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A novel genetic variant associated with benign paroxysmal positional vertigo within the *LOXL1*

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Abstract

Background: Benign paroxysmal positional vertigo (BPPV) is a common, self-limited, and favorable prognostic peripheral vestibular disorder. BPPV is transmitted in an autosomal dominant fashion, but most cases occur sporadically. Little research has been reported regarding the mutation spectrum of sporadic BPPV in a large cohort. This study attempted to identify the causative candidate variants associated with BPPV in *VDR*, *LOXL1*, and *LOXL1-AS1*.

Methods: An amplicon-targeted next-generation sequencing (NGS) method for *VDR*, *LOXL1*, and *LOXL1-AS1*, was completed in 726 BPPV patients and 502 normal controls. A total of 30 variants (20 variants from *VDR*, nine variants from *LOXL1*, seven variants from *LOXL1-AS1*) were identified in these two groups.

Results: Three of 30 variants were nonsynonymous mutations, but no significant difference was found between the BPPV group and the control group via association analysis. A single nucleotide variant (SNV), rs1078967, was identified that is located in intron 1 of *LOXL1*. The allelic frequency distribution differed significantly between the BPPV group and the control group ($p = 0.002$). Genotypic frequency was also significantly different ($p = 0.006$), as determined by gene-based analyses.

Conclusion: This report is the first to analyze the variant spectrum of BPPV in a large Chinese population.

KEYWORDS

benign paroxysmal positional vertigo (BPPV), genetic variants, *LOXL1*, next-generation sequencing (NGS)

Mingzhu Deng, Chen Liu and Weiqing Jiang contributed equally to this study.

1 | INTRODUCTION

Benign paroxysmal positional vertigo (BPPV), also known as benign recurrent vertigo (BRV), is the most common disorder in the peripheral vestibular system and is caused by changes in the position of the head with reference to gravity, with a lifetime prevalence of 2.4% (Byun et al., 2019; Kim & Zee, 2014). The typical clinical feature of BPPV is similar to the name as the term "benign" implies favorable prognosis; "paroxysmal" describes the rapid and sudden onset of spinning sensations, usually lasting less than 1 min; and "positional" indicates that the vertigo is initiated at any time by a gravity change of head position (Bhattacharyya et al., 2017; von Brevern et al., 2007). Given the notable prevalence and acute episodic symptoms of BPPV, its health care costs and societal impacts are significant and large (Benecke, Agus, Kuessner, Goodall, & Strupp, 2013; Li, Li, Epley, & Weinberg, 2000). BPPV is caused by vestibular otoliths falling off and entering the semicircular canals, which is based on the mechanism of canalolithiasis (Hall, Ruby, & McClure, 1979). The abnormal endolymphatic flow caused by the movement of otoliths in semicircular canals disturbs the vestibular afferent, which produces a series of corresponding symptoms (Parnes & McClure, 1992; Vibert, Kompis, & Häusler, 2003). BPPV (BRV1, OMIM %613106; and BRV2, OMIM %193007) might be transmitted in an autosomal dominant fashion, such as linkage of a subset of families to 22q12, mapping to 6p (Brantberg, 2003; Jen et al., 2004; Lee et al., 2006). The corresponding data were all derived from family, but most cases exist sporadically. There are currently no population-based linkage studies related to the genes identified. A comprehensive mutation spectrum of BPPV in a large population is needed.

Given that otoliths are mainly made from calcium carbonate crystals, calcium homeostasis may be associated with the synthesis and resorption of otoliths (Vibert et al., 2003). It is commonly known that vitamin D plays an important role in calcium regulation (DeLuca, 1986). Accumulated comorbidity studies show that lower vitamin D levels in BPPV patients and vitamin D supplementation could reduce vertigo attacks (Buki, Ecker, Junger, & Lundberg, 2013; Maslovara et al., 2018; Talaat et al., 2016). Therefore, it is reasonable to postulate that the expression levels of vitamin D and the related gene *VDR* might interact with BPPV. *VDR* (OMIM *601769), encoding the vitamin D3 receptor contains 12 exons, which are located on chromosome 12q13.11. We chose 20 SNVs in this gene.

Genome mapping on a three-generation BPPV family revealed a critical chromosomal 15 interval (Gizzi, Peddareddygari, & Grewal, 2015) involving *LOXL1* and *LOXL1-AS1*. *LOXL1* (OMIM *153456) encodes a member of the lysyl oxidase family of proteins associated with diseases including iris disease and exfoliation syndrome. "Exfoliation" may have a curious association with "fall off." *LOXL1-AS1* (OMIM *616800), a type of long noncoding RNA (lncRNA), can regulate the gene transcription and/or translation, and its expression is increased by repetitive mechanical stress (Hauser et al., 2015). Thus, we selected 10 variants from these two genes.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

This study was approved by the ethics committee of Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China. The study was conducted in keeping with the principles of the Declaration of Helsinki.

2.2 | Study population

All patients were recruited from July 2016 to March 2019 and were selected from the neurology outpatient clinic of Renji Hospital Affiliated School of Medicine, Shanghai Jiaotong University, after a written informed consent was obtained. Healthy controls were screened by excluding those with vestibular neuronitis and other vertigo-related illnesses.

2.3 | Diagnostic criteria

To obtain a clear and accurate diagnosis, our diagnostic criteria were strict. Each item has to be fulfilled. The criteria were the following: (1) recurrent rotatory vertigo triggered by the gravity changes of head position or having a positive reflect by the Dix-Hallpike maneuvers test (posterior canal BPPV, torsional nystagmus toward downmost ear; anterior canal BPPV, downbeat nystagmus) or the roll-test (horizontal canal BPPV, geotropic, or apogeotropic nystagmus); (2) duration of vertigo always less than 1 min; and (3) not better accounted for by other disorder. Even if a case had evidence of positional vertigo during vestibular examination, and no typical nystagmus, it was excluded.

2.4 | Procession of samples

Blood samples (3 ml) were collected from each participant and stored in a −80°C refrigerator in a clinical laboratory. We downloaded the genomic information of *VDR*, *LOXL1*, and *LOXL1-AS1*. We obtained all SNVs of the above three genes from the 1000 Genomes Project of Han Chinese population (Gibbs et al., 2003). Next, we screened tag SNVs with Haploview version 4.2 (www.broadinstitute.org), with

TABLE 1 The demographic and clinical indices of studied participants

Indices	Healthy controls ($n = 598$)	BPPV patients ($n = 726$)	p value
Gender			
Males (%)	157 (26%)	224 (31%)	0.068
Female (%)	441 (74%)	502 (69%)	
Age(years) ± *SEM*	54.59 ± 9.25	55.66 ± 14.14	0.098
Body mass index (kg/m^2) ± *SEM*	23.07 ± 3.49	23.17 ± 3.59	0.598
Vitamin D levels (ng/ml) ± *SEM*	20.91 ± 6.05	18.19 ± 8.13	**<0.001*****
PHT levels(pg/ml) ± *SEM*	38.43 ± 16.13	46.22 ± 22.21	**<0.001*****

Abbreviation: PTH, parathyroid hormone.

$^{***}p < 0.001$.

minor allele frequency (MAF) >0.2. DNA extraction from all blood samples was performed using a LifeFeng Genomic DNA Purification Kit (Lifefeng Biotech Co., Ltd., Shanghai, China). Polymerase chain reaction (PCR) reagents were purchased from Shanghai DYnastyGene Company, and every step was performed strictly in accordance with the protocol. After preparing for all sample sequences, the sequence library was tested as 150-bp paired-end reads in the Illumina X Ten platform (Illumina, USA). All data were analyzed on the Sequenom MassARRAY platform at the Bio-X Institute.

2.5 | Quality control

The process of DNA quality control was monitored by a NanoDrop 1000 Spectrophotometer (Thermo Scientific, USA). Each targeted amplicon had a specific start site and end site. To avoid base mismatch, all sequences read were demultiplexed and clipped by Trimmomatic v 0.30. The Genome Analysis Tool Kit was used to quantify base recalibration and call variants. We set a threshold in hard filtration with quality >30, read depth >100, and mapping quality >30 to obtain a false positive result. Base position (BP) was determined using sequences of *VDR* (NC_000012.11, region: 48235320…48298814), *LOXL1* (NC_000015.9, region: 74218789…74244478), and *LOXL1-AS1* (NC_000015.9, region: 74209809…74220589). The version number of genes studied is the Human Genome 19. Variants were expressed in the form of nucleotide and amino acid changes according to the sequences of *VDR* (NM_001017536.2; NP_001017536.1) and *LOXL1* (NM_005576.4; NP_005576.2).

2.6 | Statistical analysis

Analyses of the demographic and clinical indices of the studied participants were conducted using SPSS 21.0 (IBM, Chicago, USA). Gender ratio comparisons were performed using the chi-square test. Age, body mass index, level of vitamin D, and parathyroid hormone (PTH) were assessed using independent t tests. All tests were two-tailed, and a p value = 0.05 was considered to indicate significance. Clinical characteristics of semicircular canals were analyzed by GraphPad Prism 7.0. The comparison of groups used two-way ANOVA. Genetic statistical analyses were performed using free-charge the SHEsisPlus online platform (http://shesisplus.bio-x.cn/) (Li et al., 2009; Shen et al., 2016), including Hardy–Weinberg equilibrium (HWE), suggesting that allele and genotype frequencies in a population remain constant from generation to generation in the absence of other evolutionary influences (p value cutoff at 0.05, A call rate ≥0.95), and the χ^2 test, which was used for analyzing odds ratio (OR) with a 95% confidence interval (CI). The false discovery rate (FDR), also known as Bonferroni's correction, was used to control the FDR of hypothesis tests. FDR ≤0.05 is significant. The analyses of pairwise linkage disequilibrium (LD) and haplotype distributions were performed by Haploview 4.2, R^2 threshold at 0.8.

3 | RESULTS

3.1 | Baseline characteristics

The demographic and clinical indices for all participants are shown in Table 1. A total of 1324 subjects were enrolled in this study, including 726 BPPV cases and 598 healthy controls. The characteristics of gender, age, and body mass index exhibited no significant differences. BPPV patients had a higher vitamin D level ($p < 0.001$) and a lower PTH level ($p < 0.001$). The clinical characteristics of semicircular canals in 726 BPPV patients are shown in Figure 1. The incidence of BPPV in females was greater than that in males, exhibiting a ratio of approximately 2.24:1 (502:224). The incidence of posterior canal BPPV in females was significantly higher than that in males ($p < 0.01$). There were 598 posterior canal BPPV cases (female: 413, male: 185; left posterior canal: 257, right posterior canal: 341), which was clearly

more common than the lateral canal BPPV cases (female: 50, male: 27; left lateral canal: 40, right lateral canal: 37; $p < 0.001$) and anterior canal BPPV cases (female: 12, male: 4; left anterior canal: 8; right anterior canal: 8; $p < 0.001$). These results were in keeping with those of previous studies (Caruso & Nuti, 2005; Kim & Zee, 2014; Nuti & Yagi, 2010). Moreover, there were 384 BPPV cases on the right side compared with 307 on the left side, which may be observed because most patients sleeping on the right side (von Brevern, Seelig, Neuhauser, & Lempert, 2004). A total of 35 complex BPPV cases were observed, including double side BPPV, multiple canal BPPV, and atypical forms. Anterior canal BPPV is always accompanied by a posterior canal.

3.2 | Variant identification and association analyses

To identify mutations possibly causing BPPV, we selected 30 variants and performed comparative analyses. A total of 20 variants from *VDR* were detected in 1324 subjects, including one nonsynonymous (missense) mutation, three UTR variants, and 16 intron variants. No significant effect on BPPV were observed by the associated analyses (data not shown). Ten variants were observed from *LOXL1* and *LOXL1-AS1*, including two nonsynonymous (missense) mutations and eight intron variants. The allele and genotype distributions of each SNV from *LOXL1* and *LOXL1-AS1* are shown in Table 2. The comparison of alleles and genotypes between two cohorts are shown in Table 3. Among these variants, the variant rs2165241 allele exhibited a different distribution ($p = 0.02$), but the p value was 7.17e−04 in the control group, which felling short of the HWE standard, and the variant was, therefore, excluded from the analysis. For another variant rs16958477, the allelic ($p = 0.041$) and genotypic ($p = 0.016$) requirements were satisfied and met the standard HWE standard ($p = 0.925$), but, regrettably failed to reach FDR. Only one variant, rs1078967, is located in intron 1 of *LOXL1*. The allelic frequency distribution differed significantly between the BPPV group and the control group ($p = 0.002$). Genotypic frequency was also significantly different ($p = 0.006$), as determined by the gene-based analyses. Meanwhile, this variant met the HWE ($p = 0.267$) and FDR ($p = 0.02$) requirements. Pairwise LD of *LOXL1* (except rs4886761 in *LOXL1-AS1*) results are shown in Figure 2, which revealed that the variants existed in one haplotype block. Most SNVs are entirely independent and have no significantly LD.

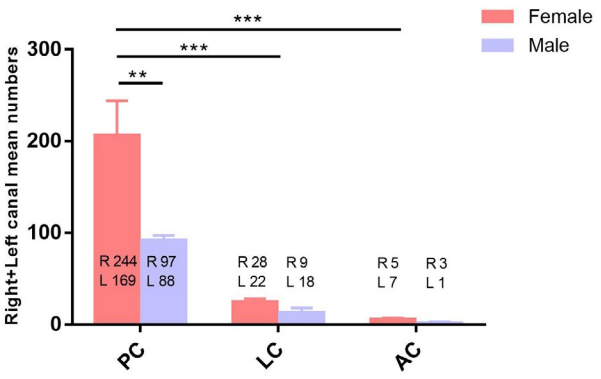

FIGURE 1 Clinical characteristics of semicircular canals in 726 BPPV patients. PC: posterior canal; LC: lateral canal; AC: anterior canal. $^{**}p < 0.01$, $^{***}p < 0.001$

4 | DISCUSSION

This study determined that the SNV rs1078967, which is located in *LOXL1*, is a potential causative mutation of BPPV. This study is the first to describe the mutation spectrum of sporadic BPPV via targeted resequencing.

Accumulating research efforts have attempted to elucidate the pathogenesis of BPPV. Based on previous studies, the majority of the evidence indicates that BPPV is caused by otoconia detaching from the otoconial membrane, also known as the "gelatinous matrix," falling into the semicircular canals and then, disturbing the vestibular afferent (Bruintjes, van der Zaag-Loonen, Eggelmeijer, & van Leeuwen, 2018; Hall et al., 1979; Kaski & Bronstein, 2014; Vibert et al., 2003). Meanwhile, predisposing factors such as vitamin D deficiency, impaired calcium metabolism, advanced age, osteopenia, and osteoporosis may contribute to the onset of the disease (Balatsouras, Koukoutsis, Fassolis, Moukos, & Apris, 2018; Kitahara et al., 2019; Vibert et al., 2003; Zhang, Tian, Li, Cao, & Song, 2019). However, little is known about the mechanism of otoconia easily detaching from the otoconial membrane. However, for reasons that have not been determined, there are many BPPVs and no susceptibility factors.

LOXL1 is mapped to chromosome 15q24.1, where there is a partial overlap with the gene *LOXL1-AS1* on the opposite strand (Gizzi et al., 2015). These two genes are reported to be associated with exfoliation syndrome (XFS; OMIM #177650). *LOXL1* encodes a member of the lysyl oxidase family of proteins (Kagan & Li, 2003; SMITH-MUNGO & KAGAN, 1998). Meanwhile, *LOXL1* localizes notably to the side of elastogenesis, interacting with fibulin-5, is an element of the scaffold, and serves to ensure spatially defined deposition of elastin (Aung et al., 2017; Liu et al., 2004). XFS is characterized by pathological deposition of abnormal elastic microfibrils (Hewitt et al., 2007; Schlötzer-Schrehardt & Naumann, 2006). Mice lacking *LOXL1* do not deposit normal elastic fibers, developing loose skin, enlarged air-space of the lung, and vascular abnormalities (Li et al., 1998). The primary components of mammalian otoconia are gelatin, glycoprotein, and glycosaminoglycans after demineralization (Mann, Parker, Ross, Skarnulis, & Williams, 1983). Through

TABLE 2 Allele and genotype distributions among BPPV and healthy group

SNV	Gene	Allele	Case	Control	Genotype	Case	Control
rs4886761	*LOXL1-AS1*	T	137 (0.094)	90 (0.075)	T/T	7 (0.009)	4 (0.006)
		C	1315 (0.905)	1106 (0.924)	C/C	596 (0.82)	512 (0.856)
					C/T	123 (0.169)	82 (0.137)
rs16958477	*LOXL1/*	C	165 (0.113)	107 (0.089)	C/C	20 (0.027)	4 (0.006)
	LOXL1-AS1	A	1287 (0.886)	1089 (0.91)	A/A	581 (0.8)	495 (0.827)
					C/A	125 (0.172)	99 (0.165)
rs1048661	*LOXL1/*	G	659 (0.466)	534 (0.454)	G/G	239 (0.338)	178 (0.303)
	LOXL1-AS1	T	755 (0.533)	640 (0.545)	T/T	287 (0.405)	231 (0.393)
					G/T	181 (0.256)	178 (0.303)
rs3825942	*LOXL1/*	G	874 (0.884)	774 (0.895)	G/G	432 (0.874)	386 (0.893)
	LOXL1-AS1	A	114 (0.115)	90 (0.104)	A/A	52 (0.105)	44 (0.101)
					G/A	10 (0.02)	2 (0.004)
rs1550437	*LOXL1/*	C	919 (0.648)	746 (0.636)	C/C	347 (0.489)	277 (0.472)
	LOXL1-AS1	T	499 (0.351)	426 (0.363)	T/T	137 (0.193)	117 (0.199)
					C/T	225 (0.317)	192 (0.327)
rs8034403	*LOXL1/*	G	1278 (0.891)	1064 (0.894)	G/G	607 (0.846)	502 (0.843)
	LOXL1-AS1	A	156 (0.108)	126 (0.105)	G/A	64 (0.089)	60 (0.1)
					A/A	46 (0.064)	33 (0.055)
rs2165241	*LOXL1/*	T	175 (0.121)	111 (0.092)	T/T	23 (0.031)	13 (0.021)
	LOXL1-AS1	C	1269 (0.878)	1083 (0.907)	C/C	570 (0.789)	499 (0.835)
					C/T	129 (0.178)	85 (0.142)
rs1078967	*LOXL1*	C	1335 (0.919)	1057 (0.883)	C/C	611 (0.841)	463 (0.774)
		T	117 (0.08)	139 (0.116)	C/T	113 (0.155)	131 (0.219)
					T/T	2 (0.002)	4 (0.006)
rs28522673	*LOXL1*	G	1286 (0.894)	1053 (0.883)	G/G	603 (0.838)	491 (0.823)
		C	152 (0.105)	139 (0.116)	C/G	80 (0.111)	71 (0.119)
					C/C	36 (0.05)	34 (0.057)
rs8041642	*LOXL1*	G	1295 (0.893)	1052 (0.879)	G/G	577 (0.795)	460 (0.769)
		A	155 (0.106)	144 (0.12)	G/A	141 (0.194)	132 (0.22)
					A/A	7 (0.009)	6 (0.01)

surface adhesion to the otoconial membrane and confinement in the filament matrix, the otoconia are fixed steadily (Lins et al., 2000). Thus, we hypothesize that the mutation of *LOXL1* may lead to the dysfunction of elastogenesis to a certain extent, which further impairs the adherence of otoconia to the gelatinous matrix and facilitates its detachment, thereby leading to the onset of BPPV.

SNV rs1078967 (c.1102+2761C>T), which is located in intron 1 of *LOXL1*, was identified. Since the variant is located within intronic regions, a mechanistic understanding of how it contributes to phenotypes is lacking. However, there is growing evidence that new pathogenic variants are located in introns (Cooper, 2010). It is noteworthy that the first intron of genes exhibits several special characteristics not seen in other introns (Jo, Choi, & Hurst, 2019). Multiple trait-associated SNVs in the first intron, which may be a location of gene expression regulation, interact with each other within a large protein-protein interaction network (Weth et al., 2014). Moreover, a report about the *LOXL1* gene mentioned a 7-kb region, bounded by the 3′-end of exon 1 and the adjacent region of intron 1, which contains a promotor (Hauser et al., 2015). Rs1078967 is located in this region and is determined to be a functional variant.

As discussed above, emerging evidence has linked vitamin D to the occurrence of BPPV. However, in this study, no associated SNV was found among the 20 variants that we selected in *VDR*. Further research is warranted to illustrate the relationship of vitamin D and BPPV at the genetic level.

In conclusion, our research identified a variant associated with BPPV in the Chinese population. Further molecular and animal studies, are necessary to confirm the contribution of the variant to the disease. A series of subsequent confirmatory

TABLE 3 The comparison of allele and genotype between two cohorts

SNV	BP	OR	95% CI	*p* (Allele)	*p* (Genotype)	*p* (FDR)	*p* (HWE)
rs4886761	7.4E+07	1.28	0.969–1.69	0.08	0.218	0.201	0.937
rs16958477	7.4E+07	1.304	1.009–1.686	**0.041**	**0.016**	0.138	0.925
rs1048661	7.4E+07	1.046	0.895–1.221	0.569	0.141	0.632	5.72E−20
rs3825942	7.4E+07	1.121	0.836–1.503	0.441	0.107	0.631	6.15E−90
rs1550437	7.4E+07	0.95	0.809–1.117	0.54	0.835	0.632	1.43E−11
rs8034403	7.4E+07	1.03	0.804–1.321	0.81	0.646	0.81	5.91E−29
rs2165241	7.4E+07	1.345	1.046–1.729	**0.02**	0.093	0.101	7.17E−04
rs1078967	7.4E+07	0.666	0.514–0.863	**0.002**	**0.006**	**0.02**	0.267
rs28522673	7.4E+07	0.895	0.701–1.142	0.382	0.755	0.624	9.47E−24
rs8041642	7.4E+07	0.874	0.687–1.112	0.294	0.497	0.549	0.588

Note: BP: base position, was determined using sequences of *LOXL1* (NC_000015.9, region: 74218789…74244478); FDR: False Discovery Rate; HWE: Hardy-Weinberg equilibrium; OR: odds ratio; CI: confidence interval. Significance threshold was $p < 0.05$ and significant *p* values were in bold. The version number of genes studied is the Human Genome 19.

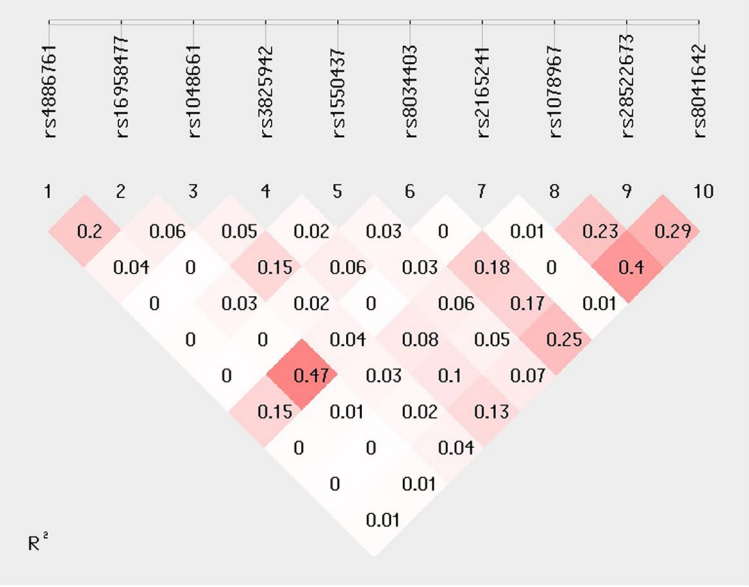

FIGURE 2 Pairwise linkage disequilibrium plot for the SNV. R^2 represents the strength of the pairwise linkage disequilibrium (LD) in *LOXL1*. It means that two SNVs are totally independent when R^2 is equal to zero. R^2 values are between 0 and 1

experiments should be conducted. Similar to the dual-luciferase reporter assay and chromatin immunoprecipitation (ChIP) in the point mutant cell line show allele-specific promotor activity. Alternatively, RNA-seq analysis is applied to mutant cell lines to confirm differentially expressed genes by gene set enrichment analyses. Furthermore, a point-mutant mouse model is employed to confirm whether the mice have phenotypes of BPPV. Whole-genome sequencing is suggested as means of detecting new causal genes and mutations associated with BPPV.

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CONFLICT OF INTEREST

The authors declare no competing interests.

AUTHOR CONTRIBUTIONS

Mingzhu Deng, Chen Liu, and Weiqing Jiang contributed to acquisition of draft and wrote the paper. YGW, Chen Liu, and Weiqing Jiang contributed to acquisition of the clinical evaluation of the patients, genetic counseling, and follow-up; Mingzhu Deng, Dong Wang, and Juan Zhou carried out the molecular analyses; Fei Wang contributed to revision; All authors discussed, read, and approved the manuscript.

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