Analysis of Xp22.31q27.1 Region Variation Detection based on SNP Array Technology

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SUMMARY

Background: The aim of the study was to investigate the value of single nucleotide polymorphism array (SNP array) technology in the prenatal diagnosis.

Methods: The variants in Xp22.31q27.1 region of 13 fetuses were analyzed by SNP array technology. Chromosome karyotype analysis was also performed for these fetuses and their parents.

Results: Chromosome karyotype analysis found no obvious chromosomal abnormality at 400 bands resolution. Using SNP array technology, we found that all fetuses had mutations in Xp22.31q27.1 region, which was mainly Xp22.31 lesion (61.5%, 8/13) that contained 2 to 5 OMIM genes. Moreover, these mutations consisted of 7 cases of repetition and 6 cases of deletion. In addition, 9 variants were inherited from their mothers, 3 mutations were inherited from the father, and 1 variant was de novo.

Conclusions: Compared to traditional analysis of chromosome karyotype, SNP-array technology can detect more chromosomal microdeletions and microduplications. SNP-array technology can act as a supplementary diagnostic method in clinical cytogenetic diagnosis.


KEYWORDS

prenatal diagnosis, SNP Array technology, Xp22.31q27.1 region variation

INTRODUCTION

Traditional methods of prenatal diagnosis rely on cytogenetic G-banding karyotyping and fluorescence in situ hybridization (FISH). However, due to the complexity of the operation, low resolution, and long cycle time, the American College of Obstetricians and Gynecologists and the Maternal-Fetal Medicine Society recommended in 2013 that the fetus with one or more major structural abnormalities confirmed by prenatal ultrasound should be considered for prenatal diagnosis. It can be detected by Chromosomal Microarray Analysis (CMA) [1]. CMA technology can be divided into two types according to chip design and detection principle: single nucleotide polymorphism array (SNP array) and
array-comparative genomic hybridization (Array-CGH). SNP-array technology is genome-wide detection of genetic material and has been widely used to detect microdeletions and microduplications in chromosomes, even microdeletions and abnormal duplications with very small degrees of variation can be detected. This study aims to investigate the application value of SNP array analysis in the detection of fetal X chromosome Xp22.31q27.1 region variation.

MATERIALS AND METHODS

Research Subjects

From January 2018 to August 2022, those with prenatal diagnosis indications in the Prenatal Diagnosis Institution of Putian First Hospital in Fujian Province were selected for genetic counseling and signed the informed consent for invasive prenatal diagnosis. Amniotic fluid was collected by invasive amniocentesis and SNP Array detection. A total of 13 patients with Xp22.31q27.1 mutation detected by SNP Array were enrolled in this study. The mean age of the pregnant women was 27.6 ± 2.4 years (range 23 to 45 years), and the mean gestational age was 20±1 weeks (range 18 ± 6 to 25 ± 4 weeks). All cases were singleton pregnant women. This study was approved by the hospital Ethics Committee. Indications for invasive amniocentesis: (1) Advanced age refers to the age of pregnant women ≥ 35 years old. (2) Fetal ultrasound soft index abnormalities including NT/NF thickening, lateral ventricle widening, choroid plexus cyst, nasal bone dysplasia, ventricular strong spot, intestinal echo enhancement, single umbilical artery, etc. (3) (3) High risk of serological screening: T18 ≥ 1/270, T21 ≥ 1/270 [4]. (4) NIPT test indicated high risk. (5) Pregnant women with a history of adverse pregnancy and childbirth.

Research methods

All pregnant women in the study completed the routine preoperative examination, and after standard sterilization, amniocentesis was performed aseptically under the localization and guidance of ultrasound instrument. About 20 mL of amniotic fluid was collected and sent to the laboratory for inoculation and culture, filming, and preoperative examination, and after standard sterilization, all pregnant women in the study completed the routine sterilization. Amniotic fluid was digested, ligated, amplified, purified, fragmented, labeled, hybridized, washed, stained, and scanned according to the standard procedures of chromosome microarray provided by Affymetrix Company. The corresponding interpretation software was used to analyze the data of the result file generated by the scanning chip. According to the international online public databases (DECIPHER database of pathogenic CNV), OMIM database of known genetic diseases and pathogenic genes, DGV data, the gene content and function database in CNV (UCSC Genome Browser and PUBMED), and our laboratory’s internal reference database (Affymetrix chip platform database CAGdb and Cellular Genome Chip International Standards Consortium database ISCA) were compared with CHAS. The results of software analysis were compared and analyzed to determine the results of CNV.

Statistical methods SPSS 23.0 statistical software was used for data analysis, and the count data was presented as [example (%)].

RESULTS

The statistical results of this study are detailed in Tables 1 and 2. Table 1 includes cases and karyotype results of 13 children, Table 2 shows SNP Array assay results of 13 children.

In this study, the chromosomal patterns of 13 children and their parents were normal karyotypes at the banding resolution of 400 bands, and no obvious abnormalities were found.

The indications for prenatal diagnosis of the 13 cases collected in this study included advanced maternal age (2 cases), abnormal fetal ultrasound soft markers (3 cases), high risk of serological screening (5 cases), adverse pregnancy history (1 case), and high risk of NIPT (2 cases). SNP Array detected variants in the X chromosome Xp22.31q27.1 segment, especially the Xp22.31 lesion was the most common, accounting for 8 cases (61.5%, 8/13), which contained 2 to 5 OMIM genes including STS.

There were 7 cases of repetition in this segment, with the longest segment being 1.6 M and the shortest segment being 307.2 Kb. There were 6 cases of deletion, with the longest fragment and the shortest being 1.6 M and 236.8 Kb, respectively.

The deletion or duplication of the 1.6 Mb fragment in the Xp22.31q27.1 region was the most common variation, which was mainly related to ichthyosis disease with X-linked recessive inheritance. The presence of a duplication of the 882.4 Kb fragment of the X chromosome Xq27.1 segment, which involves three OMIM genes, FGFl3, F9, and ATP11C. A duplication of a 307.2 Kb fragment of the X chromosome Xq21.2 segment containing a partial fragment of the CHM gene and spanning exons 2 - 15. A duplication of a 505.8 Kb segment of X chromosome Xp22.12 containing a partial fragment of the RPS6KA3 gene and spanning exon regions 1 - 6. A deletion of the 613.7 Kb fragment was present in the X chromosome Xp22.31 region contain-
### Table 1. Cases and karyotype results of 13 children.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (year)</th>
<th>Gestational weeks</th>
<th>Indications of prenatal diagnosis</th>
<th>Fetal karyotype results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>22+3</td>
<td>left and right cardiac hyperechoic foci</td>
<td>46, XY</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>18+6</td>
<td>adverse pregnancy history: multiple malformations in the first child, no abnormalities in the second child; hyperechoic foci in the left ventricle of the current fetus</td>
<td>46, XY</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>24+3</td>
<td>polyhydramnios; single umbilical artery</td>
<td>46, XY</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>22+6</td>
<td>test-tube babies; NIPT showed a 0.62 Mb microdeletion at p22.31(7.8 Mb - 8.4 Mb) on the short arm of the X chromosome</td>
<td>46, XY</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>21+3</td>
<td>tricuspid regurgitation; cardiac hyperechogenicity; fetal ventricular septal defect</td>
<td>46, XY</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>19+5</td>
<td>high risk for Down screening: T18 1/58</td>
<td>46, XY</td>
</tr>
<tr>
<td>7</td>
<td>29</td>
<td>18+3</td>
<td>high risk for Down screening: T18: 1/67; slight separation of bilateral renal sinuses</td>
<td>46, XY</td>
</tr>
<tr>
<td>8</td>
<td>33</td>
<td>18+1</td>
<td>high risk for Down screening: T18: 1/243</td>
<td>46, XY</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>20+3</td>
<td>high risk for Down screening: T18 1/140; hyperthyroidism in pregnant women</td>
<td>46, XY</td>
</tr>
<tr>
<td>10</td>
<td>38</td>
<td>22+1</td>
<td>venerable age</td>
<td>46, XY</td>
</tr>
<tr>
<td>11</td>
<td>39</td>
<td>21+6</td>
<td>venerable age; pregnant woman with unicornuate uterus; three miscarriages</td>
<td>46, XY</td>
</tr>
<tr>
<td>12</td>
<td>33</td>
<td>19+1</td>
<td>high risk for Down screening: T21 1/91; the fetal left ventricular punctate hyperechoic foci</td>
<td>46, XX</td>
</tr>
<tr>
<td>13</td>
<td>25</td>
<td>20+3</td>
<td>NIPT showed fetal sex chromosome aneuploidy is at high risk</td>
<td>46, XY</td>
</tr>
</tbody>
</table>

### Table 2. SNP Array assay results of 13 children.

<table>
<thead>
<tr>
<th>Case</th>
<th>SNP array assay results</th>
<th>The abnormal fragments involved genes</th>
<th>Heredity</th>
<th>Follow-up visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>arr [hg19] Xq27.1(138, 073, 120 - 138, 955, 526) x 2</td>
<td>male fetus; a duplication of 882.4 Kb fragment was present in the Xq27.1 region of chromosome X, involving three OMIM genes including FGF13, F9, ATP11C</td>
<td>mother</td>
<td>9 months, healthy</td>
</tr>
<tr>
<td>2</td>
<td>arr [hg19] Xq21.2(84, 990, 317 - 85, 297, 525) x 2</td>
<td>male fetus; a duplication of a 307.2 Kb fragment was present in the Xq21.2 region of chromosome X, involving a partial fragment of the CHM gene</td>
<td>mother</td>
<td>normal birth</td>
</tr>
<tr>
<td>3</td>
<td>arr [hg19] Xp22.12(20, 212, 248 - 20, 718, 134) x 2</td>
<td>male fetus; a duplication of a 505.8 Kb fragment was present in the Xp22.12 region of chromosome X, involving a partial fragment of the RPS6KA3 gene</td>
<td>mother</td>
<td>27 months, healthy</td>
</tr>
<tr>
<td>4</td>
<td>arr [hg19] Xp22.31(7, 815, 191 - 8, 428, 908) x 0</td>
<td>male fetus; A 613.7 Kb fragment deletion was present in in the Xp22.31 region of the X chromosome, involving the PNPLA4,VCX2 gene</td>
<td>mutation</td>
<td>normal birth</td>
</tr>
<tr>
<td>5</td>
<td>arr [hg19] Xp22.2(10, 630, 436 - 11, 171, 063) x 2, Xp22.13(18, 639, 794 - 19, 233, 821) x 2</td>
<td>male fetus; this patient had a duplication of a 540.6 Kb fragment in the Xp22.2 region of chromosome X, involving three OMIM genes CDKL5, PHKA2, ADGRG2 and five other OMIM genes, including MID1 and HCCS</td>
<td>mother</td>
<td>7 months, healthy</td>
</tr>
</tbody>
</table>
Table 2. SNP Array assay results of 13 children (continued).

<table>
<thead>
<tr>
<th>Case</th>
<th>SNP array assay results</th>
<th>The abnormal fragments involved genes</th>
<th>Heredity</th>
<th>Follow-up visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>arr [hg19] Xp22.31(7, 154, 869 - 7, 391, 762) x 0</td>
<td>male fetus; a deletion of a 236.8 Kb fragment was present in the Xp22.31 region of the X chromosome, involving a partial fragment of the STS gene</td>
<td>mother</td>
<td>5 months, the child has dry skin in cold weather, maternal asymptomatic</td>
</tr>
<tr>
<td>7</td>
<td>arr [hg19] Xp22.31(6, 455, 152 - 8, 135, 568) x 0</td>
<td>male fetus; a deletion of a 1.6 Mb fragment was present in the X chromosome Xp22.31 region, involving four OMIM genes including STS</td>
<td>father</td>
<td>6 months, healthy</td>
</tr>
<tr>
<td>8</td>
<td>arr [hg19] Xp22.31(6, 455, 152 - 8, 135, 568) x 0</td>
<td>male fetus; a deletion of a 1.6 Mb fragment was present in the X chromosome Xp22.31 region, involving four OMIM genes including STS</td>
<td>father</td>
<td>8 months, healthy</td>
</tr>
<tr>
<td>9</td>
<td>arr [hg19] Xp22.31(6, 458, 941 - 8, 135, 103) x 0</td>
<td>male fetus; a deletion of a 1.6 Mb fragment was present in the X chromosome Xp22.31 region, involving four OMIM genes including STS</td>
<td>mother</td>
<td>22 months, healthy</td>
</tr>
<tr>
<td>10</td>
<td>arr [hg19] Xp22.31(6, 455, 152 - 8, 135, 103) x 2</td>
<td>male fetus; a duplication of a 1.6 Mb fragment was present in the X chromosome Xp22.31 region, involving four OMIM genes including STS</td>
<td>mother</td>
<td>24 months, healthy</td>
</tr>
<tr>
<td>11</td>
<td>arr [hg19] Xp22.31(6, 455, 152 - 8, 135, 568) x 2</td>
<td>male fetus; a duplication of a 1.6 Mb fragment was present in the X chromosome Xp22.31 region, involving four OMIM genes including STS</td>
<td>father</td>
<td>29 months, healthy</td>
</tr>
<tr>
<td>12</td>
<td>arr [hg19] Xp22.31(6, 449, 837 - 8, 135, 053) x 3</td>
<td>female fetus; a duplication of a 1.6 Mb fragment was present in the X chromosome Xp22.31 region, involving five OMIM genes including STS</td>
<td>mother</td>
<td>16 months, healthy</td>
</tr>
<tr>
<td>13</td>
<td>arr [hg19] Xp22.31(6, 467, 902 - 7, 483, 102) x 0</td>
<td>male fetus; a hemizygous deletion of a 1.0 Mb fragment was present in the X chromosome Xp22.31 region, involving two OMIM genes including STS</td>
<td>mother</td>
<td>9 months, healthy</td>
</tr>
</tbody>
</table>

PNPLA4 and VCX2 genes. At follow-up, all 13 fetuses with the Xp22.31q27.1 segment variant in this study were born successfully at full term, including 12 male and 1 female. Nine of the fetal X chromosome variants were inherited from the mother. Three variants were inherited from the father. One case of mutation was de novo, and the child was a test-tube baby. NIPT examination showed that a microdeletion of approximately 0.62 Mb was present at position p22.31 (7.8 Mb - 8.4 Mb) on the short arm of the X chromosome, and the microarray results showed a deletion of a 613.7 Kb fragment in the X chromosome Xp22.31 segment. Most of the variations in Xp22.31q27.1 segment in these 13 cases were unclear. The 13 children in this study were followed up from birth up to a maximum age of 27 months, and their developmental course was not significantly different from that of their peers. Only one male infant, who inherited the Xp22.31 variant from his mother and was associated with ichthyosis, showed dry skin on cold days without substantial pathological changes, and his mother had no dry skin.

**DISCUSSION**

G-banded karyotyping was the "gold standard" for prenatal cytogenetic diagnosis, which could identify structural abnormalities of more than 10 Mb, such as balanced translocation, inversion, and insertion. However, the analysis took a long time and the results were inaccurate, mainly due to the failure to detect small chromosomal duplications and deletions. With the continued development of sequencing and gene chip-related technologies, chromosomal microarrays enable genome-wide analysis of chromosomal abnormalities, addressing the limitations of conventional detection techniques. It has good applications in the detection of various chromosomal abnormalities such as chromosomal karyotype abnormalities, structural abnormalities, chimera, and...
SNP Array Detects Microdeletions and Microduplications

homozgyous regions. Moreover, the detection does not require long cell cultures and has the advantage of being quick and having high-throughput, high-resolution, and high-accuracy, which can be a beneficial complement to traditional cytogenetic analysis methods in clinical cytogenetic diagnosis. In this study, karyotype and SNP-array detection techniques were used to provide pregnant women with more accurate fertility diagnoses and genetic counseling.

Case 1 had amniocentesis for hyperechoic foci in the left and right chambers of the heart on ultrasonography with karyotype 46, XY. The microarray result was arr [hg19] Xq27.1 (138, 073, 120 - 138, 955, 526) x 2, i.e., there was a duplication of 882.4 Kb fragment in the Xq27.1 region of the X chromosome. Data comparison and analysis of the results generated by CHAS software analysis from the international online public database and the internal reference database of our laboratory indicated that this fragment involved three OMIM genes, including GFG13, F9, and ATP1C. Mutations in the FGF13 gene [7] were associated with the X-linked dominant developmental and epileptic encephalopathy 90 diseases, and the clinical phenotypes included epileptic spasms, generalized tonic-clonic, etc. Mutations in the F9 gene were associated with X-linked recessive Hemophilia B and other diseases, with clinical phenotypes including abnormal bleeding and prolonged coagulation time. Mutations in the ATP1C gene [8,9] were associated with congenital hemolytic anemia disease with X-chromosome-linked recessive inheritance. This abnormality is currently considered to be a clinically uncertain variant of significance. The abnormal variant in this child was inherited from her mother. The mother was 24 and healthy, and this was her first child. There was no history of medication or exposure to adverse factors during pregnancy and no family history of these conditions. The child was followed until the age of 9 months and was developing like a child of the same age. Case 2 ultrasonography showed hyperechoic foci in the fetal left ventricle, and SNP Array resulted in a duplication of a 307.2 Kb fragment in the Xq21.2 region of the X chromosome, including a partial fragment of the CHM gene, spanning exons 2 - 15. This gene mutation was associated with X-linked dominant inherited Choroideremia, and its clinical phenotypes included choroideremia, chorosclerosis, visual loss, night blindness, etc. [10]. The ClinGen database showed a haplinsufficiency score of 3 for the gene contained in this fragment. In the ClinVar database, all pathogenic/likely pathogenic CHM deletions/duplications were point mutations or larger deletions/duplications. The clinical significance of this duplication was reportedly unclear. No abnormality was found in the physical examination at 42 days of age. The mutation of Xq21.2 region of the X chromosome was inherited from his mother. The mother was healthy, and there were no choroideremia patients in the family. The mother was pregnant three times, and the first fetus was found to have multiple fetal malformations by ultrasound examination, so labor was induced. No abnormality was found in the second child, a full-term daughter was born smoothly, and her growth and development were no different from that of her peers.

Case 3 was a male fetus with a 505.8 Kb duplication on the X chromosome Xp22.12 (arr [hg19] Xp22.12 (20, 212, 248 - 20, 718, 134) and a single umbilical artery because of polyhydramnios. It contains a portion of the RPS6KA3 gene and spans 1 - 6 exons regions. The mutation of this gene was associated with Coffin-Lowry syndrome and other diseases of X-linked dominant inheritance [11]. There were few cases of Xp22.12 duplication in PubMed, DECIPHER, ISCA and other databases. Compared with the data in the database, the clinical phenotypes of the reported cases abroad included skeletal deformities and growth retardation [12]. It has also been reported that copy number duplications involving the RPS6KA3 gene were detected in male patients with varying degrees of mental retardation, psychiatric disorders [13], and epilepsy [14]. It has also been reported that a microduplication of about 625 Kb in Xp22.12 region involving exon 1 - 7 of RPS6KA3 gene was detected in a male patient with mild mental retardation [15], which was inherited from a mother with normal phenotype and random inactivation of the X chromosome. Tejada et al. reported a boy carrying a 1.05 Mb duplication in the Xp22.12 region, involving seven genes, including SH3KBP1, BC046187, CXorf-23, MAP7D2, E1F1AX, SCARNA9L, and RPS6KA3 [16]. Although his clinical symptoms were mental retardation and language learning difficulties, his facial and skeletal development were normal. His maternal grandmother and mother carried the same duplication, but their appearance and intelligence were normal. The ClinGen database showed a score of 3 for evidence of haplotype insufficiency for the RPS6KA3 gene contained in this segment. However, according to the existing literature reports, it was suggested that the microduplication in Xp22.12 region might lead to abnormal phenotypes, which had clinical heterogeneity. Whether the RPS6KA3 gene has a dosage effect needs further investigation. The patient in this case, who has a repeat variant inherited from his mother and has no clinically abnormal phenotype, is now 27 months old and has been growing smoothly without obvious abnormalities.

Case 4, a test-tube baby, was diagnosed prenatally because of a 0.62 Mb deletion at Xp22.31 (7.8 Mb - 8.4 Mb) on the short arm of X chromosome by NIPT. SNP-Array results showed that the fetus was male, and the gender was consistent with the karyotype. The results of the microarray report were arr [hg19] Xp22.31 (7, 815, 191 - 8, 428, 908) x 0, and there was a 613.7 Kb deletion in the Xp22.31 region of the X chromosome, which contained PNPLA4 [17] and VCX2 [18] genes. No definite disease has been reported in the literature, and the clinical significance of this deletion is still unclear. The infants in this study were born at full term, and no obvious abnormalities were found in various examinations at birth. The microchip results of his parents were nor-
mal, and it was inferred that the X chromosome deletion in the child was a de novo mutation, the cause of which was not known.

Case 5 had tricuspid regurgitation, cardiac hypertonicty, ventricular septal defect in the fetus, and a 46, XY karyotype in the amniotic fluid. The microarray results were arr [hg19] Xp22.2 (10, 630, 436 - 11, 171, 063) x2, Xp22.13 (18, 639, 794 - 19, 233, 821) x 2. The patient had a 540.6 Kb duplication in the Xp22.2 region of the X chromosome involving three OMIM genes, including MID1 and HCCS. Mutations in the MID1 gene have been reported to be associated with X-linked recessive OpitzGBBB syndrome type 1 [19]. Clinical phenotypes included various degrees of facial dysmorphism, defects of larynx and esophagus, genital malformations, cleft lip/palate, developmental delays, and intellectual disabilities. Mutations in the HCCS gene were associated with X-linked dominant linear skin defects with multiple congenital anomalies 1 [20]. Clinical phenotypes included microcephaly, ventricular septal defects, and diaphragmatic hernia. However, the clinical significance of this duplication remains unclear based on current data. The microarray analysis also revealed that the patient had a 594.0 Kb duplication in the Xp22.13 region of the X chromosome involving five OMIM genes, including CDKL5, PHKA2, and ADGGR2. Mutations in the CDKL5 gene were associated with X-chromosome-linked recessive inheritance of early infantile epileptic encephalopathy 2. Clinical phenotypes included seizures, developmental delays, language abnormalities, facial dysmorphic disorder, and sleep disorders [21]. Mutations in the PHKA2 gene were associated with X-linked recessive glycogen storage disease (type IA2), with clinical phenotypes including growth retardation [22]. Mutations in the ADGGR2 gene were associated with X-linked congenital bilateral aplasia of Vas deferens [23]. The Xp22.2 duplication was inherited from a mother with a normal phenotype, while the 594.0 Kb duplication of Xp22.13 was a de novo mutation. The infant was born with a normal appearance, weight of 3,470 g, and Apgar score of 8-9-9. No significant abnormalities were found over the 7-month follow-up period.

It has been reported that the microdeletion fragment in Xp22.31 region covers the STS region of X-linked recessive ichthyosis (XLI), resulting in the deletion of all exons of the STS gene and HDHD1 gene. It is common in XLI, accounting for about 85% - 90% of all XLI patients [24]. Ichthyosis is a hereditary dyskeratosis skin disease characterized by a disorder or abnormal differentiation of the dynamic stability mechanism of epidermal cells, resulting in ichthyosinscaled dry skin. Most ichthyosis are inherited and can be characterized by characteristic genetic mutations, which can be classified as ichthyosis vulgaris, X-linked ichthyosis, lamellar ichthyosis, congenital non-bullous ichthyosis-like erythema, acquired ichthyosis, colloidal-infantile, and severe colloidal-infantile. XLI is caused by mutations in the STS gene that encodes steroid sulfatase, also known as steroid sulfatase deficiency. It is only transmitted from the mother of the heterozygous carrier to the male. The disease mainly occurs in males, and females are generally only carriers of the pathogenic gene. The skin of children with XLI often shows a more severe phenotype than ichthyosis vulgaris [25]. XLI can occur as an independent skin disease, but it can also be accompanied by asymptomatic corneal opacity (50%), male cryptorchidism (20%), etc. Some studies have also reported that the duplication of Xp22.31 region of STS gene is associated with mental retardation, chondrodysplasia punctata [26], epilepsy, short stature [27], and behavioral abnormalities as a syndrome, such as Rud syndrome, Conradi syndrome, Kallmann syndrome [28], etc.

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The clinical symptoms of XLI may depend in part on the size and gene content of the deletion [27]. Spanish scholars found that 23% of XLI patients showed signs of atopic dermatitis [30]. A recent German study of XLI also found a high incidence of atopic dermatitis [31]. In the study, 8 cases of X chromosome variation occurred in the Xp22.31 region, containing several OMIM genes such as STS. Of these, five of the variants were deleted and three of the variants were duplicated. The size of the deletion fragment was different in 5 cases, with 1.6 Mb as the most common and 236.8 Kb as the smallest deletion fragment. The size of the duplication was 1.6 Mb in all 3 cases. There is currently no cure for XLI,
but the disease does not affect the normal life functions of patients. All eight patients with the XLI mutation, which is associated with myelodysplastic syndromes, were born at term. Follow-up showed that the development of the eight children with the Xp22.31 region mutation was not different from that of children of the same age, with only one showing mild dry skin in cold weather. The eight children in the study were young enough that no other abnormalities were apparent at this time. Further studies will be carried out later as they grow.

Compared to conventional karyotype analysis, SNP-array can detect more microdeletions and microduplications. For cases of unknown clinical significance detected in this paper, CNV testing and genetic counseling should be performed in combination with parental counseling. Not all mutations lead to very adverse outcomes. Decades of clinical experience have shown that even when carrying a pathogenic variant, the impact on quality of life and longevity is manageable with targeted clinical management. It is generally less clinically significant if it is hereditary and more significant if it is de novo, but the effects of incomplete epiphenomena and clinical phenotypic differences still need to be taken into account. Therefore, abnormal fetal ultrasound indicators, high-risk screening for Down's syndrome, and advanced age are important indications for prenatal diagnosis. Chromosome microarray analysis can simultaneously obtain more genetic information than conventional chromosomal karyotype analysis and provide better clinical decision making for fetal growth and development, prognosis assessment, and genetic counseling.

CONCLUSION

The Xp22.31q27.1 region contains OMIM genes such as FGF13, F9, ATP11C, PNPLA4, VCX2, MID1, HCCS, CDKL5, PHKA2, ADGRG2, STS, CHM gene and RPS6KA3 gene. Variations in the Xp22.31q27.1 region are particularly common, and are mainly associated with myelodysplastic syndromes with X-linked recessive inheritance. The clinical significance of the Xp22.31q27.1 mutation remains unclear. Most of the Xp22.31q27.1 variants are inherited from mothers with normal phenotypes. Compared to conventional karyotyping analysis, the SNP-array technique has a clear advantage in detecting more chromosomal microdeletions and microreplcations. SNP-array technology can be a useful complement to traditional cytogenetic analysis methods for clinical cytogenetic diagnosis. Not all mutations result in very adverse outcomes, and even those that carry the disease-causing variant are manageable with targeted clinical management and quality of life and length of life effects.

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Declaration of Interest:
The authors declare that they have no conflict of interest in the publication of this article. This study is original research that has not been published previously, and not under consideration for publication elsewhere.

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