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Clinical diagnosis and genetic analysis of a rare case of Duchenne muscular dystrophy and spinal muscular atrophy

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Abstract

Objective To explore the clinical and genetic features both spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD) diagnosed in a child.

Methods A child was diagnosed with SMA combined with a duplication of exons 2–20 in the *DMD* gene at another hospital. Optical genome mapping (OGM) was employed to assess whether the duplication of exons 2–20 in the *DMD* gene affected its function.

Results The patient was a 19-month-old boy who presented with delayed motor development and generalised hypotonia. Whole exome sequencing (WES) and multiplex ligation-dependent probe amplification (MLPA) performed at another hospital indicated that the patient had a hemizygous duplication involving exons 2–20 of the *DMD* gene, which was maternally inherited. Additionally, the patient had a homozygous deletion of *SMN1* exons 7 and 8 (zero copies) and 3 copies of *SMN2* exons 7 and 8. Both parents carried one copy of *SMN1*. Additionally, the mother harboured two copies of *SMN2*, whereas the father had three copies of *SMN2*. OGM analysis revealed a tandem duplication of exons 2–20 in the *DMD* gene in the patient and his mother.

Conclusion We describe a rare case of a patient with concomitant DMD and SMA. When a patient's phenotype cannot be explained by a single genetic disorder, the possibility of multiple genetic disorders coexisting due to multiple mutations must be considered. OGM is a valuable diagnostic tool for determining the pathogenicity of *DMD* exon duplications, as it can definitively establish their genomic location and structure.

Keywords Duchenne muscular dystrophy, Spinal muscular atrophy, Optical genomics mapping technology, Tandem repeats

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Introduction

Duchenne muscular dystrophy (DMD; OMIM #310200) and spinal muscular atrophy (SMA; OMIM #253300) are two common neuromuscular disorders. Both disorders share a clinical presentation in infancy or childhood, typically including progressive muscle weakness and delayed motor milestones. They are progressive disorders that ultimately impact quality of life and are life-limiting. DMD is an X-linked recessive disorder with an incidence of approximately 1/5,000. Moreover, it is caused by mutations in the *DMD* gene, which encodes the dystrophin protein, thereby leading to a loss of functional dystrophin. DMD is characterised by proximal muscle weakness resulting in an unsteady gait, difficulty climbing stairs, frequent falls, and apparent calf muscle hypertrophy in childhood [1]. *SMA* is mapped to chromosome 5q13 and consists of two genes (*SMN1* and *SMN2*). *SMN1* is the pathogenic gene of SMA, whereas *SMN2* functions as a disease-modifying gene that determines phenotypic severity in patients with SMA [2]. The incidence of SMA is approximately 1/10,000, and the carrier rate in the Chinese population is approximately 1/48–1/42 [2]. The clinical manifestations of SMA include progressive, symmetric muscle weakness and atrophy, which predominantly affect the proximal limbs. Based on the age of onset and clinical phenotype, SMA can be broadly classified into five subtypes [3]: type 0, type I, type II, type III, and type IV.

The diagnosis of rare diseases poses significant challenges, primarily due to their nonspecific early presentations, age-dependent progression, and substantial phenotypic overlap. Consequently, clinicians may prematurely make a single diagnosis based on the predominant symptoms, thus potentially missing the rare possibility of two co-occurring diseases. Studies have demonstrated that the prevalence of co-occurring genetic diseases caused by two or more pathogenic variants can be as high as 7%, and several cases have been documented in the literature [4–6]. In 1994, Oldfors et al. [7] reported the first confirmed case of DMD combined with SMA, which was diagnosed via muscle biopsy. Unfortunately, the child died from respiratory failure at the age of 11 months. Xia et al. [8] reported the second case of a patient with both DMD and SMA who was diagnosed through whole exome sequencing (WES) and multiplex ligation-dependent probe amplification (MLPA). The results revealed that the patient had a homozygous deletion of the *SMN1* gene combined with a hemizygous deletion of exon 50 in the *DMD* gene. Here, we report a case of maternally inherited *DMD* duplications identified in a Chinese patient who presented with combined features of SMA and DMD. OGM revealed a tandem duplication of the *DMD* gene in the patient, which disrupted the reading frame. Our findings reveal the pathogenic mechanisms underlying the *DMD* gene duplication and provide critical guidance for the personalised treatment of patients.

Materials and methods

Patients

One child with mutations in both the *SMN1* gene and the *DMD* gene who presented to the Affiliated Women's and Children's Hospital of Ningbo University in July 2025 was selected as the research subject. Informed consent was obtained from both parents of the child, along with the approval of the Medical Ethics Committee of the Affiliated Women's and Children's Hospital of Ningbo University (Approval No.: EC2023Z178).

Clinical data collection

A retrospective approach was adopted to collect the relevant clinical data of the child in this study, including his medical history, physical examination results, laboratory test results, and imaging examination results.

DNA extraction

Three-millilitre peripheral blood samples from the child and his parents were collected in EDTA anticoagulant tubes. Ultralong DNA molecules were extracted from the blood samples using the Bionano Prep SP Blood and Cell DNA Isolation Kit (v2 reagent kit, Bionano Genomics, USA), and the DNA was quantified using the Qubit® BR (Broad Range) dsDNA Assay Kit (Thermo Fisher Scientific, USA).

Optical genome mapping (OGM)

Ultralong DNA molecules were fluorescently labelled and stained using the DLS DNA Labelling Kit (Bionano Genomics, USA). The operation process mainly consists of four steps: utilisation of the fluorescent transfer enzyme DLE-1 (Bionano Genomics, USA) for whole-genome labelling; purification and removal of free fluorescent groups via dialysis; subsequent staining of the double-stranded DNA molecular framework with the DNA backbone dye (Bionano Genomics, USA); and a final quantification of the labelled staining products using a Qubit v3.0 fluorescence quantitative instrument (Thermo Fisher Scientific, USA). The concentration of the labelled DNA was between 4 ng/uL and 12 ng/uL, and the coefficient of variation (CV) value was less than 0.25. These samples were processed for the subsequent chip operation. The samples containing the labelled DNA were loaded onto the Saphyr G2.3 chip (Bionano Genomics, USA), and quantitative analysis was performed using the Saphyr instrument. Chromosome structural variations in the samples were detected using the analysis software provided by Bionano (Bionano Solve v3.4, USA).

Results

Clinical manifestations

The patient (a boy) was the first-born child of healthy nonconsanguineous Chinese parents. He was born at full term following an uneventful pregnancy and normal delivery. He achieved early milestones of head control at 3 months and rolling over at 5 months. However, by 8 months of age, he demonstrated regression in both head control and the ability to roll over independently while concurrently exhibiting decreased spontaneous limb movements and reduced muscle tone. At 10 months of age, testing at a local hospital revealed a significantly elevated creatine kinase (CK) level of 5091 U/L (reference range: 50–310 U/L), and electromyography (EMG) revealed a mixed pattern of injury (predominantly myopathic). The child was admitted to the Children's Hospital of Shanghai at 11 months of age for further assessment and genetic testing. WES-based CNV (copy number variation) sequencing suggested that the child concurrently had a duplication of exons 2–20 in the *DMD* gene and a homozygous deletion of exons 7 and 8 in the *SMN1* gene. Further MLPA validation confirmed that the duplication in exons 2–20 of the *DMD* gene was maternally inherited. Additionally, MLPA validation confirmed that the child had 0 copies of exons 7–8 in the *SMN1* gene and 3 copies of exons 7–8 in the *SMN2* gene. Both parents were identified as carriers, with one copy of the *SMN1* gene. The father has three copies of the *SMN2* gene, and the mother has two copies of the *SMN2* gene. (Fig. 1).

An intrathecal injection of nusinersen was subsequently initiated at the Children's Hospital of Zhejiang University, and rehabilitation training was commenced at the Ningbo Rehabilitation Hospital concurrently at 13 months of age. To clarify whether the child also had DMD, the patient, at 18 months of age, was admitted to the Affiliated Women's and Children's Hospital of Ningbo University for consultation, where OGM testing was performed. At 19 months of age, the patient had completed five doses of nusinersen injections, with the most recent dose being administered in August 2025. Compared with day 0 (before the first injection), the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) score increased from 16 to 40 points, the fine motor function measure (FMFM) score increased from 40.01 to 43.07 points, and the Wee Functional Independence Measure (Wee FIM) score increased from 19 to 26 points. Muscle strength assessment revealed mild improvement, with scores of 3- being observed in the upper limbs and 2 being observed in the lower limbs (compared to the pretreatment score of less than 2 + throughout the body). The child remains unable to sit independently and is fully dependent on his parents for activities of daily living.

Optical genome mapping

A structural variant was identified via OGM: an approximately 530 kb duplication ogm[GRCh38] dup(X)(p21.1p21.1) involving Chr X: 32,477,780 ~ 32490617:33 012568 ~ 33,025,411 was detected. Tandem duplication had disrupted the open reading frame of the *DMD* gene (Fig. 2).

Discussion

In this study, the child exhibited motor regression at 8 months of age, which manifested as unstable head control and reduced spontaneous limb movements. Serum CK levels were significantly elevated, and electromyography revealed mixed but predominantly myopathic features. Based on the clinical manifestations, SMA was considered a strong working diagnosis. Genetic testing in other hospitals at the age of 11 months revealed a maternally inherited duplication of exons 2–20 in the *DMD* gene and a homozygous deletion in the *SMN1* gene. Follow-up OGM testing confirmed a tandem duplication of exons 2–20 in the *DMD* gene. After the molecular findings were integrated with the clinical phenotype, a definitive diagnosis of concurrent DMD and SMA was established.

Following the advent of genetic testing, molecular testing methods such as WES, copy number variation sequencing (CNV-seq) and MLPA have become the gold standard for diagnosing neuromuscular diseases such as SMA and DMD. These techniques possess distinct advantages and limitations. Therefore, clinicians should tailor their diagnostic approach based on the specific clinical scenario. Although widely used for DMD diagnosis and capable of accurately diagnosing a majority of patients, these technologies cannot identify balanced structural rearrangements, nor can they determine the exact location of duplicated or rearranged genomic material. In recent years, OGM has emerged as a novel method for genetic disease testing. This technique has made significant advances in assessing the pathogenicity of copy number variations and detecting genomic structural variants; moreover, it is gaining increasing traction in clinical application. Wang et al. [9] demonstrated that OGM can accurately map breakpoints with a resolution of up to 10 kb, and the identified locations were consistent with those determined by karyotyping. Dharmadhikari et al. [10] applied OGM to 33 cases of copy number duplications with uncertain significance. The analysis revealed 26 tandem duplications and 7 complex rearrangements. Of these cases, 27 cases were subsequently reclassified as likely benign variants. OGM technology provides a powerful new approach for diagnosing genetic diseases, leveraging its high resolution, whole-genome coverage, and superior ability to detect structural variants.

DMD duplications are a common type of pathogenic variant in Chinese individuals, accounting for

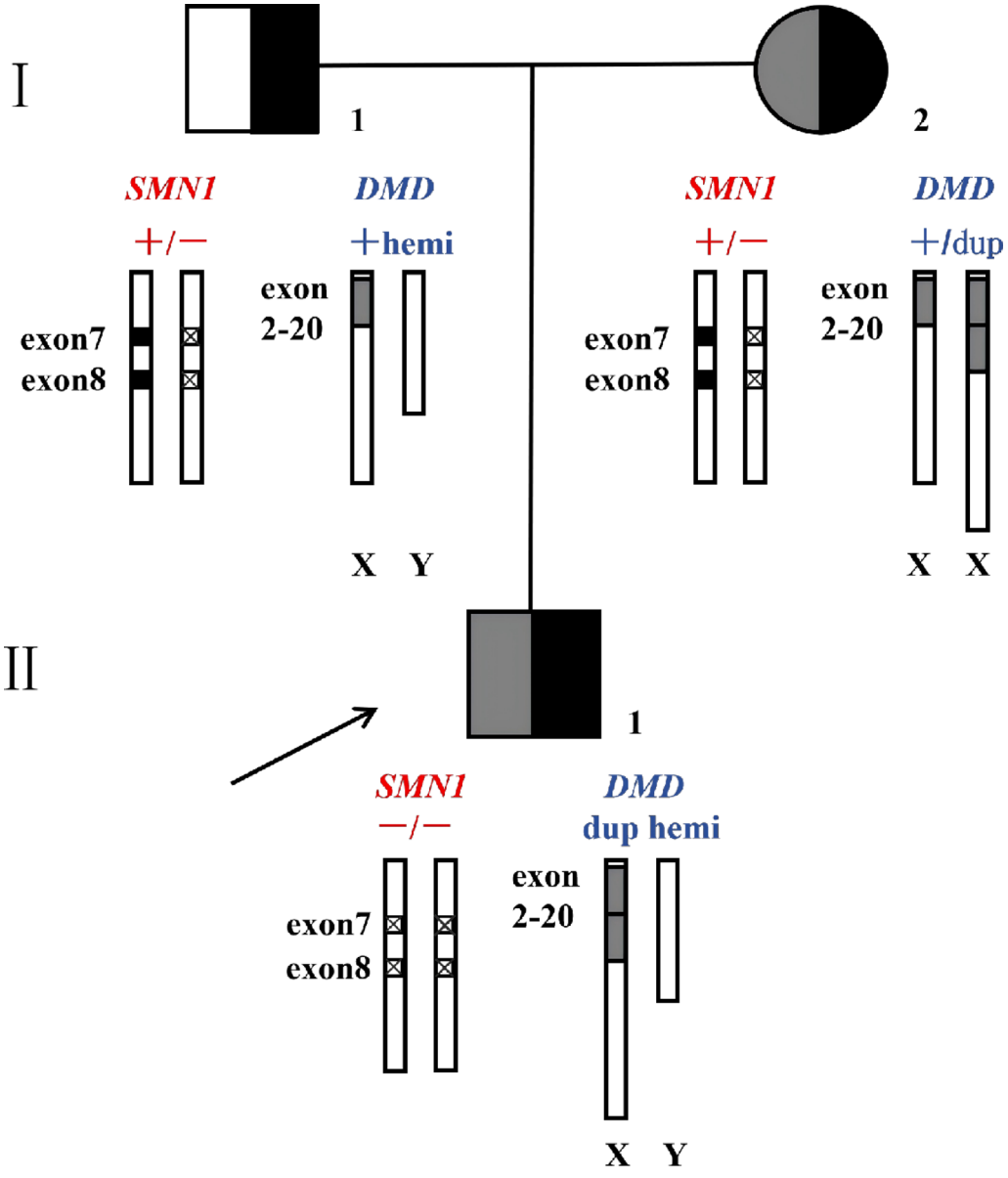

Fig. 1 Pedigree and genotypes of a Chinese family with *DMD* duplications and *SMN1* deletion. We use "×" to indicate the deletion. The black-filled symbol represents individuals with *SMN1* deletion. The gray-filled symbol represents individuals with *DMD* duplications. I-1: Father's genetic testing revealed heterozygous deletions in exons 7 and 8 of the *SMN1* gene, and no deletions or duplications were detected in the *DMD* gene; I-2: Mother's genetic testing showed only one copy in exons 7 and 8 of *SMN1*, and there was a duplication in exon 2–20 of the *DMD* gene; II-1 (proband): The patient's genetic testing showed homozygous deletions of *SMN1* in exon 7 and exon 8, and a duplication in exon 2–20 of the *DMD* gene. dup: *DMD* duplications; hemi: hemizygous *DMD*

approximately 9% of all mutations [11]. On the basis of the location of the duplicated region, it can be further categorised into two classes: intragenic duplications (in which both breakpoints are located within the gene) and terminal duplications (where one breakpoint is located inside the gene and the other is located beyond the 5' or 3' end of the gene). In addition, the structural configuration of duplications can be either tandem or interspersed, and approximately 80% of genomic duplications are tandem duplications [12, 13]. Based on the guidelines, researchers hypothesise that duplications encompassing the 5′ or 3′ end of the *DMD* gene tend to be likely benign as such tandem duplications generally preserve the structural and functional integrity of the gene. In contrast, intragenic duplications disrupt the reading frame of *DMD*, thereby resulting in pathogenic variants. Furthermore, multiple studies have provided clinical evidence in support of this hypothesis. Using CNV-seq, Liu et al. [14] identified phenotypically normal males carrying *DMD* gene duplications. They hypothesised that duplications

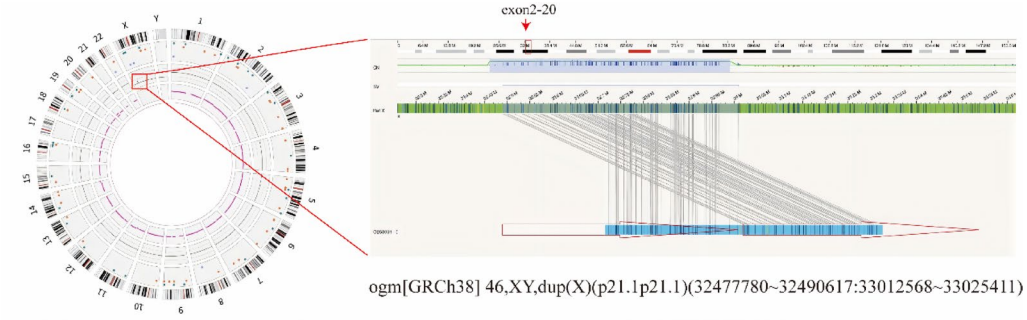

Fig. 2 Genome structural variation involving the gene *DMD* identified in the proband. The circos plots are shown on the left, with the copy-number gains on Xp21.1 framed with red boxes. The amplified genomic browser views of the Xp21.1 duplications are shown on the right. The alignments of the sample's consensus map (blue bar) with the reference consensus map (green bar) illustrate duplications of 530 kb, which is tandemly duplicated (indicated by the red arrows and gray lines)

encompassing the 5' or 3' end of the *DMD* gene may be nonpathogenic, as they do not compromise the integrity of the gene. Zhang et al. [15] also reported that healthy males in three families harboured a 1.2–1.4 Mb duplication in the Xp21.1 region, which involved the 5' UTR up to exon 12 of the *DMD* gene. In addition, OGM testing revealed a tandem insertion of the duplicated fragments into the upstream 5' UTR, thus prompting a reclassification of the variant as likely benign. Ma et al. [16] reported a duplication of exons 64–79 in the *DMD* gene in two otherwise healthy brothers. OGM confirmed a tandem duplication of exons 64–79, which was reclassified as benign due to the preservation of the structural integrity of the *DMD* gene. Ding et al. [17] identified tandem duplications in multiple patients with DMD using long-read sequencing technology and classified them as pathogenic variants. Consistent with previous studies, the duplication of exons 2–20 in the *DMD* gene identified in this study was also a tandem duplication, which was predicted to disrupt gene function and was consequently classified as a pathogenic variant.

Additionally, interspersed duplications in the *DMD* gene have been reported in the literature. Ma et al. [16] reported a duplication of exons 10–13 in the *DMD* gene of an 8-year-old boy, who exhibited a typical DMD phenotype. OGM revealed an inverted insertion of exons 10–13, which disrupted the normal structure and function of the *DMD* gene. He et al. [18] reported three nonconsecutive duplications in the *DMD* gene (exons 51–53, exons 64–79, and intron 55) in a healthy father and daughter. OGM revealed that all the duplicated fragments were located outside the *DMD* gene, thus confirming that the father's *DMD* gene remained structurally intact. Bai et al. [19] reported a duplication of *DMD* exons 56–61 in an asymptomatic male individual. Long-read sequencing revealed that the duplicated segment was interspersed and inserted more than 4 Mb away from its original genomic location. Ding et al. [17] reported intragenic *DMD* duplications in 15 patients. Four patients with clinical indications had pathogenic tandem duplications. The remaining 11 patients without clinical indications of dystrophinopathy had interspersed duplications, with duplications in four patients subsequently being reclassified as likely benign, duplications in two patients as likely pathogenic, and duplication in one patient as uncertain. In summary, these cases demonstrate that not all *DMD* duplications are pathogenic. The most prudent to classify incidentally detected *DMD* duplications as VUS until proven otherwise. Rather, the pathogenicity of *DMD* duplications depends on their structural configuration in the following ways: (1) if the duplicated fragment occurs outside the gene, it generally remains nonpathogenic regardless of the genomic region covered; (2) if one breakpoint is situated within the 5' or 3' UTR, tandem duplication usually preserves the integrity of the reading frame of the *DMD* gene; and (3) if both breakpoints are located within the *DMD* gene, either tandem or inverted duplication is likely to disrupt gene integrity.

Nusinersen is the first approved antisense oligonucleotide therapy for the treatment of SMA. It is administered via intrathecal injection and targets the intron 7 splicing inhibitory element of SMN mRNA, thereby regulating the splicing of SMN2 mRNA transcripts and promoting the production of the full-length SMN protein [20]. However, disease-modifying therapies for SMA are associated with certain limitations, including high costs and age-restricted applicability. Multiple international clinical studies have established that presymptomatic treatment for SMA maximises long-term benefits and leads to a more favourable disease prognosis compared with post-onset therapy [21–23]. The established management for DMD involves the use of oral glucocorticoids to modify disease progression. Notably, this treatment should be avoided in children under two years of age and in those who have not achieved full motor development [24]. Other Food and Drug Administration-approved treatments for DMD include exon-skipping therapies. These drugs are mutation-specific and target specific

exons, such as exons 51, 53, and 45 [25]. Similar to our case, Xia et al. [8] reported concurrent DMD and SMA in an 11-year-old patient who harboured zero copies of the *SMN1* gene, three copies of the *SMN2* gene, and a deletion in exon 50 of the *DMD* gene. This patient was started on nusinersen at 6 months of age. After five doses, he showed significant clinical improvement, including the ability to control his head in the prone position, prop up his upper body with his arms extended, sit more steadily, and demonstrate increased lower limb strength. In contrast, the child in our study began to receive nusinersen treatment at 13 months of age. Following five doses of treatment (current age: 19 months), our patient's motor function did not significantly improve, and he exhibited a floppy state. This effect is largely attributable to the delayed initiation of therapy in this case.

Diagnostic difficulty is attributed to the concurrent occurrence of two similar rare diseases in a single individual. Previous molecular testing indicated that the child carried variations in two genes, thus leading to a definitive diagnosis of SMA. However, although the child also demonstrated a duplication variant in the *DMD* gene (which is classified as "likely pathogenic" referred to the "tandem presumption"), it is still insufficient to serve as a basis for diagnosing DMD due to the unclear positional effect. In terms of clinical phenotype, the child's creatine kinase level exceeded the upper limit of normal by more than tenfold, which is significantly higher than the mild elevation typically seen in SMA patients. This abnormality suggests a potential superimposed effect of a second disease. The subsequent use of OGM testing ultimately confirmed the co-diagnosis of SMA and DMD in this patient. Therefore, when a patient's clinical manifestations are complex and cannot be fully explained by a single genetic variant, multiple diagnostic methods should be comprehensively utilised to systematically analyse the relationship between genotype and phenotype, in order to achieve a precise diagnosis.

Although our study provides valuable insights, it has limitations. OGM has a resolution of approximately 500 bp and can provide only an approximate genomic interval for breakpoints, thereby leading to ambiguity regarding the precise sequence surrounding the breakpoints. For certain highly homologous regions, OGM may be insufficient to determine the precise location, thus necessitating validation using other techniques such as Sanger sequencing and long-read sequencing. Nonetheless, these limitations do not affect the interpretation of the findings in this study. Our findings emphasise the importance of precise structural evaluation using OGM in the genetic diagnosis of dystrophinopathies and other similar monogenic disorders.

Conclusion

In conclusion, this study presents the third case worldwide and the second from mainland China with concurrent DMD and SMA. This case demonstrates the significant advantages of OGM testing in identifying complex structural variations in the *DMD* gene and determining their pathogenicity, thus providing crucial evidence for precise diagnosis. For families at high risk of concurrent DMD and SMA, prenatal diagnosis or third-generation IVF technology should be offered to effectively prevent the occurrence of severe genetic disorders.

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Author contributions
Yingwen Liu and Minmin Wang is responsible for genetic testing and thesis writing. Keji Zhang is responsible for clinical diagnosis and treatment. Changshui Chen, Haibo Li and Lulu Yan provided funding acquisition. Haibo Li revised the paper and provided comments and provided funding acquisition. All authors have read and approved the manuscript.

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Data availability
The data that support the findings of this study are available in this article.

Declarations

Ethics approval and consent to participate
The research was approved by the Medical Ethics Committee of the Affiliated Women's and Children's Hospital of Ningbo University (Approval No. EC2023Z178). The guardians of the child gave informed consent to the study.

Consent for publication
The guardians of the child gave informed consent to the study.

Competing interests
The authors declare no competing interests.

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