faster diagnosis, prenatal

testing, and improving the understanding of the molecular pathogenesis of idiopathic congenital nystagmus.

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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.

Authors' contributions

JZ, FG and YZ designed the experiments. YX, YH, TY, MP, YY and WF performed the experiments. YX, JZ and YZ analyzed the results and wrote the manuscript.

Ethics approval and consent to participate

All procedures performed in the present study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent for participation in the study was obtained from all participants or their legal guardians prior to their inclusion.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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