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# Prenatal diagnosis and clinical evaluation of fetuses with structural X chromosome abnormalities: a ten-year single-center retrospective study

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## Abstract

**Background** Structural X chromosome abnormalities are rare conditions and pose great challenges in prenatal genetic counseling. The present study aimed to identify and investigate the pregnancy outcome of fetuses with X chromosome structural abnormalities in the Chinese population.

**Methods** A total of 12 fetuses with X chromosome structural abnormalities were collected from 16,817 individuals who underwent prenatal diagnosis at Quanzhou Women's and Children's Hospital. Karyotype and/or chromosomal microarray analysis (CMA) were utilized to detect chromosomal abnormalities.

**Results** Among the 12 fetuses with structural X chromosome abnormalities, one case had a balanced X; autosome chromosome translocation, the other 11 cases had unbalanced X; autosome or X-Y chromosome rearrangements. Eight subjects performed CMA detection, the CMA result was inconsistent with karyotype analysis result in Case 4, in which an additional 2q37.2q37.3 microduplication observed in the fetus. Finally, the karyotype of Case 4 was described as 46,X, der(X)t(X;2)(q22.3;q37.2). Parental origin verification was performed in 9 of the 12 cases, of which four cases were *de novo* and five cases inherited from the pregnant women. Prenatal ultrasound examination were available for 8 out of 12 cases, all the fetuses exhibited soft ultrasound abnormalities.

**Conclusion** The present study reports a series of 12 cases with structural X chromosome abnormalities. Our findings suggest that parental verification is valuable for guiding genetic counseling and managing pregnancy outcomes in fetuses with structural X chromosome abnormalities. In addition, CMA would be benefit for investigating the precise chromosome break points detected by karyotype analysis.

**Keywords** Karyotype analysis, Chromosomal microarray analysis, X chromosome abnormality, Prenatal diagnosis

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## Introduction

Structural X chromosome abnormalities are rare conditions, including X chromosomal balanced translocations and X chromosome imbalanced recombination, which may exhibit variable phenotypes and carrying a high risk of birth defects. Balanced X chromosome translocations are rare, with a reported prevalence of 1:30,000 live births [1]. Unlike autosomal balanced translocations, balanced X chromosome translocations would lead to variable clinical phenotypes. Individuals with X; autosome translocations carry a high risk of short stature, intellectual disability, germinal aplasia and X-linked disorders, which may due to X chromosome inactivation (XCI) in abnormal X chromosome [2–4]. However, chromosome X-autosome balanced translocations may also lead to an unremarkable clinical phenotype due to XCI in normal X chromosome, but may cause abnormal pregnancy such as recurrent spontaneous abortion, stillbirths, and congenital disabilities in the offspring [5].

Turner syndrome (TS) is a sexual chromosome disorder that occurs in 1:2,500 ~ 3,000 live births. It is caused by the total or partial loss of the second sex chromosome and is characterized with high variable features, includes short stature, gonadal dysgenesis, and other anomalies [6, 7]. X chromosome monosomy is the most frequent anomaly in TS. In contrast, structural X chromosome abnormalities are found in 20 to 30% of TS, including the isochromosome, rings, Xp or Xq chromosome deletions, and X or Y chromosome-derived chromosomal markers, which can be either inherited or *de novo* [8]. At present, structural X chromosome abnormalities represent a major challenge in prenatal genetic counseling, but there is little known about the prenatal ultrasound characteristics and prognosis of fetuses with such abnormalities.

The aim of this study was to investigate the prenatal diagnostic data and fetal prenatal ultrasound phenotype, and pregnancy outcome of fetuses with balanced and imbalanced structural X chromosome abnormalities, and provide additional clinical data for references.

## Materials and methods

### Subjects

A total of 12 fetuses with structural X chromosome abnormalities were collected from 16,817 subjects who underwent prenatal diagnosis at Quanzhou Women's and Children's Hospital, China, between September 2017 to April 2023. All of individuals performed prenatal karyotype analysis and/or CMA using amniotic fluid cells obtained via invasive amniocentesis during the second trimester of pregnancy. Informed consents were obtained from all the enrolled subjects. The study protocol was approved by the Ethics Committee of the aforementioned hospital (2022 No.46).

### Karyotype analysis

Approximately 30 mL of amniotic fluid was collected from each pregnant woman for karyotype analysis (20 mL) and chromosomal microarray analysis (CMA) (10 mL). Chromosomes were prepared using the Sinochrome Chromprep II automatic chromosome harvesting system (Shanghai Lechen Biotechnology Co., Ltd.) according to the karyotype operation procedure established by the Prenatal Diagnosis Department of our hospital [9]. Nomenclature and diagnosis of the karyotypes were performed following to the International System for Human Cytogenomic Nomenclature (ISCN 2020).

### DNA extraction

Amniotic fluid samples of approximately 10 mL was obtained from each enrolled pregnancy woman. Genomic DNA was extracted using the QIAamp DNA Blood Kit (QIAGEN, Germany) following the manufacturer's protocol (www.qiagen.com).

### Chromosomal microarray analysis

CMA was perform using the Affymetrix Cytoscan 750 K chip (Life Technologies, American) according to a previously described protocol [10]. Briefly, the single-nucleotide polymorphism (SNP) and copy number variants (CNVs) were analyzed using Genotyping Console and Chromosome Analysis Suite software. Databases such as the Database of Genomic Variants (DGV) (http://dgv.tcag.ca/dgv), Online Mendelian Inheritance in Man (OMIM) (https://omim.org/), DECIPHER (https://decipher.sanger.ac.uk/), PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), and other relevant databases were used for CNVs analysis. According to the five categories of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen) guidelines, variants were scored and classified as pathogenic (≥ 0.99), likely pathogenic (0.90 to 0.98), variant of uncertain clinical significance (VUS, – 0.89 to 0.89), likely benign (– 0.90 to – 0.98), or benign ( ≤ – 0.99) [11].

## Results

### Sample information

In the present study, a total of 12 unrelated subjects who had structural X chromosome abnormalities were enrolled from 16,817 subjects who underwent amniocentesis prenatal diagnosis at our hospital, reaching a detection rate of 0.07% (12/16,817). As demonstrated in Table 1, eight out of 12 cases had available prenatal ultrasound examination results, all of them exhibited prenatal soft ultrasound abnormalities, including polyhydramnios and other abnormalities. Of the other 4 cases without prenatal ultrasound examination results, Case 1 and Case 12 underwent prenatal diagnosis due to high-risk results from prenatal serological screening, while Case 2 and

**Table 1** Results of karyotype and chromosomal microarray analysis of the enrolled subjects

| Cases | High risk factors | Ultrasound findings | Karyotype results | CMA results | Origin | Follow-up results |
|---|---|---|---|---|---|---|
| Case 1 | High risk Down syndrome screening | / | 46,X, del(X)(q24q27.3) | / | Maternal | Born with normal phenotype |
| Case 2 | High risk NIPT | / | 46,X, i(X)(q10) | / | / | TOP |
| Case 3 | High risk Down syndrome screening | Pericardial effusion | 46,X, del(X)(q23.3) | / | *De novo* | TOP |
| Case 4 | High risk NIPT | / | 46,X, der(X)t(X;2)(q22.3;q37.2)dn | arr[GRCh37]Xq22.3q28(105321721_155233098)×1,49.9 Mb; 2q37.2q37.3(236645015_242782258)×3,6.1 Mb | *De novo* | TOP |
| Case 5 | High risk NIPT | Left choroidal plexus cyst | 46,X, add(X)(p22.3) | / | / | TOP |
| Case 6 | High risk NIPT | Polyhydramnios | 46,X, der(X)t(X;4)(p21.3;q28.2)mat | arr[GRCh37]Xp22.3p21.3(168551_27213664)×1,27 Mb; 4q28.2q35.2(129108987_190957460)×3,61.8 Mb | Maternal | Born with normal phenotype |
| Case 7 | High risk NIPT | Polyhydramnios | 46,X, der(X)t(X; Y)(p22.3;q11.21)dn | arr[GRCh37]Xp22.33(168551_2696762)×1,2.5 Mb; Yq11.21q11.23(14559329_28799654)×1,14.2 Mb | *De novo* | TOP |
| Case 8 | Maternal chromosomal abnormalities | Left ventricular punctate echogenicity | 46,X, t(X;2)(p21.2;p25) | arr[GRCh37]arr(1–22)×2,(XN)×1 | Maternal | Born with normal phenotype |
| Case 9 | High risk NIPT | Widening of posterior cranial fossa pool | 46,X, i(X)(q10) | arr[GRCh37]Xp22.3p11.21(168552_55737762)×1,55.5 Mb; Xp11.21q28(55742640_155233098)×3,99.4 Mb | / | TOP |
| Case 10 | High risk NIPT; Maternal chromosomal abnormalities | Right subclavian artery vagus, left ventricular dilation | 46,X, del(X)(q21.3q24)mat | arr[GRCh37]Xq21.33q24(96549171_119766253)×1,23.2 Mb | Maternal | Born with normal phenotype |
| Case 11 | Maternal chromosomal abnormalities | Enhanced intestinal echo | 46,X, der(X)t(X; Y)(p22.3;q11.2)mat | arr[GRCh37]Xp22.3p22.31(168552_8499916)×1, 8.3 Mb; Yq11.221q11.23(16014973_28799654)×1,12.7 Mb | Maternal | Born with normal phenotype |
| Case 12 | High risk Down syndrome screening | / | 46,Y, del(X)(q21.2q21.3)dn | arr[GRCh37]Xq21.2q21.33(84765913_96093522)×0,11.3 Mb | *De novo* | TOP |

*CMA* chromosomal microarray analysis, *TOP* terminated of pregnancy, *NIPT* non-invasive Prenatal Testing

Case 4 had high-risk results from non-invasive prenatal testing (NIPT).

### Karyotype analysis results

All the enrolled 12 cases performed karyotype analysis and the results were available for all. As listed in Table 1, one case with balanced X chromosome translocation was identified, additionally, the remaining 11 cases had unbalanced structural X chromosomal rearrangements, including two cases of 46,X, i(X)(q10), four cases of derived X chromosomes, and five cases of partial Xq deletions.

### Chromosomal microarray analysis results

Of the 12 fetuses with structural X chromosome abnormalities, eight underwent further CMA detection. Among them, seven cases reported consistence results with karyotype, while, Case 4 exhibited inconsistent results. The initial karyotype of Case 4 was described as 46,X, del(X)(q22.2), while, the subsequent CMA results demonstrated a 49.9-Mb Xq22.3q28 deletion combined with a 6.1-Mb microduplication in 2q37.2q37.3 region in the fetus (Fig. 1). Finally, combined with parental verification results, the karyotype of Case 4 was revised to 46,X, der(X)t(X;2)(q22.3;q37.2)dn.

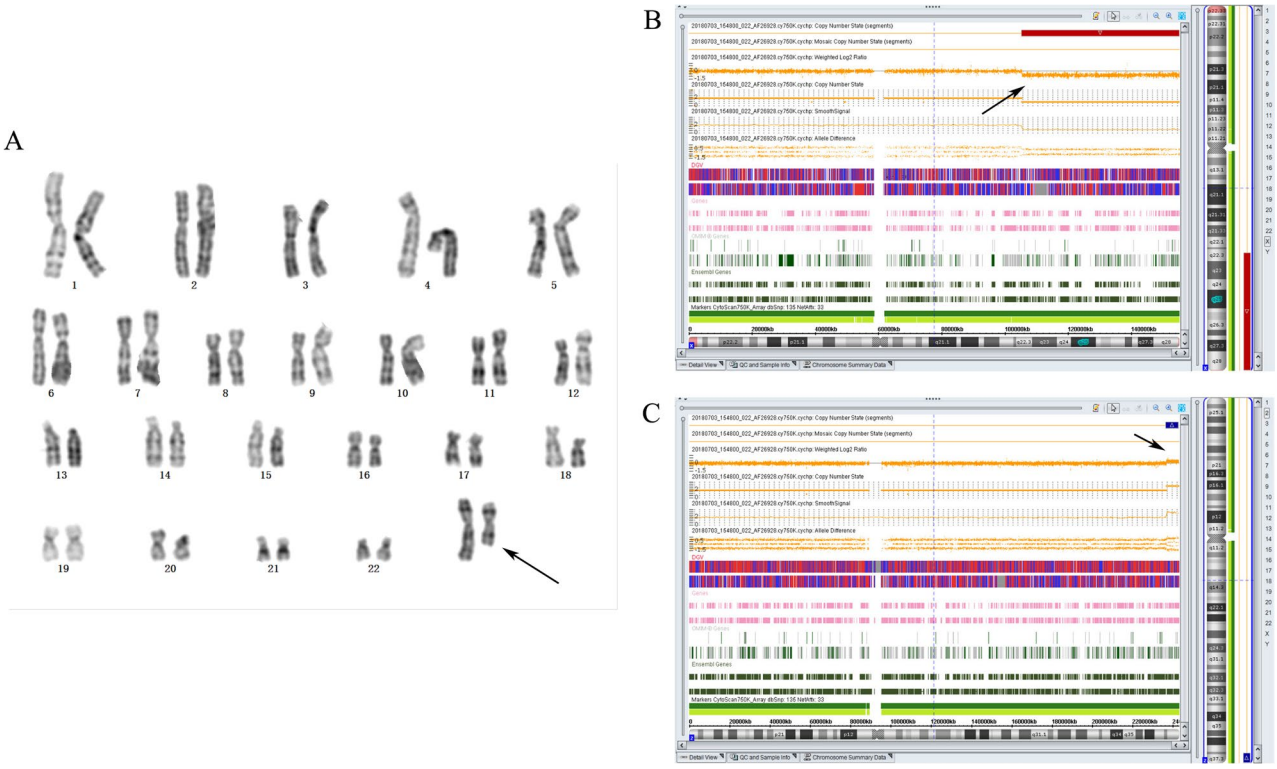


**Fig. 1** Karyotype and CMA analysis results in Case 4. **A**: The karyotype analysis result in Case 4 was initially described as 46,X, del(X)(q22.2). **B**: The subsequent CMA results demonstrated a 49.9 Mb Xq22.3q28 deletion in the fetus. **C**: A 6.1 Mb 2q37.2q37.3 microduplication was also identified in the fetus

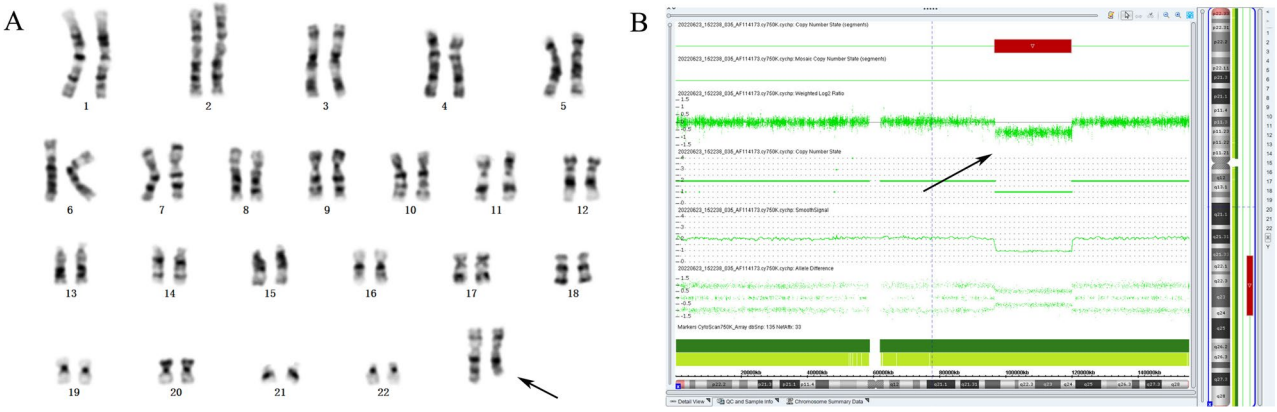


**Fig. 2** Karyotype and CMA analysis results in Case 10. **A**: The karyotype of the fetus was described as 46,X, del(X)(q21.3q24). **B**: CMA result confirmed a 23.2 Mb deletion in Xq21.33q24 region in the fetus, which was consistence with karyotype result

Among the other four cases that were initially described as having partial Xq deletion (Case 1,3,10,12), two of them (Case 10 and Case 12) performed CMA investigation. In Case 10, a 23.2 Mb deletion in Xq21.33q24 region was identified [arr[GRCh37]Xq21.33q24(96549171_119766253)×1]. The Xq21.33q24 deletion was inherited from the normal mother, finally, the karyotype was described as 46,X, del(X)(q21.3q24)mat (Fig. 2). In the Case 12, a 11.3 Mb deletion in Xq21.2q21.3 region was observed using CMA [arr[GRCh37]Xq21.2q21.33(84765913_96093522)×0]. Combined with parental karyotype analysis results, the karyotype result was described as 46,Y, del(X)(q21.2q21.3)dn.arr[GRCh37]Xq21.2q21.33(84765913_96093522)×0 (Fig. 3).

In this study, one fetus (Case 8) had a balanced X-autosome translocation of 46,X, t(X;2)(p21.2;p25), which was inherited from the mother with normal clinical phenotype. No obvious ultrasound anomalies were observed in the fetus, except left ventricular punctate echogenicity. Interestingly, a male pediatric patient was described in the family of Case 8, carrying a 2.96 Mb deletion in 2p25.3 region and a 22.92 Mb duplication

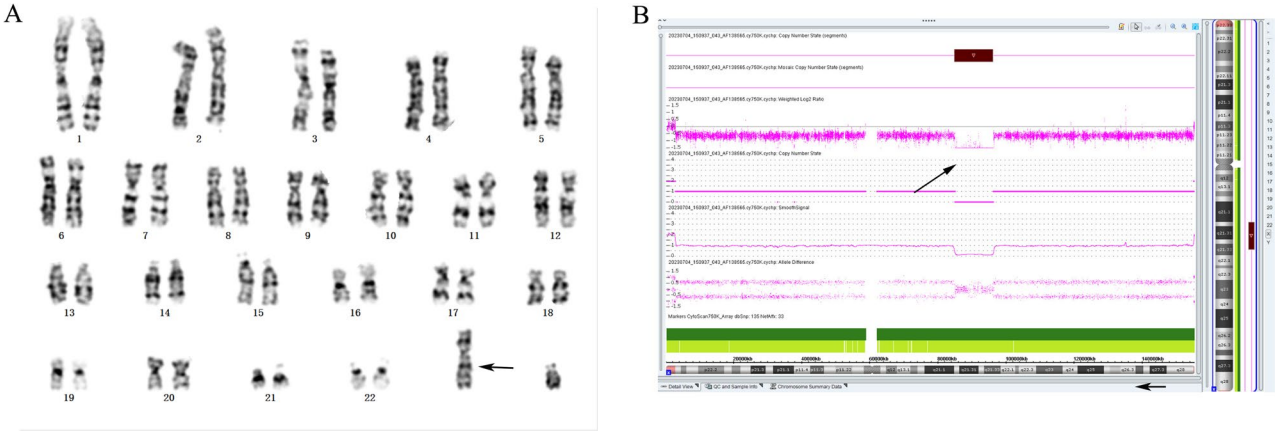

**Fig. 3** Karyotype and CMA analysis results in Case 12. **A**: The karyotype analysis result indicated a 46,Y, del(X)(q21.2q21.3) in the fetus. **B**: A 11.3 Mb deletion in Xq21.2q21.3 region was identified in the fetus using CMA

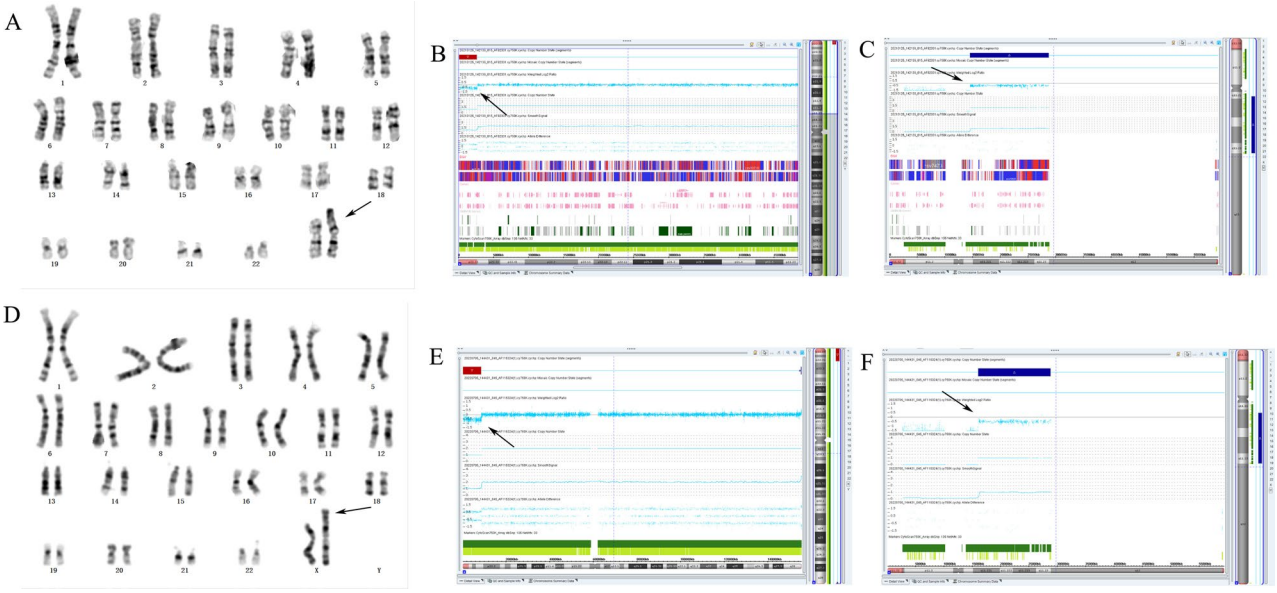

**Fig. 4** Karyotype and CMA analysis results in Case 7 and Case 11. **A**: An initial karyotype analysis result was described as 46,X, add(X)(p22.3) in Case 7. **B**, **C**: CMA results demonstrated a 2.5 Mb deletion in Xp22.33 region combined with a 14.2 Mb duplication in Yq11.21q11.23 region in the fetus, finally, the karyotype could be revised as 46,X, der(X)t(X; Y)(p22.3;q11.21). **D**: An initial karyotype analysis result was also described as 46,X, add(X)(p22.3) in Case 11. **E**, **F**: A 8.3 Mb deletion in Xp22.33p22.31 region and 12.7 Mb duplication in Yq11.221q11.23 region were identified in the fetus. Finally, the karyotype was revised as 46,X, der(X)t(X; Y)(p22.3;q11.2)

in Xp22.33p21.3 region (date not shown), which was ascribed to the maternal t(X;2). Currently, at his 6 aged follow up, remarkable developmental delay was observed, his is unable to sit and stand independently, and cannot speak.

Four fetuses with derived X chromosome abnormalities were identified in this study, including one fetus (Case 6) with 46,X, add(X)(p22), which was ultimately defined as 46,X, der(X)t(X;4)(p21.3;q28.2), and has been previously reported by our team [10]. Three fetuses with 46,X, add(X)(p22.3) were also identified (Case 5,7,11), two of them (Case 7 and Case 11) underwent further CMA investigation. In addition, as summarized in Table 1, the derived X chromosomes in both Cases 7 and 11 consisted of X and Y chromosomal material. In Case 7, the parents had normal karyotype results, so the final karyotype of the fetus was described as 46,X, der(X)t(X; Y)(p22.3;q11.21)dn (Fig. 4). In contrast, the derived X chromosome in Case 11 was inherited from the normal mother, the fetus's karyotype was revised as 46,X, der(X) t(X; Y)(p22.3;q11.2)mat (Fig. 4).

### Parental origin verification and pregnancy outcome follow-up results

As listed in Table 1, nine out of 12 cases underwent parental verification, of which four cases were *de novo*

and five cases were inherited from the mother. All the 12 enrolled cases were successfully followed up. In the present study, seven cases chose to terminate their pregnancies, and the remaining five cases chose to continue their pregnancies, all infants born with normal appearances and normal clinical phenotype during one-year follow-up after birth.

## Discussion

Structural X chromosome abnormalities that containing balanced X chromosomal translocations and unbalanced X chromosome recombination are rare conditions, which may lead to variable clinical phenotypes and pose great challenges in prenatal genetic counseling and pregnancy decision-making. In the present study, 12 subjects with structural X chromosome abnormalities were enrolled from 16,817 subjects in the Chinese population who underwent prenatal diagnosis, aiming to investigate the pregnancy outcome of fetuses with structural X chromosome abnormalities in the Chinese population and providing additional data for genetic counseling. To date, few studies have focused on structural X chromosome abnormalities in the prenatal period. The detection rate of structural X chromosome abnormalities was 0.07% (12/16,817) in this study, which is slightly higher than the 0.03% (4/13,795) reported in a previous study [12].

In the early stages of embryonic development, one of the two X chromosomes in each chromosome is randomly inactivated in female embryonic cells, known as X-chromosome inactivation (XCI), which is an epigenetic mechanism that ensures X-linked dose compensation between female (XX karyotype) and male (XY) cells [13–15]. Previous study indicated that inactivate of derived/translocated X chromosome leads to the spread of XCI to the autosomal segment [16, 17]. Usually, in balanced X-autosome translocations the normal X chromosome is inactive to maintain functional euploidy [18]; despite that, there may be an increased risks of abnormal pregnancy, and congenital anomalies in offspring [5]. In addition, a previous study review of 122 cases of female balanced X-autosome translocations revealed that the translocated X chromosome escaped XCI in 77% of patients, who predominantly exhibited a normal phenotype or isolated gonadal dysgenesis; conversely, in 23% of cases, the translocated X underwent XCI in a fraction of cells, resulting in functional disomy of the relevant X chromosomal segment. Notably, breakpoints at Xp22 and Xq28 are associated with a significantly higher incidence of functionally disomic cells [19]. In this study, the fetus (Case 8) and the pregnant woman had a balanced translocation of t(X;2)(p21.2;p25), and born with normal clinical features, while, a male pediatric patient with remarkable developmental delay was observed in this family, who had a 2p25.3 deletion associated with a Xp22.33p21.3 duplication, which partial inherited from the maternal t(X;2). Individuals who carrying a balanced translocation of the X chromosome and autosomes may experience clinical phenotype abnormalities if the abnormal X chromosome is inactivated. Interestingly, a previous study conducted by Myszka et al. [20] reported a girl harbored a balanced *de novo* translocation 46,X, t(X;13)(p11.2;p13) and exhibited dysmorphic features and developmental delay in psychomotor, that due to XCI involved in translocation. Therefore, the differences of XCI may lead to the normal or abnormal phenotype in individuals with structural X chromosome abnormalities.

Individuals harboring an X derived chromosome resulting from unbalanced rearrangements may exhibit mild clinical phenotypes due to the XCI skewing of the derived X chromosome, which spreads to autosomes [17, 21]. Similarly, in Case 6, the fetus had a 4q28.3-qter duplication combined with a Xp21.3-p22.3 deletion and born with a normal appearance, which inherited from the pregnant woman who exhibited a mild clinical phenotype limited to short stature [10]. It is known that X-Y chromosome translocation are rare events, with Xp22 and Yq11 being the major breakpoints [22]. The short stature homeobox gene (*SHOX*), located on Xp22.3, is one of the major growth genes in humans and would escaping XCI [7, 23]. Previous study indicated that females with Xp; Yq translocations are usually normal except for short stature [24]. However, a previous study reported a girl with a *de novo* der(X)t(X; Y)(p22;q11) and exhibited clinical anomalies including short stature, mental retardation and facial dysmorphisms [25]. Notably, in the present study, two fetuses with unbalanced X; Y chromosome recombination were identified. In Case 7, a *de novo* 46,X, der(X)t(X; Y)(p22.3;q11.21) was identified in the fetus with polyhydramnios, ultimately, the family chose to terminate the pregnancy. In Case 11, the 46,X, der(X)t(X; Y)(p22.3;q11.2) was identified in the fetus, which containing the *SHOX* gene deletion, and was inherited from the pregnant woman who exhibit normal features expect short stature. The family chose to continue the pregnancy, a female infant born with normal appearance, a long-term follow-up will be required for this infant in the future.

The isochromosome of the long arm of the X chromosome, i(Xq), is the most common structural abnormality described in TS [26]. In the present study, two cases with i(Xq) were identified in this study, both chose to terminate their pregnancies. In TS case series, the frequency of deletion of the long arm of the X chromosome is reported to be 2%, which exhibit mild patient phenotype and has fewer typical features [6, 27]. In addition, studies have shown that, in addition to the preferential inactivation of the structurally abnormal X chromosome, an additional gene-to-gene protection mechanism occurs

at the transcription level of the normal X chromosome to counteract the harmful effects of large Xq deletions [28]. The critical regions for premature ovarian failure (POF) have been reported to be located in Xq26-q28 and Xq13.3-q21.3 [29, 30]. In this study, four cases with Xq deletion were identified, all of them partial covering the critical regions of POF, three of them inherited the Xq deletion from the pregnant women who had normal clinical features, without POF presently. However, in the Case 1, the fetus inherited the Xq deletion from the pregnant woman, which was inherited from the pregnant woman's mother who had POF, and has been described previously by our team [31]. Thus, long-term follow-up will be helpful in clarifying the impact of the detected Xq deletions on the development of POF.

In the present study, eight of the 12 subjects underwent further CMA. Interestingly, one case with 46,X, del(X)(q22.2) karyotype results was confirmed to carry 46,X, der(X)t(X;2)(q22.3;q37.2) following CMA detection. CMA detection is helpful in revealing the abnormal break point of X chromosome structure and the origin of derived chromosomes, that initially described by karyotype analysis. Furthermore, prenatal ultrasound findings in the 12 enrolled cases with structural abnormalities of the X chromosome demonstrated no distinct phenotypic clustering, except for two fetuses that presented with polyhydramnios. Interestingly, both cases (Case 6 and Case 7) involved a deletion of the Xp22.33 segment. Currently, no studies have investigated the correlation between this specific segment and prenatal polyhydramnios. Nevertheless, to our best knowledge, only one study [32] has documented prenatal polyhydramnios in a male fetus with a karyotype of 46,Y, del(X)(p22.3). This finding, combined with our report, may support a potential association between Xp22.33 deletion (containing the *SHOX* gene) and prenatal polyhydramnios. However, further research and more supportive evidence are still warranted. The main limitation of this study is the absence of XCI analysis in subjects with structural X chromosome abnormalities. As such, further research focusing on XCI investigation is warranted to ascertain the underlying mechanism for individuals with variable phenotypes. In addition, sustained long-term follow-up of the live-born infants included in this study is necessary to further enrich and validate the clinical dataset.

In conclusion, the present study reported a series of 12 cases with structural X chromosome abnormalities. Our findings indicated that CMA would be helpful in revealing the break point of structural X chromosome abnormalities detected by karyotype analysis. Additionally, due to clinical phenotype variability of patients with structural X chromosome abnormalities, parental verification would benefit in guiding genetic counseling and pregnancy decision-making in fetuses with such abnormalities.

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**Authors' contributions**
JZ and LZ wrote the article; WC and XC recruited the participants and performed clinical consultation; LZ, NH and JZ revised and polished the paper. All authors have approved the final version of the article.

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**Data availability**
The datasets used and analyzed in the current study were obtained from the corresponding author on reasonable request.

## Declarations

**Ethics Approval and Consent to Participate**
Ethics Committee approval was obtained from the Institutional Ethics Committee of Quanzhou Women's and Children's Hospital for the commencement of this study (2022No.46). Informed consent was obtained from all study participants, who agreed to the publication of the study report. All procedures involving human participants adhered to the ethical standards of the institutional and/or national research committees and were in accordance with the 1964 Helsinki Declaration and its subsequent amendments or comparable ethical standards.

**Consent for publication**
Written informed consent was obtained from the parents of the patients for the publication of their genetic data and relevant information, including that of their children. The written informed consent is available upon request.

**Competing interests**
The authors declare no competing interests.

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