Kabuki syndrome: novel pathogenic variants, new phenotypes and review of literature

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Abstract

Objective: This study describes 5 novel variants of 7 KMT2D/KDM6A gene and summarizes the clinical manifestations and the mutational spectrum of 47 Chinese Kabuki syndrome (KS) patients.

Methods: Blood samples were collected for whole-exome sequencing (WES) for 7 patients and their parents if available. Phenotypic and genotypic spectra of 40 previously published unrelated Chinese KS patients were summarized.

Result: Genetic sequencing identified six KMT2D variants (c.3926delC, c.5845delC, c.6595delT, c.12630delG, c.16294C > T, and c.16442delG) and one KDM6A variant (c.2668-2671del). Of them, 4 variants (c.3926delC, c.5845delC, c.12630delG, and c.16442delG) in KMT2D gene and the variant (c.2668-2671del) in KDM6A gene were novel. Combining with previously published Chinese KS cases, the patients presented with five cardinal manifestations including facial dysmorphism, intellectual disability, growth retardation, fingertip pads and skeletal abnormalities. In addition, 29.5% (5/17) patients had brain abnormalities, such as hydrocephalus, cerebellar vermis dysplasia, thin pituitary and white matter myelination delay, corpus callosum hypoplasia and Dandy-Walker malformation.

Conclusion: In this report, five novel variants in KMT2D/KDM6A genes are described. A subset of Chinese KS patients presented with brain abnormalities that were not previously reported. Our study expands the mutational and phenotypic spectra of KS.

Keywords: Kabuki syndrome, KMT2D, KDM6A, Chinese patients, Brain abnormalities

Introduction

Kabuki syndrome (KS, OMIM#147920) is a rare syndrome with multiple congenital anomalies. It was first reported by Japanese researchers Kuroki and Niikawa [1, 2]. KS is a heterogeneous condition, two causative genes having been identified so far. The causative gene of KS was identified in 2010 when Bögershausen et al. [3] reported de novo heterozygous variants in KMT2D gene, which is located on chromosome 12q13. Later, in 2012, variants in the KDM6A gene, which is located on chromosome Xp11.23, were identified as another causative gene for KS [4].

Consistent features of KS included distinctive facial dysmorphism (long palpebral fissures, depressed nasal tip and large ears), short stature, intellectual disability, skeletal abnormalities and dermatoglypic abnormalities. Other recurrent features such as congenital cardiac anomalies, ureter malformation and hip joint dislocation had been reported in non-Chinese KS patients [5]. In addition, uncommon features had also been reported. Topcu et al. reported perisylvian cortical dysplasia in a KS patient from Turkey [6]. However, there is little information about brain abnormalities in KS patients.

Herein, we analyzed 7 patients, and identified 7 deleterious KMT2D/KDM6A variants including 6 truncating and 1 missense variants. Of them, 5 variants were novel. To date, 40 sporadic Chinese KS patients had been reported [7–15]. We evaluated the phenotype spectra of
all Chinese KS patients and paid particular attention to the brain abnormalities among a total of 47 unrelated Chinese KS patients.

Subjects and methods

Subjects

Seven patients with clinical presentation of Kabuki syndrome were enrolled from Fuzhou Children’s Hospital of Fujian and Beijing Children’s Hospital, China. This study was approved by the Ethics Committee of Fuzhou Children’s Hospital of Fujian, and written informed consents were obtained from the participants’ legal guardians.

Whole-exome sequencing and variants interpretation

Genomic DNA was extracted from peripheral blood leukocytes of each patient. Blood samples from the parents were also collected if available. The whole-exome sequencing (WES) was performed at Shanghai Children’s Medical Center and MyGenostics, Beijing, China. An adapter-ligated library was prepared using SureSelect Human All Exon Kit (Agilent Technologies, Santa Clara, America) according to the manufacturer’s protocol. Target regions were sequenced on an Illumina Hiseq X Ten System (Illumina, San Diego, America). Paired end reads were aligned to the GRCh37/hg19 human reference sequence. BAM files were generated by Picard and sequence variants were called by Genome Analysis Toolkit (GATK) Haplotype Caller.

Variants were annotated by T'Gex and putative pathogenic variants detected in the patients by WES were validated by Sanger sequencing. Variants were classified following the ACMG/AMP standards and guidelines [16].

Results

Clinical manifestations of seven Chinese patients with KS

We enrolled 7 patients with clinical diagnosis of KS (three males and four females). The age of initial diagnosis ranged from 7 days to 3.2 years. These patients exhibited a diverse phenotype. The clinical features of the seven Chinese patients are listed in Table 1. The main characteristics were as following: facial dysmorphism (n = 7), cardiac abnormalities (n = 6), intellectual disability (n = 5), short stature (n = 4), skeletal abnormalities (n = 3), hearing impairment (n = 3) and dermatoglyphic abnormalities (n = 2).

Pathogenic variants in KMT2D and KDM6A

By WES, we identified six variants (c.3926delC/p.P1309Qfs‘21, c.5845delC/p.Q1949Sfs‘98, c.6595delT/p.Y2199Ifs‘65, c.12630delG/p.Q4210fs‘5, c.16294C > T/p.R5432W and c.16442delG/p.C5481Lfs‘6) in exon 12, 27, 31, 39, 51 and 52 of KMT2D gene (NM_003482.3), respectively, and one variant (c.2668-2671del) in exon 18 of KDM6A gene (NM_021140.3). The variants identified (c.5845delC, c.2668-2671del and c.12630delG) in 3 patients were confirmed by Sanger sequencing, and they were absent from their parents. The other 4 patients’ parental DNA were not available for genetic testing. Four variants (c.3926delC, c.5845delC, c.12630delG and c.16442delG in KMT2D gene, and the variant in KDM6A gene) were novel. Those 6 frameshift variants were predicted to lead to nonsense-mediated decay of mRNA. These null variants can all be classified as pathogenic according to the ACMG/AMP standards and guidelines (c.3926delC, c.5845delC, c.6595delT, c.12630delG, c.16442delG and c.2668-2671del).

The remaining missense variant c.16294C > T; p.R5432W in KMT2D gene has been previously reported [17]. The variant c.16294C > T; p.R5432W was predicted to be deleterious by multiple in silico software, including SIFT (damaging), PolyPhen-2 (probably damaging), MutationTaster (disease causing), PROVEAN (deleterious), and CADD (damaging). Therefore, it can be considered to be likely pathogenic.

Phenotypic spectrum of 47 Chinese KS patients

Forty Chinese patients had been previously reported with KMT2D/KDM6A mutations. With the new 7 patients adding, we summarized the phenotypic features of a total of 47 Chinese KS patients (Table 1). The major clinical signs were as following: facial dysmorphisms (47/47; 100%), intellectual disability (36/45; 80%), short stature (27/47; 57.4%) patients, fingertips pads (25/47; 53.1%), finger clinodactyly (23/47; 48.9%), 5th finger clinodactyly (23/47; 48.9%), congenital cardiac anomalies (20/47; 42.5%) and hip joint dislocation (11/47; 23.4%). Additionally, brain imaging datasets were available for 17 patients and five patients (5/17, 29.4%) exhibited disparate brain anomalies.

Discussion

The genotypic spectrum of 47 Chinese KS patients (23 females, 24 males, 3 are sibs), including 42 KMT2D variants and 3 KDM6A variants were summarized (Table 2). Of the 42 KMT2D variants, there are 1 splicing, 1 nonframeshift indel, 10 nonsense, 13 frameshift and 17 missense variants. All of the nonsense and frameshift variants were categorized as pathogenic because the protein structure was significantly altered. We used silico prediction models including PolyPhen-2, PROVEAN, MutationTaster to analyze the missense variants. Two missense variants (c.7130C > T and c.11638C > A) are predicted to be benign, neutral or polymorphism by at least two of the three silico prediction models. The pathogenicity of the two variants (c.7130C > T and c.11638C > A) was inconclusive and could potentially be non-pathogenic according ACMG/AMP standards and guidelines. The p.R5432W variant was most common,
| Patient | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Literature (N = 40) | Chinese cohort (N = 47) | Non-Chinese cohort (N = 86) (Ref. 17) |
|---------|---|---|---|---|---|---|---|-------------------|------------------------|--------------------------|
| Gender  | Female | Female | Male | Female | Male | Male | Female | | | |
| Age of diagnosis | 1.3 yrs | 11 Months | 5 Months | 7d | 7 yrs | 2.6 Months | 3.2 yrs | | | |
| Growth | | | | | | | | | | |
| Short stature | + | – | – | – | + | + | + | 23 | 57.4% | 57% |
| Neurological abnormalities | | | | | | | | | | |
| Intellectual disability | + | – | + | NA | + | + | + | 32 | 80.4% | 90% |
| Seizures | – | – | – | – | – | – | – | 4 | 8.5% | 15% |
| Cerebellar vermis dysplasia | – | – | – | – | – | – | – | 1 | 2.1% | |
| Corpus callosum hypoplasia | – | – | – | – | – | – | – | 1 | 2.1% | |
| Dandy-Walker malformation | – | – | – | – | – | – | – | 1 | 2.1% | |
| Thinning of pituitary | – | – | – | + | – | + | – | 0 | 2.1% | |
| Delay myelination of cerebral | – | – | + | – | – | – | – | 0 | 2.1% | |
| Hydrocephalus | – | – | – | – | – | – | – | 1 | 2.1% | |
| Craniofacial features | | | | | | | | | | |
| Microcephaly | – | + | + | – | – | – | – | 3 | 10.6% | 41% |
| Micrognathia | – | – | – | – | – | – | – | 3 | 6.3% | 39% |
| High forehead and hairline | + | – | – | – | – | – | – | 0 | 2.1% | |
| Low hairline | + | – | – | – | – | – | – | 2 | 6.3% | |
| Hypertelorism | – | – | + | – | – | + | – | 8 | 21.2% | |
| Epicanthus | – | – | – | – | + | – | – | 8 | 19.1% | |
| Long palpebral fissures | – | + | + | – | – | – | + | 15 | 38.2% | 99% |
| Strabismus | – | – | – | – | – | – | – | 1 | 2.1% | 37% |
| Eversion of lateral third of lower eyelids | + | – | + | – | + | – | + | 14 | 38.2% | 87% |
| Long eyelashes | + | – | – | – | – | – | + | 9 | 23.9% | |
| Arched eyebrows | + | – | – | – | – | – | + | 2 | 8.7% | |
| Sparse eyebrows | – | – | – | – | – | + | – | 18 | 42.5% | |
| Depressed nasal tip | + | + | – | – | – | + | – | 29 | 70.2% | 80% |
| Wide nasal bridge | + | + | – | – | – | + | – | 7 | 21.9% | |
| A diplastic ear | – | + | – | – | – | – | – | 3 | 8.7% | |
| Large ears | – | + | – | – | + | – | – | 29 | 68.0% | 79% |
| High-arched/cleft palate | – | + | + | – | – | – | + | 24 | 57.4% | 66% |
| Thin upper vermilion | + | – | – | – | + | – | + | 2 | 10.6% | 76% |
| Abnormal dentition | – | – | – | – | – | – | – | 5 | 10.6% | 51% |
| Congenital heart defect | + | + | + | – | + | + | + | 14 | 42.6% | 42% |
| Aortic coarctation | – | + | – | – | – | – | – | 1 | 4.3% | |
| Atrial septal defect | + | – | + | – | + | – | – | 6 | 21.7% | |
| Ventricular septal defects | + | + | – | – | + | – | – | 6 | 21.7% | |
| Patent ductus arteriosus | – | – | – | – | + | – | – | 1 | 6.5% | |
| Patent foramen ovale | + | + | + | – | + | – | + | 5 | 21.7% | |
| Aortic arch dysplasia | – | – | – | + | – | – | – | 0 | 2.2% | |
| Internal organ problem | | | | | | | | | | |
| Feeding difficulties | + | – | – | – | – | – | – | 3 | 8.5% | |
| Anal atresia | – | – | – | – | – | + | – | 3 | 8.5% | |
observed in 3 unrelated patients (P2, P28 and P46), which may be a hot spot for KMT2D gene variation in Chinese Patients. Thirty four KMT2D variants and 3 KDM6A variants were confirmed by Sanger sequencing. Of them, 2 variants (c.16273C > A and c.7130 C > T) in KMT2D gene were inherited from their respective biological father, and 1 variant (c.335-1G > T) in KDM6A were inherited from mother, whereas the other 34 variants were de novo.

A phenotypic comparison between the 47 Chinese patients and a cohort of 86 patients from other populations was showed in Table 1. It was reported that the long palpebral fissures were observed in 99% of non-Chinese KS patients, and the eversion of lateral third of lower eyelids 87% [17]. The Chinese patients showed a significantly lower frequency (38.2% for both features). While a lack of clinical acuity in recognizing these features by clinicians could account for some differences, we think it may more likely reflecting the ethnicity difference in feature presentations. Additionally, The Chinese patients had higher frequency of hearing impairment but lower frequency of microcephaly, micrognathia, strabismus, abnormal dentition, fifth finger clinodactyly and fingertip pads. The frequencies of other phenotypes including short stature, intellectual disability, cardiac defects, large eras, hypoglycemia and high-arched/cleft palate were consistent with previously reported [17].

KMT2D/KDM6A affects genes and biological processes globally. The clinical consequence of KMT2D/KDM6A gene mutations also seems to have a global effect on development and growth, both craniofacial, cardiac, neural and musculoskeletal (presented with short stature) tissue [18]. Across the board, the Chinese KS patients had typical facial features. These dysmorphic features included long palpebral fissures, depressed nasal tip and large ears (most prominent from the profile), similar to the KS patients from other ethnicities, indicating a consistent and highly penetrant facial dysmorphic profile across populations.

Thirty-one Chinese patients presented with intellectual disability, most were mildly affected. Mehmet et al. [19] reported one and Parisi et al. [20] reported three KS patients with autism spectrum disorder, yet none of the Chinese KS patients exhibited autistic features or significant behavioral issues. Various structural brain anomalies had been infrequently described in KS patients. Topcu et al. reported perisylvian cortical dysplasia [6], Cedrik et al. reported two patients presented with holoprosencephaly [21]. Furthermore, based on MRI, significantly decreased grey matter volume in the bilateral hippocampus and dentate gyrus have been described in KS patients [22]. We found the brain abnormalities including thinning of pituitary and myelination of cerebral white matter in Chinese KS patients, which were not previously reported in KS patients. We also found that hydrocephalus, corpus callosum hypoplasia and Dandy-Walker malformation which had been reported previously both in Chinese patients and other populations [7, 23].

### Table 1 Phenotypic summary of Chinese KS patients (Continued)

| Patient | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Literature (N = 40) | Chinese cohort (N = 47) | Non-Chinese cohort (N = 86) (Ref. 17) |
|---------|---|---|---|---|---|---|---|-------------------|-----------------------|-------------------------------|
| Bilateral inguinal hernia | – | – | – | – | – | – | – | 2 | 4.2% | – |
| Splenomegaly | – | – | – | – | – | – | – | 1 | 4.2% | – |
| Cryptorchidism | – | – | – | – | – | – | – | 1 | 2% | – |
| Hearing impairment | – | + | + | – | – | + | – | 13 | 34.0% | 25% |
| Otitis media | – | – | – | – | – | – | – | 12 | 27.6% | – |
| Cholesteatoma | – | – | – | – | – | – | – | 2 | 6.4% | – |
| Cochlear dysplasia | – | – | – | – | – | – | – | 0 | 2.1% | – |
| Renal/ureter malformation | – | – | – | + | + | – | – | 2 | 10.6% | 40% |
| Musculoskeletal features | | | | | | | | | | |
| Hip joint dislocation | – | – | – | + | – | + | – | 9 | 23.4% | 26% |
| Right diaphyseal femoral fracture | – | – | – | – | – | – | + | 0 | 2.1% | – |
| Fifth finger clinodactyly | + | – | – | – | – | – | – | 22 | 48.9% | 84% |
| Absent palmer transverse crease | – | – | + | – | – | – | – | 5 | 12.7% | – |
| Fingertip pads | + | – | – | – | – | – | – | 24 | 53.2% | 89% |
| Endocrine | | | | | | | | | | |
| Hypoglycemia | – | + | + | – | – | – | – | 2 | 8.5% | 7–8% |
| Early breast development | – | – | – | – | – | – | – | 1 | 4.2% | 28% |
| Case ID | Literature | Genes involve | Mutation | Predicted protein changes | Type of mutation | Inheritance | Exon | Pathogenic classification |
|---------|------------|---------------|----------|---------------------------|------------------|-------------|------|----------------------------|
| 1       | This study | KMT2D         | c.5845delC | p.Q1949fs*98              | Frameshift del    | De novo     | 27   | Pathogenic                 |
| 2       |           | KMT2D         | c.16294C>T | p.R5432W                  | Missense          | NA          | 51   | Likely Pathogenic          |
| 3       |           | KDM6A         | c.2668-2671del | p.N891V6*27   | Frameshift del    | De novo     | 18   | Pathogenic                 |
| 4       |           | KMT2D         | c.6595delT | p.Y2199fs*65             | Frameshift del    | NA          | 31   | Pathogenic                 |
| 5       |           | KMT2D         | c.16442delG | p.C5481Lfs*6             | Frameshift del    | NA          | 52   | Pathogenic                 |
| 6       |           | KMT2D         | c.3926delC | p.P1390Qfs*21            | Frameshift del    | NA          | 12   | Pathogenic                 |
| 7       |           | KMT2D         | c.12630delG | p.Q4120Xfs*5             | Frameshift del    | De novo     | 39   | Pathogenic                 |
| 8       |           | KMT2D         | c.12199C>T | p.R5432Q                  | Missense          | De novo     | 51   | Likely Pathogenic          |
| 9       |           | KMT2D         | c.4664C>T  | p.S1555F                 | Missense          | De novo     | 17   | Likely Pathogenic          |
| 10      |           | KMT2D         | c.8639T>C  | p.L2880P                 | Missense          | De novo     | 34   | Likely Pathogenic          |
| 11      |           | KMT2D         | c.3095delT | p.L1032Rfs*24X           | Frameshift del    | NA          | 11   | Pathogenic                 |
| 12      |           | KMT2D         | c.96C>G    | p.D32E                   | Missense          | De novo     | 2    | Likely Pathogenic          |
| 13      |           | KMT2D         | c.4395dupC | p.K1466Qfs25X            | Frameshift del    | NA          | 15   | Pathogenic                 |
| 14      |           | KMT2D         | c.11638C>A  | p.L3880M                 | Missense          | NA          | 39   | Uncertain significance     |
| 15      |           | KMT2D         | c.4140T>A  | p.C1370X                 | Nonsense          | NA          | 14   | Pathogenic                 |
| 16      |           | KDM6A         | exon1-2del | c.11718-11723delGCAACA   | Frameshift del    | De novo     | 39   | Likely Pathogenic          |
| 17      |           | KMT2D         | c.12697C>T | p.Q4233X                 | Nonsense          | De novo     | 39   | Pathogenic                 |
| 18      |           | KMT2D         | c.12696C>T | p.Q4232H                 | Missense          | De novo     | 39   | Pathogenic                 |
| 19      |           | KMT2D         | c.3495delC | p.P1165Lfs*39            | Frameshift del    | De novo     | 11   | Pathogenic                 |
| 20      |           | KMT2D         | c.10881delT | p.L3627Rfs*31            | Frameshift del    | De novo     | 39   | Pathogenic                 |
| 21      |           | KMT2D         | c.16498C>T | p.R5500W                 | Missense          | NA          | 53   | Likely Pathogenic          |
| 22      |           | KMT2D         | c.12560G>A | p.G4187E                 | Missense          | NA          | 39   | Likely Pathogenic          |
| 23      |           | KMT2D         | c.16273G>A | p.E5425X                 | Missense          | NA          | 51   | Likely Pathogenic          |
| 24      |           | KMT2D         | c.4485C>A  | p.Y1495S                 | Missense          | De novo     | 16   | Pathogenic                 |
| 25      |           | KMT2D         | c.5235delA | p.A1746Lfs*39            | Frameshift del    | De novo     | 22   | Pathogenic                 |
| 26      |           | KMT2D         | c.7048G>A  | p.Q2350*                 | Frameshift del    | De novo     | 31   | Pathogenic                 |
| 27      |           | KMT2D         | c.12307C>T | p.Q4013X                 | Nonsense          | De novo     | 38   | Pathogenic                 |
| 28      |           | KMT2D         | c.16294C>T | p.R5432W                 | Nonsense          | De novo     | 51   | Likely Pathogenic          |
### Table 2 Genotypic summary of Chinese KS patients (Continued)

| Case ID | Literature | Genes involved | Mutation | Predicted protein changes | Type of mutation | Inheritance | Exon | Pathogenic classification |
|---------|------------|----------------|----------|---------------------------|------------------|-------------|------|--------------------------|
| 29      |            | KMT2D          | c.5993A > G | p.Y1998C                 | Missense         | De novo     | 28   | Likely Pathogenic        |
| 30      |            | KMT2D          | c.16273G > A | p. E5425K                | Missense         | Father      | 51   | Likely Pathogenic        |
| 31      |            | KMT2D          | c.16273G > A | p. E5425K                | Missense         | Father      | 51   | Likely Pathogenic        |
| 32      |            | KMT2D          | c.16273G > A | p. E5425K                | Missense         | Father      | 51   | Likely Pathogenic        |
| 33      |            | KMT2D          | c.8743C > T  | p.R2915X                 | Nonsense         | De novo     | 34   | Pathogenic               |
| 34      |            | KMT2D          | c.5269C > T  | p.R1757X                 | Nonsense         | De novo     | 22   | Pathogenic               |
| 35      |            | KMT2D          | c.16273G > A | p.E5425K                 | Missense         | De novo     | 51   | Likely Pathogenic        |
| 36      |            | KMT2D          | c.7650-1delCT | p.P2550Rfs2604X          | Frameshift del   | De novo     | 31   | Pathogenic               |
| 37      |            | KMT2D          | c.16135C > T  | p.Q5379X                | Nonsense         | De novo     | 51   | Pathogenic               |
| 38      |            | KMT2D          | c.15326G > T  | p.C5109F                 | Missense         | De novo     | 48   | Pathogenic               |
| 39      |            | KMT2D          | c.16498C > T  | p.R5500W                 | Missense         | De novo     | 53   | Pathogenic               |
| 40      | [13]       | KMT2D          | c.7130C > T"  | p.P2377L                | Missense         | Father      | 31   | Uncertain significance   |
| 41      |            | IVS9 + 2 T > G |          |                           | Splice mutation  | De novo     |      | Pathogenic               |
| 42      | [14]       | KMT2D          | c.11770C > T  | p.Q3924X                | Nonsense         | De novo     | 39   | Pathogenic               |
| 43      |            | KMT2D          | c.13033A > T  | p.K4345X                | Nonsense         | De novo     | 39   | Pathogenic               |
| 44      |            | KMT2D          | c.1763C > G  | p.S588X                  | Nonsense         | De novo     | 10   | Pathogenic               |
| 45      |            | KMT2D          | c.5848delT    | p.1950Pfs*97            | Frameshift       | De novo     | 27   | Pathogenic               |
| 46      |            | KMT2D          | c.16294C > T  | p.R5432W                | Missense         | De novo     | 51   | Likely Pathogenic        |
| 47      | [15]       | KDM6A          | c.335-1G > T  |                           | Splice site mutation | mother   |      | Likely Pathogenic        |

*No sufficient evidence supporting it's pathogenicity *Denotes a frameshift change as the first affected amino acid
In addition, cerebellar vermis dysplasia was initially reported in Chinese patients [11]. These observations suggested a strong association between various brain abnormalities and KS. Further study is needed to explore the clinical consequences of these brain abnormalities.

Conclusions
We described five novel variants that are causal for the seven KS Chinese patients, and confirmed that the Chinese KS presented with typical clinical phenotypes as previously reported in non-Chinese patients, but of variable feature prevalence. We also pointed out that brain structural abnormalities including thinning of pituitary and delay myelination of cerebral white matter may be part of KS phenotype that warrant further investigation.

Abbreviations
ACMG/AMP: American College of Medical Genetics and Genomics and the Association for Molecular Pathology; KDM6A: lysine (K)-specific methylase 6A; KMT2D: lysine (K)-specific methyltransferase 2D; KS: Kabuki syndrome; WES: whole-exome sequencing

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Authors’ contributions
HS and CS conducted the data analysis and interpretation and wrote the manuscript. JW, CG and RC contributed to the study design and helped to analyze data and revise the first draft. QQ and BC assisted to conduct data analysis. All authors read and approved the final manuscript.

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Availability of data and materials
The dataset supporting the conclusions of this article is included within the article.

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Fuzhou Children’s Hospital of Fujian, and written informed consents were obtained from the participants’ legal guardians.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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