Genetic etiology and phenotypic characteristics of fetuses with 11q deletion syndrome (11q23.3-q25)

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Abstract. The 11q deletion (11q-) syndrome is a rare consecutive polygenic deletion disorder. Characterization of the clinical features, genetic etiology and diagnostic strategies associated with 11q deletion syndrome in the prenatal setting is important to understand this syndrome in its entirety. A retrospective review at Longgang District Maternity & Child Healthcare Hospital of Shenzhen City (Shenzhen, China) involving four fetuses diagnosed with 11q- syndrome was conducted to examine the clinical features of this syndrome. The cases were identified through prenatal screening, including maternal serum biochemistry, non-invasive prenatal screening (NIPS), chromosomal microarray analysis (CMA) and karyotyping. Pregnant women with high-risk results from NIPS or prenatal serological screening received early interventional prenatal diagnosis and genetic counseling. Of the two cases that showed a high-risk of 11q- by NIPS, invasive diagnostic procedures confirmed the presence of large terminal deletions on chromosome 11q, encompassing telomeric regions. CMA identified the deletions while karyotyping revealed underlying structural rearrangements, including balanced translocations in both cases. Prenatal ultrasound identified cardiac anomalies, such as ventricular septal defects and truncus arteriosus. The variability and incomplete penetrance of these malformations suggest the influence of polygenic (e.g., modifier genes, genetic background, copy number variations), epigenetic (e.g., DNA methylation, histone modification) and environmental factors (e.g., diet, lifestyle, exposure to toxins). The results demonstrated that the phenotypic expression of 11q- syndrome varies according to the size and gene content of the deleted region. The integration of CMA and karyotyping improves diagnostic accuracy and elucidates the origin of chromosomal alterations. In the single case present in the current study that involved a parental chromosomal translocation, karyotyping was essential for determining the risk of recurrence. These findings contribute to a more precise understanding of genotype-phenotype associations and support the provision of informed prenatal counseling and the clinical management of 11q- syndrome.

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Abbreviations: 11q-, 11q deletion; CNV, copy number variation; CMA, chromosomal microarray analysis; NIPS, non-invasive prenatal screening; VSD, ventricular septal defect

Key words: 11q- syndrome, Jacobsen syndrome, congenital heart abnormalities, balanced translocation

Introduction

Copy number variations (CNVs) are common structural variations in the genome that represent a notable source of genetic diversity and disease. CNVs are primarily detected through chromosomal microarray analysis (CMA) and have been increasingly associated with a wide range of developmental disorders, such as premature closure of cranial sutures and craniofacial malformations (1).

11q deletion (11q-) syndrome is a rare contiguous gene deletion disorder, which is also known as Jacobsen syndrome, and has an estimated incidence of 1 in 100,000 live births worldwide (2). 11q- syndrome has a female predominance (with a male-to-female ratio of 1:2) and arises *de novo* in most cases (3). 11q- syndrome results from terminal deletions on the long arm of chromosome 11, typically involving breakpoints at 11q23 or 11q24, which includes the telomeric region. The size of this deletion ranges from 7-20 megabases (Mb) and contains protein-coding genes such as ETS1, FLI1, SENCR and KCNJ5, which are closely related to the development functions of the heart and the immune system (4). The phenotypic presentation of patients with 11q- syndrome is variable and depends on the number and function of the deleted genes. Common clinical features include behavioral problems, intellectual disability, craniofacial anomalies and bleeding disorders (5).

Additionally, patients often exhibit malformations of the heart, kidneys and central nervous system (6,7).

Prenatal diagnosis of 11q- syndrome can be achieved using karyotyping, multiplex ligation-dependent probe amplification or CMA (8). The present study aimed to characterize the genetic basis and prenatal phenotype of 11q- syndrome in a small cohort and to evaluate the utility of different diagnostic approaches, particularly in the context of structural chromosomal rearrangements. These findings will contribute to a deeper understanding of genotype-phenotype associations and inform clinical strategies for the early diagnosis, counseling and management of 11q- syndrome.

Materials and methods

Study participants. Between February 2023 and September 2024, 3,745 pregnant women underwent CMA at the Central Laboratory of Longgang District Maternity & Child Healthcare Hospital of Shenzhen City (Shenzhen, China). From this cohort, four fetuses diagnosed with 11q- syndrome were retrospectively selected for detailed analysis. Maternal demographic and clinical data were collected. The mean maternal age was 31±5 years, ranging from 25-38 years. All genetic testing was conducted on surplus biological material obtained during medically indicated amniocentesis procedures (not collected solely for research). The study was approved by the Ethics Review Committee of Longgang District Maternity & Child Healthcare Hospital of Shenzhen City (approval no. KYXM-2023-037), and written informed consent was obtained from all participants.

Prenatal serological analysis. First trimester analysis (gestational age, 9^{+0} to 13^{+6} weeks) included measuring serum-free β-human chorionic gonadotropin (β-HCG) and pregnancy-associated plasma protein A, using the AutoDELFIA 1235 automatic fluorescence immunoassay system (PerkinElmer, Inc.). Risk calculations for fetal trisomies 21 (T21), 18 (T18) and 13 (T13) were based on nuchal translucency (NT), maternal age, gestational age (due to the need for an accurate date, *in vitro* fertilization prioritized over ultrasound and last menstrual period) and maternal weight (9). In the second trimester (15^{+0} to 20^{+6} weeks), the measured concentrations of serum markers (alpha-fetoprotein, free-floating β-HCG and unconjugated estriol) were converted into multiple of the median, which is the ratio of a pregnant woman's specific biochemical marker level to the median level of that marker in a normal pregnant population at the same gestational age. This was combined with the pregnant woman's age to evaluate the risk for fetal T21, T18 and T13, as well as neural tube defects (NTD) (9).

Non-invasive prenatal screening (NIPS). The NIPS experimental procedures were carried out using the NIFTY® Test in accordance with the manufacturer's reagent instructions (06974783040109; BGI Genomics). Cell-free fetal DNA was extracted from maternal plasma and processed for end-repair (BGI Genomics). The mixture was incubated at 37˚C for 10 min followed by an incubation at 65˚C for 15 min. After ligation, the library was denatured (95˚C, 5 min) and circularized (37˚C, 25 min) based on DNA concentration. Fluorescently labeled DNA nanospheres were prepared and sequenced using combined probe-anchored polymerase sequencing method (G400 SM FCL SE35 Universal Sequencing Kit (SN: W0125042401718); BGI Genomics). The Qubit 3.0 fluorometer (Thermo Fisher Scientific, Inc.) was used to detect the integrity of DNA. DNA samples for sequencing were prepared using the Combinatorial Probe-Anchor Polymerization Sequencing Kit (SN: W012504241895; MGI Tech Co., Ltd.). Sequencing was performed as 35 bp single-end sequencing. The final library was loaded at a concentration of 160 pM. Data analysis was conducted using the Halos v4.1 software (NIPTY v4.0.7, Sonata Software).

Short tandem repeat (STR) and CMA analysis. Amniotic fluid (10 ml) or prenatal villi was obtained for genetic analysis. DNA was extracted using the QIAamp DNA Blood Mini Kit (Qiagen GmbH) as per the manufacturer's protocol and quantified (Nano-300; Hangzhou Allsheng Instruments Co., Ltd.) for purity and concentration. STR analysis was conducted using PCR amplification and capillary electrophoresis (3500 Dx Genetic Analyzer; Applied Biosystems; Thermo Fisher Scientific, Inc.), to confirm fetal origin and exclude maternal contamination.

Following quality control, CMA was performed using CytoScan 750K or Optima arrays (Thermo Fisher Scientific, Inc.). The workflow included enzymatic digestion, ligation, PCR amplification, purification, fragmentation, labeling, hybridization and chip scanning. All the experimental procedures were carried out in accordance with the instructions provided by the reagent supplier. The sequences of primers used are not available by the supplier. CNVs were analyzed using the Affymetrix Chromosome Analysis Suite (version 4.3; Affymetrix, Thermo Fisher Scientific, Inc.) and interpreted according to the American College of Medical Genetics (ACMG) guidelines (10).

Chromosome karyotyping. Amniotic fluid, villi samples and parental peripheral blood were cultured under sterile conditions into dual-line media at 37˚C with 5% CO_2 (amniotic fluid cell culture medium; HE NENG BIO). After adequate fetal-derived cell growth (12-14 days), the chromosomes were harvested, prepared and banded (Rai-Giemsa combined staining solution; 25˚C, 2 min; Zhuhai Besuo Biotechnology Co., Ltd.). Metaphase spreads with well-resolved bands were analyzed using a CytoVision DX instrument (Leica Biosystems) to identify chromosomal abnormalities in terms of both structure and number.

Results

Clinical characteristics of the study cases. Table I summarizes the clinical backgrounds of the four pregnant women whose fetuses were diagnosed with 11q- syndrome. Case 2 was of advanced maternal age (≥35 years), while two patients had experienced first-trimester miscarriages (Table I). Case 4 showed a high risk of T21 (1:55) alongside a history of adverse pregnancy outcomes, as indicated by prenatal serological screening. By contrast, case 1 showed low-risk serum screening results; however, the patient reported taking cold and fever medications for 3 days during the early stages of

Table I. Basic clinical information of four cases with 11q deletion syndrome.

Case	Age, years	Gestational weeks	Pregnancy history	Down syndrome screening	Non-invasive prenatal screening results
1	30	17	G1P0	Low risk	del(11q24.2-q25,7.98 Mb)
2	38	14	G1P0	/	del(11q24.1-q25,13.54 Mb) dup(11q21-q22.1,5.12 Mb) dup(11q23.1-q23.3,10.27 Mb)
3	25	8+	/	/	-
4	31	13+	G3P1A1	T21; risk, 1:55	-

G, garida (number of pregnancies); P, para (number of live or stillbirths); A, abortion (number of abortions or fetal demises before 20 weeks' gestation); Mb, megabases; del, deletion; dup, duplication; T21, trisomy 21; /, indicates no detection.

Table II. Prenatal serological results of two cases with 11q deletion syndrome.

A, First trimester analysis (gestational age 9^{+0} to 13^{+6} weeks)

Variable (MoM)	Case 1	Case 4	Reference Interval
β-HCG	0.65	1.12	0.34-2.5
PAPP-A	0.89	0.68	>0.43
NT	0.9	2.1	/

B, Second trimester (gestational age 15^{+0} to 20^{+6} weeks)

Variable	Case 1	Case 4	
AFP	1.31	/	0.6-2.5
β-HCG	0.56	/	0.34-2.5
uE3	0.95	/	>0.6
NTD	Low risk	/	

The MoM value in Down syndrome screening refers to the multiple of the median, which is the ratio of a pregnant woman's specific biochemical marker level to the median level of that marker in a normal pregnant population at the same gestational age. β-HCG, β-human chorionic gonadotropin; PAPP-A, pregnancy-associated plasma protein A; AFP, α-fetoprotein; uE3, unconjugated estriol; NT, nuchal translucency; NTD, neural tube defects; /, indicates no detection.

their pregnancy (Buprofen and others). Currently, to the best of our knowledge, there is no research indicating a direct correlation between fever during the early pregnancy and a high risk of Down syndrome screening. However, if the fever persists or is severe, it may increase the risk of fetal developmental abnormalities. The initial ultrasound scan in case 1 revealed no embryonic cardiac tube pulsation and a small intrauterine fluid collection. Following regular monitoring of HCG levels and the development of the embryo, fetal development proceeded normally. The prenatal serological marker test results for cases 1 and 4 were all within the normal range after being adjusted using the multiple of the median value (Table II). Cases 2 and 3 did not undergo this screening because they experienced miscarriages in the early stages of pregnancy.

Cases 1 and 2 underwent NIPS, which revealed a partial deletion in chromosome 11q. Fig. 1 illustrates the NIPS results for cases 1 and 2 demonstrating 11q- syndrome. The breakpoint was located at 11q24.2 with a size of 7.98 Mb deletion region for case 1, and case 2 had a breakpoint on 11q24.1 with a size of 13.54 Mb deletion region, which raised suspicion of 11q- syndrome. Case 2 also demonstrated additional copy number gains on chromosome 11. CMA was subsequently performed to confirm these findings. Cases 3 and 4 underwent abortion or termination of pregnancy before undergoing NIPS testing due to their relatively early gestational age.

CMA and ultrasound findings. STR analysis confirmed the fetal origin of the prenatal samples and maternal blood contamination was excluded. CMA results (Fig. 2) revealed heterozygous deletions in the 11q- syndrome region across all four fetuses. This region includes key genes, such as *FLI1, BARX2* and *B3GAT1* (6). The *FIL1* gene had a

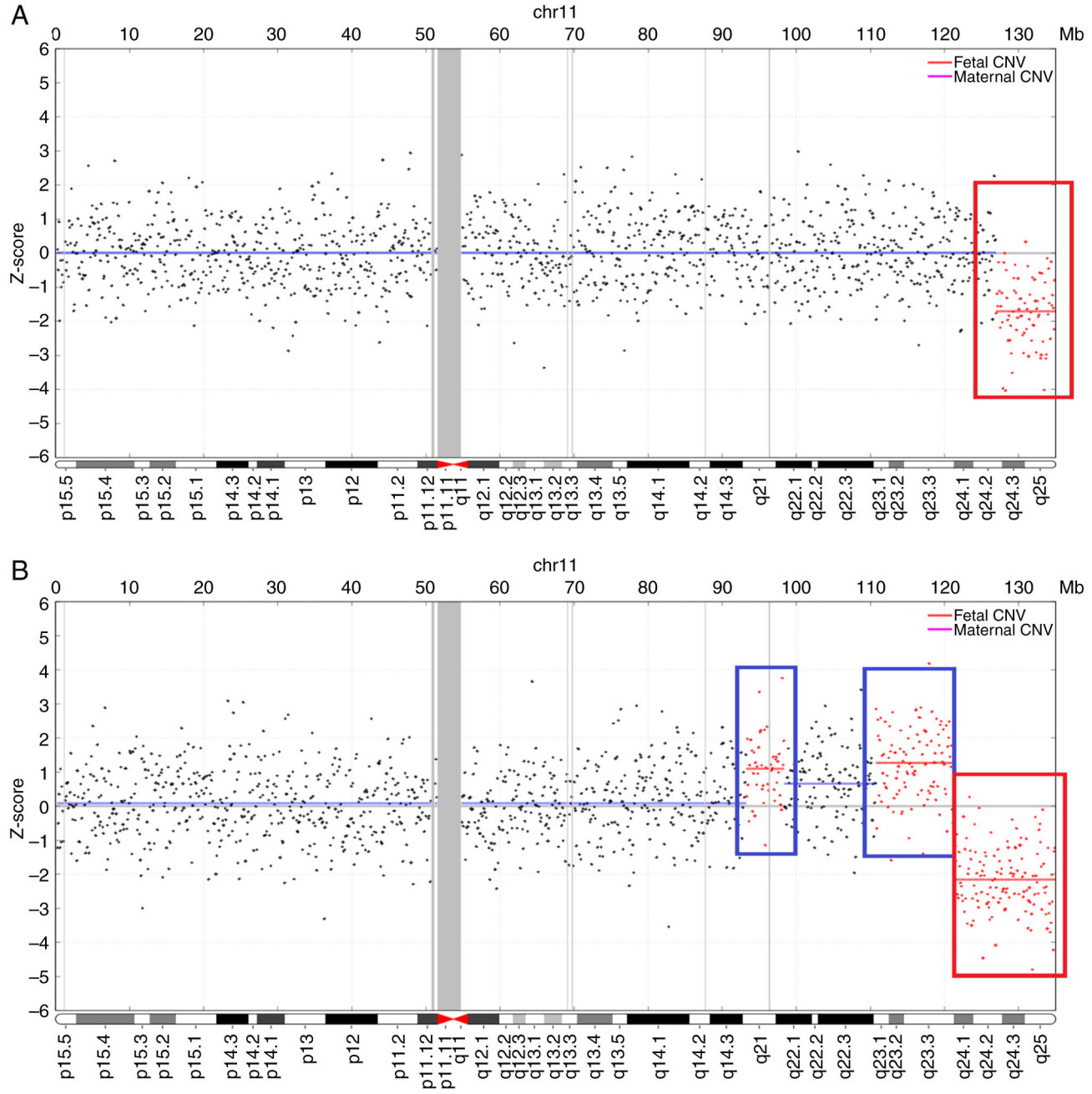

Figure 1. Non-invasive prenatal screening results indicating copy number variations at chromosome 11q. (A) Case 1: A 7.98 Mb deletion at 11q24.2 is highlighted by the red box. (B) Case 2: The red box indicates a 13.54 Mb deletion at 11q24.1. Blue boxes indicate a 5.12 Mb duplication and a 10.27 Mb duplication at 11q21 and 11q23.1, respectively. Each point represents a 50 Kb region. Black points represents normal copy number. Red points represents CNVs. Red frame represents deletion region. Blue frame represents duplication region. CNV, copy number variation; Mb, megabases.

haploinsufficiency score of 1 (obtained from the ClinGen database; https://clinicalgenome.org/).

Of the four cases, two fetuses were female, and two were male (Table III). According to prior studies, the clinical features associated with 11q- syndrome include developmental delay, ventricular septal defects (VSD), craniofacial anomalies and thrombocytopenia, among others (11,12). The size of the deletion may be associated with phenotypic severity. In the present study, the CMA results indicated that case 1 had a deletion of 7.924 Mb. By contrast, case 2 involved a 13.402 Mb deletion and was associated with notable cardiac abnormalities, including VSD (Fig. 3A) and a single arterial trunk (Fig. 3B and C). CMA results did not indicate copy number gains or duplication, contrary to the NIPS results. Following genetic counseling, the patient chose to terminate the pregnancy. The CMA results for both cases 1 and 2 indicated that both deletions were attributed to a single pathogenic CNV.

Cases 3 and 4 exhibited 11q23.3q25 deletions alongside large duplications on other autosomes. Case 3 presented a 13.728 Mb duplication at 16q23.1q24.3, encompassing several protein-coding genes, such as *ACSF3*. This duplication was classified as a pathogenic CNV according to CNV evaluation criteria (10). Case 3's ultrasound results indicated no abnormalities were detected. Case 4 had a 44.549 Mb duplication at 15q21.3q26.3, involving >300 protein-coding

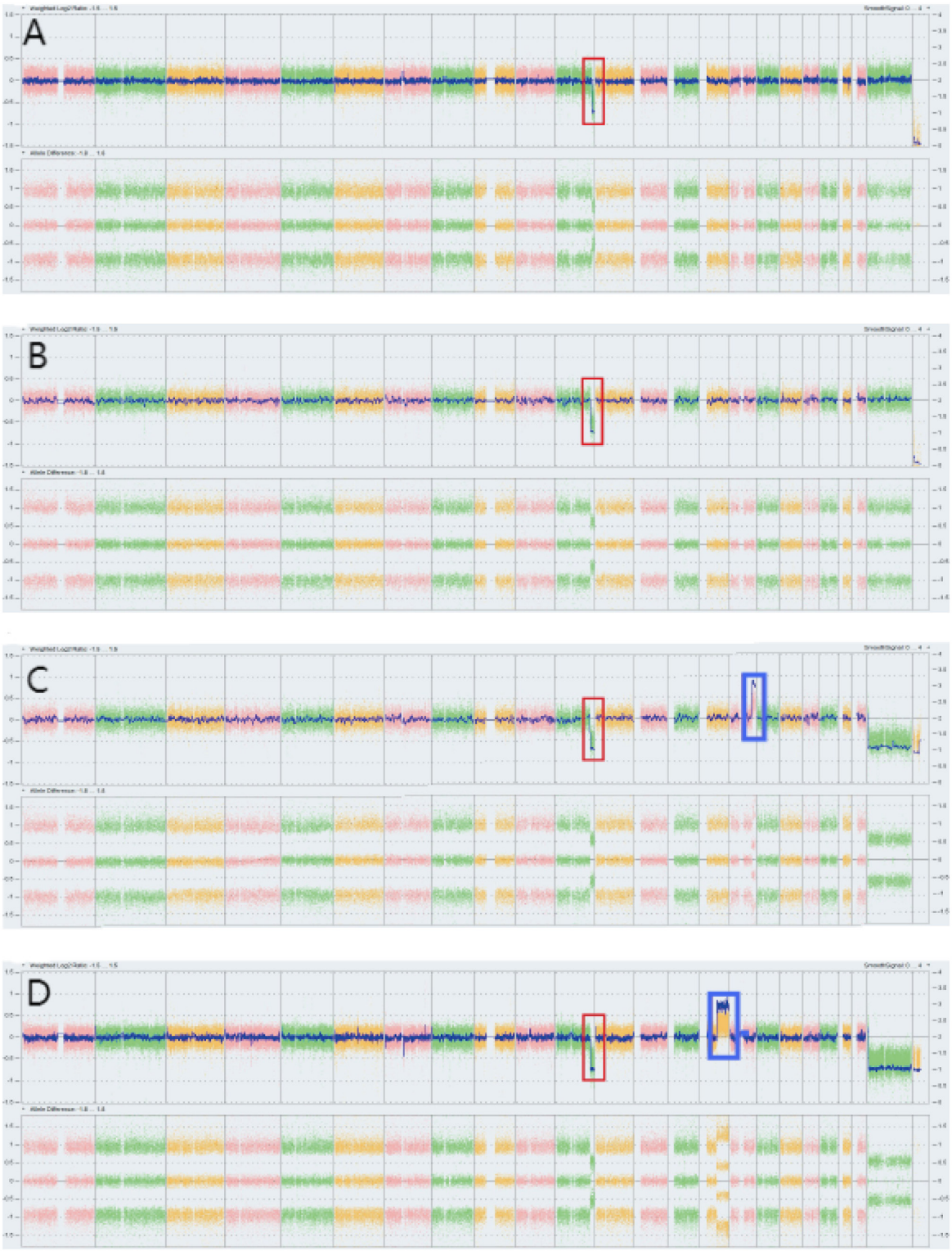

Figure 2. Chromosomal microarray analysis detection of pathogenic CNVs. (A) Case 1: A 7.924 Mb heterozygous deletion at 11q24.2 was detected, the specific location of which was 11q24.2q25(127,013,810-134,937,416) based on GRCh37. (B) Case 2: A 13.402 Mb pathogenic deletion at 11q24.1 was detected, the specific location of which was 11q24.1q25(121,536,011-134,938,470) based on GRCh37. (C) Case 3: Two pathogenic CNVs were detected, a 14.781 Mb deletion at 11q23.33q25(120,157,168-134,938,470) and a 13.728 Mb duplication at 16q23.1q24.3(76,426,996-90,155,062). (D) Case 4: Two pathogenic CNVs were detected, a 44.549 Mb duplication at 15q21.3q26.3(57,879,724-102,429,040) and a 14.638 Mb deletion at 11q23.3q25(120,299,416-134,937,416). Red frame represents deletion region. Blue frame represents duplication region. CNV, copy number variation; GRCh37, Genome Reference Consortium Human Build 37; Mb, megabases.

genes. Recurrent deletion CNVs in this region (such as in patients 253968, 256144 and 264125, as reported in the DECIPHER database; v11.33; https://www.deciphergenomics.org/) are associated with intellectual impairment, atrial septal defect and hypotonia. Case 4's ultrasound results indicated an increased NT (Fig. 3D). CMA results suggested that the

Table III. Prenatal diagnosis methods and imaging results of four cases with 11q deletion syndrome.

Case	Sample type	Short tandem repeat results	Chromosomal microarray analysis results		Sex	Ultrasound results	Pregnancy outcome
			Chromosomal alteration	Size, megabases			
1	Amniotic fluid	No abnormalities	11q24.2q25(127,013,810-134,937,416)x1	7.924 (deletion)	F	No abnormalities	TOP
2	Abortion tissue	/	11q24.1q25(121,536,011-134,938,470)x1	13.402 (deletion)	F	Ventricular septal defect, single trunk artery	TOP
3	Abortive villi	/	11q23.3q25(120,157,168-134,938,470)x1 16q23.1q24.3(76,426,996-90,155,062)x3	14.781 (deletion) 13.728 (duplication)	M	/	Spontaneous abortion
4	Prenatal villi	No abnormalities	11q23.3q25(120,299,416-134,937,416)x1 15q21.3q26.3(57,879,724-102,429,040)x3	14.638 (deletion) 44.549 (duplication)	M	Nuchal translucency, 3.2 mm	TOP

F, female; M, male; TOP, termination of pregnancy; /, indicates no detection.

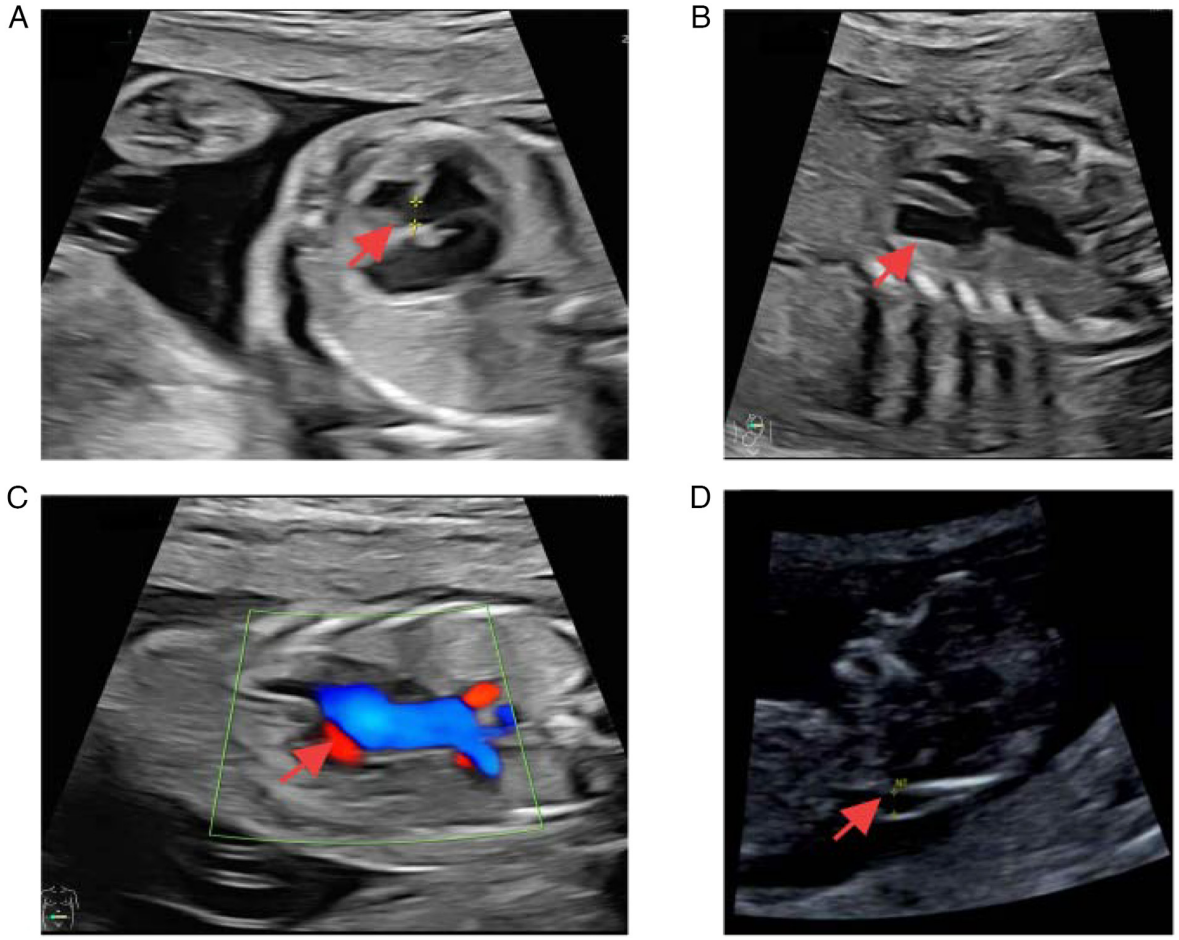

Figure 3. Abnormal ultrasound results of the fetuses with 11q syndrome. (A) Case 2 four-chamber view ultrasound result indicated a continuous interruption of the ventricular septum. (B) Case 2 two-dimensional ultrasound result indicated a single arterial trunk. (C) Case 2 three-vessel cross-sectional ultrasound result indicated the presence of a large artery. (D) Case 4 ultrasound results indicated thickening of the NT. NT, nuchal translucency.

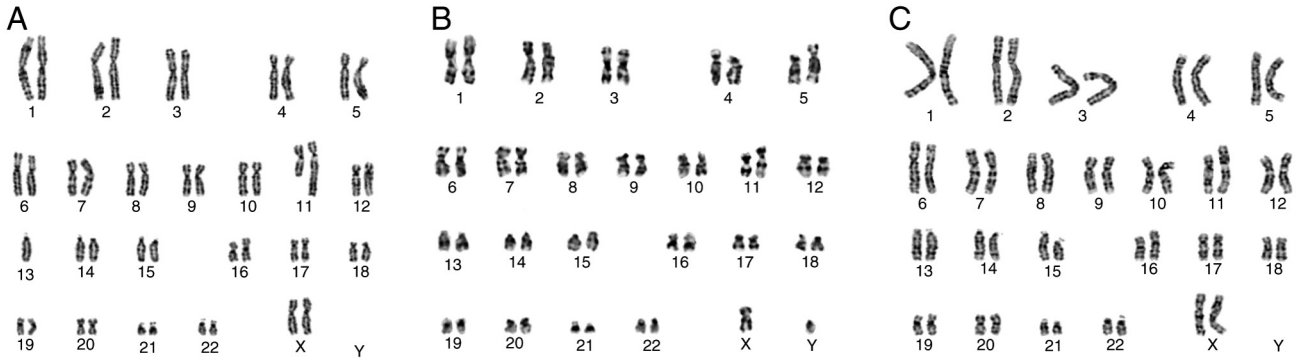

Figure 4. Karyotyping results from amniotic fluid cells and parent' peripheral blood. (A) Case 1: 45,XN,der(11)t(11;13)(q24.2;q12),-13. (B) Case 4: 46,XN,der(11)t(11;15)(q23.3;q21.3). (C) Maternal karyotype of case 4 [46,XX,t(11;15)(q23;q21)], indicating a balanced translocation.

chromosomal imbalances likely arose from parental structural rearrangements; therefore, karyotype analysis was necessary.

Chromosome karyotyping results. The karyotype result of case 1 was 45, XN, der(11)t(11;13)(q24.2;q12),-13 (Fig. 4A). This indicates that the fetus has newly derived a new chromosome formed by a translocation of chromosome 11 and chromosome 13. This structural rearrangement resulted in a terminal deletion of chromosome 11q, consistent with the CMA findings, and the results revealed additional chromosomal alterations (the occurrence of balanced translocation). Unfortunately, cases 2 and 3 resulted in miscarriage before any chromosome karyotype analysis was conducted on the fetuses.

The karyotype of case 4 was 46, XN, der(11)t(11;15)(q23.3;q21.3) (Fig. 4B). This indicates a derivative chromosome formed by a translocation between chromosomes 11 and 15. This resulted in a terminal deletion on 11q and a terminal duplication on 15q. To identify the source of variation, chromosome karyotype analysis was performed on the peripheral blood from the parents. The mother was identified as a balanced translocation carrier of 46, XX,t(11;15)(q23;q21) (Fig. 4C), whereas the karyotype of the father was normal.

Pregnancy outcome. Case 3 experienced a miscarriage at 8 weeks of pregnancy. For cases 1, 2 and 4, after obtaining full informed consent and undergoing genetic counseling, the pregnant women chose to terminate their pregnancies.

Discussion

11q-syndrome is a rare multigenic disorder resulting from terminal chromosomal deletions on chromosome 11q. In the present study, several pregnancies were considered high-risk due to factors, such as advanced maternal age (case 2), history of spontaneous abortion (case 4) and potential teratogenic exposure during the early stages of gestation (case 1). Taking medication during the early stage of pregnancy may not be related to the occurrence of chromosomal structural abnormalities in the fetus, but it cannot be ruled out that there might be an impact. These findings reinforce the importance of systematic prenatal screening and follow-up imaging to detect structural and genetic anomalies.

While first- and second-trimester serum screening is primarily intended to detect aneuploidies such as T21, the results of the present study showed that notable variations in serum markers could also indicate the presence of substantial CNVs. For example, in case 4 serum analysis yielded a high-risk result for T21 (1:55), despite no numerical chromosomal abnormality being detected, highlighting the possibility of underlying structural variants. In addition, NIPS was able to detect partial deletions in the 11q region; however, as demonstrated in case 2, false positives occurred, emphasizing the need for confirmatory testing, such as CMA or karyotyping.

In the present study, the incidence of congenital heart anomalies was 1 in 4. Structural cardiac defects, particularly VSD and double outlet right ventricle, are among the most common anomalies in this syndrome, affecting ~0.7% of live births (13). Amniocentesis and CMA should therefore be considered when congenital cardiac abnormalities are identified by ultrasound.

In the present cohort, all four cases exhibited deletions within the 11q23.3-q25 region, which included multiple genes involved in development and immune function. Deletion of the *ETS1* gene, which is essential for the function of cardiac neural crest cells, has specifically been associated with congenital heart defects (13,14). Similarly, deletions involving *FLI1* and *ETS1* have been linked to immune dysregulation and an increased susceptibility to bacterial, viral and fungal infections (15). Children with 11q- syndrome have also been reported to exhibit symptoms of motor neuron dysplasia, thrombocytopenia and immunodeficiency (16,17). Other genes within the 11q24.2-q25 interval, including *NTM*, *KIRREL3* and *ARHGAP32*, have been associated with an increased risk of autism spectrum disorder (18). The spectrum of clinical features depends not only on which genes are deleted and their degree of expression, but also on environmental modifiers, resulting in variable expressivity and incomplete penetrance. This variability complicates ultrasound-based diagnosis, particularly during early gestation, as illustrated by the absence of sonographic abnormalities in case 1.

Karyotyping was essential to identify structural chromosomal anomalies in the current cases. In case 4, a derivative chromosome resulted from a maternal balanced translocation between chromosomes 11 and 15. This translocation produced both a terminal deletion on 11q and a duplication on 15q. A similar mechanism was observed in case 1, where a translocation between chromosomes 11 and 13 resulted in a terminal deletion on chromosome 11q. Parental karyotyping confirmed the source of the imbalance.

It is important to note that in carriers of balanced translocations, only two of the 18 possible gametes are chromosomally normal or balanced, and the remaining combinations often result in miscarriage or congenital anomalies (19).

To date, of the >200 cases that have been reported worldwide, 11q deletions inherited from a parent account for ~15% of cases with a balanced translocation, whereas ~85% occur *de novo* (3). This highlights the importance of performing parental karyotype analysis when a fetal 11q deletion is detected. Combining CMA with conventional karyotyping improves the accuracy of detection of the origin of chromosomal aberrations, which is essential for assessing recurrence risk and guiding genetic counseling. Due to the limited number of samples obtained through prenatal diagnosis, functional validation was not conducted in the present study. In the future, more cases should be collected for functional validation using methods such as western blotting, quantitative PCR and RNA-sequencing, with the aim to further explore the potential pathogenesis of CNVs.

In summary, the present study highlighted the importance of integrating multiple diagnostic tools, such as NIPS, CMA and karyotyping, to accurately diagnose 11q- syndrome prenatally. While NIPS can serve as an effective early screening method, confirmation via CMA is essential, especially in cases involving sonographic anomalies or suspected structural rearrangements. Karyotyping adds further value by identifying balanced translocations, which have implications for recurrence risk and family planning.

In conclusion, fetuses with 11q- syndrome can be detected in the first trimester through NIPS; however, confirmation by CMA and karyotyping remains essential. Due to the variability in phenotypic expression, driven by genetic, epigenetic and environmental factors, integrated genetic testing is necessary for a definitive diagnosis. When a balanced parental translocation is identified, recurrence risk counseling becomes a critical component of prenatal care. The findings of the present study support the combined use of molecular and cytogenetic approaches to improve detection rates, understand genotype-phenotype associations and inform clinical management.

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Availability of data and materials

The CMA assay data generated in the present study may be found in the Gene Expression Omnibus database under accession number GSE287321 or at the following URL: https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE287321. The NIPS data generated in the present study may be found in the National Center for Biotechnology Information BioProject database under accession number PRJNA1297978 or at the following URL: https://www.ncbi.nlm.nih.gov/bioproject/?term=PRJNA1297978. The other data generated in the present study may be requested from the corresponding author.

Authors' contributions

TZ designed and performed all the experiments. XCo and LH contributed to the design of the article. ZL and FW confirm the authenticity of all the raw data. XCa and XL contributed to acquiring the experimental results. ZL, YL and FW conducted the analysis and interpretation of the experimental data. LH collaborated on manuscript writing. WL performed acquisition and analysis of the data. FW supervised the study and corrected the manuscript. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Review Committee of Longgang District Maternity & Child Healthcare Hospital of Shenzhen City (approval no. KYXM-2023-037; Shenzhen, China), and written informed consent was obtained from all participants before testing.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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