Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2023**; 50(10): 215
https://doi.org/10.31083/j.ceog5010215

Original Research

Prenatal Diagnosis of Complex Copy Number Variants in the Fetus and Associated Cytogenetic Findings in Parents

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Academic Editor: George Daskalakis
Submitted: 28 June 2023 Revised: 25 July 2023 Accepted: 2 August 2023 Published: 18 October 2023

Abstract

Background: Co-occurrence of complex copy number variants (CNVs) is associated with more severe clinical expressivity of known syndromes. Few studies discuss diagnosis and genetic counseling for fetuses identified with multiple CNVs. This cohort study aims to summarize findings of complex copy number variants identified via prenatal diagnosis along with the results of parental studies. **Methods**: 2746 pregnant women were included and diagnosed by chromosomal microarray analysis (CMA) according to different clinical indications. A total of 12 fetuses were diagnosed with complex CNVs (a fetus identified with two or more CNVs simultaneously). Parental analysis was performed by CMA, G-band karyotype analysis, and whole-genome low-coverage mate-pair sequencing (WGL-MPS) based on the size of the fetal imbalances and method resolution. **Results**: Fetuses carrying complex CNVs were identified as being 0.4% (12/2746) in our cohort. The parental validation study was performed in 8 of 12 complex CNVs cases with the permission of the patients. The primary results suggested that 62.5% (5 out of 8) of fetuses with complex CNVs were from parental inheritance. In these cases, 4 out of 5 were derived from maternal or paternal balanced translocation carriers. Recurrent spontaneous abortion was found in balanced translocation carrier family. **Conclusion**: In this study, in 4/8 of the fetuses detected with complex CNVs was inherited from a parental balanced translocation. Given the risk of parental balanced rearrangements when fetal complex CNVs are identified, genetic counseling for future pregnancies may be useful for these families.

Keywords: complex CNVs; prenatal diagnosis; genetic counseling; balanced translocation; parental analysis

1. Introduction

It is well known that the role of copy number variants (CNVs) has become increasingly apparent. Researchers have found that CNVs have been linked to numerous variety of human diseases, including intellectual disability (ID), multiple congenital anomaly syndromes, and complex neurodegenerative and neuropsychiatric disorders [1,2]. Structural genomic rearrangements such as duplications, deletions, translocations, and inversions were the major cause of CNVs [3,4]. If a parent carries the structural abnormalities of chromosome balance including balanced translocation, Robertsonian translocation or inversion without any loss or gain of genetic material, it is likely to result in CNVs in the offspring [5,6].

With the rapid development of chromosomal microarray technology, few complex CNVs (number of CNV $\geq$2) cases have been reported over the last decade. Researchers hypothesized that the complex CNVs were associated with more severe clinical expressivity of known syndromes. Bertini *et al*. [7] suggested that additional CNVs outside the 22q11.2 region may possibly modulate the variable phenotype and incomplete penetrance of DiGeorge syndrome, as well as proposed "Additional Hit" to explain severe expressivity [8]. The majority of 22q cases are *de novo* (93%) and are usually a result of non allelic homologus recombination [9]. The most common known balanced translocation in chromosomes 11 and 22 increase the risk of an unbalanced gamete with 22q11 (up to 6% risk) [9]. Therefore, it is important that parental study and genetic counseling be performed in prenatal cases with complex CNVs.

The objective of this report is to describe 12 cases of complex fetal CNVs diagnosed by prenatal chromosomal microarray. We will also review the available parental studies, including use of karyotype, chromosomal microarray analysis (CMA), and whole-genome low-coverage mate-pair sequencing (WGL-MPS) to better clarify the complex fetal rearrangement.

2. Materials and Methods

2.1 Clinical Subjects

From 2017 to 2020, 2746 pregnant women received prenatal diagnosis with chromosomal microarray analysis (CMA) in Changzhou Maternal and Child Health Care Hospital in China. All cases were included in our cohort study according to their clinical indications: advanced maternal age ($\geq$35 years), pregnancy screening abnormality (maternal serum screening, non-invasive prenatal testing, and fetal ultrasonography), abnormality in previous pregnancy, or

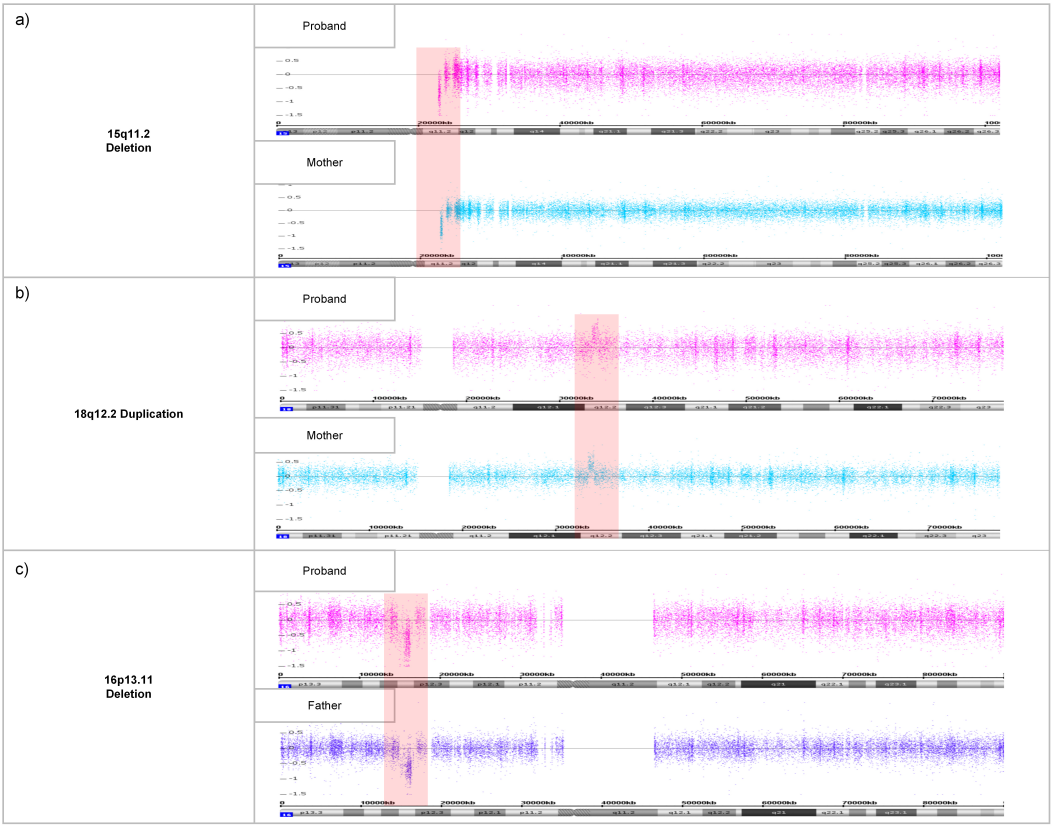

Fig. 1. Chromosomal microarray CNV log2 ratio profile of Case 10. (a) 15q11.2 deletion region profile of the proband and his mother. (b) 18q22.2 duplication imbalance of the proband and his mother. (c) 16p13.11 deletion region profile of the proband and his father. CNV, copy number variant.

a maternal/paternal chromosomal abnormality or other related conditions. This study was performed based on the Declaration of Helsinki and approved by the Ethics Committee of Changzhou Maternity and Child Health Care Hospital. Informed consents were obtained from each patient.

2.2 Sample Preparation and Chromosomal Microarray Analysis

Genomic DNA was extracted from the collected amniotic fluid using the QIAamp DNA Micro Kit (56304, Qiagen, Hilden, German) according to instructions. Around 250 mg of genomic DNA was digested and ligated to adapters before being amplified by polymerase chain reaction (PCR). The samples were purified and digested to short fragments (around 25–125 bp). Hybridization was subsequently carried out with Affymetrix CytoScan 750K Array (901859, Thermo fisher Scientific, Santa Clara, CA, USA) including both CNV and SNP probe at 50 °C for 16–18 hours. The hybridized arrays were then washed and stained with Fluidics Station 450 (Version 2.0, Thermo fisher Scientific, Santa Clara, CA, USA). All data were analyzed with Affymetrix Chromosome Analysis Suite (ChAS) software (Version 1.2, Thermo fisher Scientific, Santa Clara, CA, USA) package using Genome Reference Consortium Human Build 37 (GRCh37). The reporting copy number variant was set as >100 Kb DNA length as well as >50 marker counts. According to American College of Medical Genetics (ACMG) guidelines and databases such as Online Mendelian Inheritance in Man (OMIM), Clinical Genome Resource (ClinGen), and Database of Genomic Variants (DGV), all 12 complex fetal CNVs cases reported in this study were classified as pathogenic (P) and variants of uncertain significance (VUS) [10].

2.3 Parental Study

Follow-up parental validation was conducted and 8 families voluntary participated via telephone interview. We have a follow up with these families not only in hospital but also 6 months, 1 year and 2 years after they discharge. Parental peripheral blood samples were collected to perform parental validation studies with CMA, G-band karyotype analysis, and whole-genome low-coverage mate-pair sequencing (WGL-MPS) [11]. G banding karyotype analysis was performed at a resolution of approximately 320~400 bands according to protocol. The accuracy of WGL-MPS analysis of breakpoints was 1 Kb. 50-bp-end multiplex sequencing analysis was carried out by BGISeq-500 after a non-size selected mate-pair library was constructed, and all pair-end reads were aligned to GRCh37.

Table 1. 12 prenatally diagnosed patient cases with complex fetal CNVs.

No.	Gestational age (week)	Maternal age (years)	Indication	Microarray finding in fetal			CNV classification	Pregnancy outcome
				Imbalance	Position	Size (Mb)		
1	25	35	Ultrasound anomaly: cystic hygroma, aortic stenosis, ventricle septal defect	Deletion	arr[GRCh37]4p16.3p15.31(68,345–18,451,423) × 1	18.4	P	TOP
				Duplication	arr[GRCh37]11p15.5p15.1(230,680–20,167,667) × 3	19.9	P	
2	19	32	Abnormal pregnancy history: 2 times of Induction of labor (one for FGR and the other for CHD and spina bifida)	Deletion	arr[GRCh37]7q33q36.3(137,754,586–159,119,707) × 1	21.4	P	TOP
				Duplication	arr[GRCh37]20q13.2q13.33(51,222,942–62,913,645) × 3	11.7	P	
3	15	26	Ultrasound anomaly: cystic hygroma	Duplication	arr[GRCh37]1q41q44(221,478,235–249,104,496) × 3	27.6	P	TOP
				Deletion	arr[GRCh37]18q22.3q23(70,367,252–78,013,728) × 1	7.6	P	
4	18	34	Abnormal pregnancy history:3 fetal death (premature delivery, cardiac anomaly and no anus), 1 child with leukemia	Duplication	arr[GRCh37]9p24.3p22.3(208,454–16,574,838) × 3	16.4	P	TOP
				Deletion	arr[GRCh37]10q26.11q26.3(121,512,561–135,426,386) × 1	13.9	P	
5	24	29	Abnormal pregnancy history: a child with infantile autism; DS: 1/186; patient with hearing disorder	Deletion	arr[GRCh37]5p15.33p15.31(113,576–9,478,788) × 1	9.4	P	TOP
				Duplication	arr[GRCh37]5p15.31p13.2(9,482,842–36,907,849) × 3	27.4	P	
6	23	27	Ultrasound anomaly: hypoplastic left heart, ventricle septal defect, congenital aortic arch abnormality	Deletion	arr[GRCh37]21q22.3(45,643,517–48,093,361) × 1	2.4	P	TOP
				Duplication	arr[GRCh37]21q21.1q22.3(18,715,778–44,958,722) × 2–3	26.2	P	
7	19	24	DS: 1/123	Deletion	arr[GRCh37]8p23.3p23.1(158,048–6,999,114) × 1	6.8	P	TOP
				Duplication	arr[GRCh37]13q31.3q34(93,233,450–115,107,733) × 3	21.9	P	
8	19	28	DS: 1/24	Duplication	arr[GRCh37]15q13.2q13.3(30,386,398–32,915,723) × 3	2.5	P	TOP
				Deletion	arr[GRCh37]Xp22.31(6,455,151–8,135,053) × 0	1.6	P	
9	19	31	DS: 1/280	Deletion	arr[GRCh37]4q32.3q35.2(169,133,858–190,957,460) × 1	22	P	TOP
				Duplication	arr[GRCh37]20q13.2q13.33(53,962,867–62,913,645) × 3	9	P	
10	25	28	Ultrasound anomaly: ventricular septal defect, EIF	Deletion	arr[GRCh37]15q11.2(22,770,421–23,625,785) × 1	0.85	P	TOP
				Deletion	arr[GRCh37]16p13.11(14,910,158–16,520,463) × 1	1.6	P	
				Duplication	arr[GRCh37]18q12.2(33,443,479–34,124,037) × 3	0.68	VUS	
11	24	25	Ultrasound anomaly: FGR, cardiac anomaly, ventricular septal defect, spina bifida, strephexopodia	Deletion	arr[GRCh37]4p16.3(68,345–3,609,390) × 1	3.5	P	TOP
				Duplication	arr[GRCh37]19q13.31q13.43(44,258,567–58,956,816) × 3	14.7	P	
12	26	30	Ultrasound anomaly: inferior worm of cerebellum anomaly	Deletion	arr[GRCh37]1p31.1(75,240,045–76,259,955) × 1	1	VUS	TOP
				Deletion	arr[GRCh37]2p21p16.3(45,944,325–50,394,478) × 1	4.5	P	

TOP, termination of pregnancy; FGR, fetal growth restriction; CHD, congenital heart disease; EIF, echogenic intracardiac focus; DS, screening for Down's syndrome; CNV, copy number variant; VUS, variants of uncertain significance.

Table 2. CNV origin analysis results for 8 cases.

Case No.	Parental ages		Pregnancy history	Parental studies*			Origin
	M	PA		Method	M	PA	
1	35	39	G2P0	K	46, XX	46, XY, t (4; 11) (p16; p15)	PA
2	32	33	G3P0	K	46, XX, t (7; 20) (q33; q13.2)	46, XY	M
7	24	28	G1P0	K	46, XX	46, XY	DN
8	28	30	G2P1	K+W	46, XX	46, XY	DN
9	31	32	G1P0	K	46, XX, t (4; 20) (q33; q13.2)	46, XY	M
10	28	28	G1P0	CMA	arr[GRCh37]15q11.2(22,770,421–23,282,798) × 1 arr[GRCh37]18q12.2(33,461,107–34,096,773) × 3	arr[GRCh37]16p13.11(14,892,975–16,527,659) × 1	M+PA
11	25	31	G2P0	K	46, XX	46, XY, t (4; 19) (p16.1; q13.1)	PA
12	30	30	G3P1	K+W	46, XX	46, XY	DN

G, gestation; P, parturition; M, maternal; PA, paternal; DN, *de novo*; K, karyotype; W, WGL-MPS; CMA, chromosomal microarray analysis.

*All parents in this study have normal clinical phenotype.

Table 3. Review of case reports related to complex CNVs.

Year	CNV	CNV origin	Title
1999 [9]	3p25 del 7q36 dup	Paternal 46, XY, t (3; 7) (p25; q36)	Coexistence of an unbalanced chromosomal rearrangement and spinal muscular atrophy in an infant with multiple congenital anomalies
2012 [7]	22q11.21 del Xp22.31 del	N/A	Co-existence of other copy number variations with 22q11.2 deletion or duplication: a modifier for variable phenotypes of the syndrome
2018 [10]	22q11.2 del 10p14 del	*De novo*	Co-occurrence of 22q11 deletion syndrome and HDR syndrome
2016 [14]	2p37.1 del Xp22.3 del	Maternal	X-linked ichthyosis and crigler-Najjar syndrome I: coexistence in a male patient with two copy number variable regions of 2q37.1 and Xp22.3
2017 [8]	22q11.2 del 2q37 dup	*De novo* Maternal	A case of 22q11 deletion syndrome (22q11 Down syndrome (DS)) with a panayiotopoulos epileptic pattern: are additional copy-number variations a possible second hit in modulating the 22q11DS phenotype
2018 [13]	17q12 del 22q11.2 del	N/A	22q and two: 22q11.2 deletion syndrome and coexisting conditions
2020 [15]	8q22.2q24.3 dup 13q33.2q34 del	Maternal 46, XX, t (8; 13) (q22; q32)	The fetus of 8q22.2q24.3 duplication and 13q33.2q34 deletion derived from a maternal balanced translocation
2020 [16]	5p15.2p15.3 del 4q32.3q35.2 dup	Maternal 46, XX, t (4; 5) (q33; p15)	Partial trisomy 4q and monosomy 5p were inherited from a maternal translocation t (4; 5) (q33; p15) in three adverse pregnancies

Del, deletion; Dup, duplication; N/A, not applicable; DS, down syndrome; HDR, hypoparathyroidism, sensorineural deafness and renal dysplasia syndrome.

3. Results

Of the 2746 cases diagnosed with CMA, fetuses that carried complex CNVs were identified in 0.4% of cases (12/2746). Clinical information and microarray findings of 12 cases are summarized in Table 1.

Among the 12 cases, gestational age of patients were between 15 and 26 (21.3 $\pm$ 3.6) weeks and maternal age were from 24 to 35 (29.1 $\pm$ 3.4) years old. Clinical indications included ultrasound anomaly, abnormal pregnancy history and abnormal prenatal screening. These results were recorded as fetal growth restriction (FGR), congenital heart disease (CHD), screening for Down's syndrome (DS) ratio or other high-risk indicators of chromosomal anomaly. Ninety two percent (11/12) of cases carried two complex CNVs, and only Case 10 had co-occurrence of 3 complex CNVs. CNVs of all cases were classified as P and VUS according to the ACMG guideline and relevant database. In accordance with CMA findings and clinical indications, all patients voluntarily chose termination of pregnancy after prenatal genetic counseling and they do not have the pregnancy plan at the end of our 2-year follow up. Unfortunately, all families refused autopsy due to Chinese taboo.

The parental validation study was carried out in 8 of 12 complex CNVs cases with the permission of the patients, while others have declined the study. All study details are shown in Table 2. On the basis of different CNVs sizes, which were from 680 Kb to 21.9 Mb, parental specimens were performed by different validation methods. G banding karyotype (Case 1, 2, 7, 8, 9, 11, and 12), CMA (Case 10), and WGL-MPS analysis (Case 8 and 12) were selected depending on the resolution of methods and CNVs sizes to determine the origin of the variants. Case 8 and 12 were analyzed by karyotype and then validated by WGL-MPS analysis due to the relatively small imbalance size. The primary results suggested that 62.5% (5 out of 8) of fetuses carried complex CNVs that were inherited, of which 4 cases were derived from maternal or paternal balanced translocation carriers. Miscarriage history was found in some of the balanced translocation carriers (Case 1, 2 and 11).

According to Tables 1,2, Case 0 showed a rare complex CNVs with three microduplications and microdeletions that were all inherited from her healthy parents. Considering the size of loss and gain, this case was validated using CMA directly (seen in Fig. 1).

The proband was diagnosed with 15q11.2 BP1-BP2 microdeletion (Burnside-Butler) syndrome with incomplete and highly variable penetrance at around 10.4% [12], with typical phenotypes including neurodevelopmental disorders with changes in cognition and behavior, 16p13.11 microdeletion syndrome and a VUS CNV duplication at 18q12.2. The proband's mother carried the 15q11.2 deletion involving four OMIM genes (*TUBGCP5*, *CYFIP1*, *NIPA2*, *NIPA1*) and 18q12.2 duplication including 6 OMIM genes (*MIR187*, *RPRD1A*, *SLC39A*, *ELP2*, *MOCOS*, *FHOD3*). She did not have a family history of intellectual disability or developmental delay. Copy number variant on 16p13.11 region with incomplete penetrance and highly variable phenotypic manifestations, which were 1.6 Mb encompassing 11 OMIM genes (i.e., *NED1*), were inherited from the phenotypically normal father of the proband. These parents choose to terminate the pregnancy after genetic counseling.

4. Discussion

In this study, we described 12 prenatal coexisting CNVs cases diagnosed by CMA, 8 of which were followed by parental validation analysis performed via different genetic approaches. Sixty-two and one half percent (5/8) of complex CNVs were inherited and 80% (4/5) of these cases found in balanced translocation carriers. Under these circumstances, CNVs inheritance mode (paternal/maternal or *de novo*) can have a serious impact on genetic counseling for the recurrence risk in future pregnancies of families experiencing complex CNVs [8].

Coexisting CNVs cases were not common during in the past [9]. From 2017 to 2020, complex CNVs (co-occurrence of two or more) in one fetus were a rare phenomenon in our local prenatal CMA cohort, accounting for 0.4%. Previous studies have shown that coexisting abnormalities can occur in the context of complex CNVs (Table 3, Ref. [7–10,13–16]).

Regarding prenatal diagnosis and complex CNVs interpretation, CNVs origin can have an impact on patients and their families. In this study, half of the inherited complex CNVs cases were derived from a balanced translocation in the parents. In the general population, the percentage of balanced translocation carriers is 0.08~0.3 [17]. Balanced translocation carriers have an increased risk for recurrent miscarriage, infertility, or birth of a child with CNVs [18,19]. Therefore, it is necessary for the genetic counselor assist the parents in understanding the genetic information if the family has a diagnosis of fetal complex CNVs.

Genetic counseling can have a significant impact on the pregnancy by providing information, support, and guidance to expectant parents [20]. Meanwhile, the genetics counselor is able to assist families to cope with the stress and uncertainty that can accompany a diagnosis of a fetal anomaly or complex CNVs, and then provide resources or support to promote positive mental health outcomes for the parents [21]. Moreover, in cases where a fetal anomaly is detected, genetic counselors can help parents understand the implications of the diagnosis and provide support as they make decisions about how to proceed. This may include decisions about whether to continue or terminate the pregnancy, as well as decisions about future family planning [20].

In our study, counseling was performed on all patients based on their CMA results and parental analysis. For *de novo* cases, the risk of recurrence of these complex imbalances is estimated at 1% according to the literature (includ-

ing germinal mosaicism), which is reassuring for patients considering their next pregnancy [22]. Likewise, prenatal diagnosis and counseling are highly recommended for their next pregnancy. Considering cases carrying complex CNVs that are transmitted by their balanced translocation parents, the risk of imbalances recurruring is relatively higher than in *de novo* cases and it is more difficult for carriers to have a healthy baby due to repeated spontaneous abortion and imbalance occurrence in future pregnancies [22]. Therefore, genetic counseling has a significant role for these families' future pregnancies. For carriers who are willing to have further attempts for natural conception, early invasive prenatal diagnosis might be a choice for their pregnancy during the first trimester. For patients who have experienced miscarriages, infertility, and birth of sick children, as well as having adequate financial ability, preimplantation genetic diagnosis (PGD) is another option to increase the likelihood of successful pregnancy and decrease the risk of a genetic disorder in their offspring [23].

However, the limitations of this cohort study should be noted. Even though this research has a large cohort with 2746 pregnant patients with complete fetal data and whole genome parental studies for accurate parental genotyping, the number of complex CNVs cases were relatively small. Furthermore, other limitations are the loss of follow up of 4/12 parents, no data from patients about pregnancy experience or impact of genetic counseling and lack of the follow up on future pregnancies of proband families. In the future, we will expand the number of cases and extend the time of data collection with more CNVs origin analysis, making more efforts to initiate complex CNVs counseling and follow-up studies on patients.

5. Conclusion

In conclusion, we used CMA technology to diagnose complex CNVs in fetuses followed by parental analysis via different validation methods according to various resolutions and sizes of CNVs. Complex CNVs cases were rare in our cohort (0.4%) as well as in previous reported studies (0.9%) [8,12,13]. In these cases, parental analysis can vastly change the recurrence risk for patients. For our study, the CNVs origin analysis demonstrated that the inherited complex CNVs account for 62.5% and 80% of inherited cases were transmitted from balanced translocation parents. Based on the complexity of CNVs cases and the wide range of possible recurrence risks, these patients will benefit from prenatal genetic counseling. Prenatal counseling can assist patients to make informed decisions about their current and future pregnancies.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding authors upon request.

Author Contributions

WW, JW and BZ designed the research study. WW and JW performed the research. YS and BZ provided help and advice on the CMA and parental study experiments. WW and JW analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study design and protocol were reviewed and approved by the ethics committee of Changzhou Maternal and Child Health Care Hospital (Approval number: 2017003). Written informed contents were obtained from the patients before screening. All patients signed written informed consent for publication of their clinical data.

Acknowledgment

We are thankful to the patient and the family for their participation in this study.

Funding

This study was funded by National Natural Science Foundation Youth Fund (No. 82103853), Changzhou science and technology support project (Social development) (CE20225066) and Top Talent of Changzhou "The 14th Five-Year Plan" High-Level Health Talents Training Project (2022CZBJ089).

Conflict of Interest

The authors declare no conflict of interest.

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