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Prenatal Silver-Russell Syndrome in a Chinese Family Identified by Non-Invasive Prenatal Testing

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Established Facts

- Non-invasive prenatal testing (NIPT) for common aneuploidies has been widely applied with high sensitivity and specificity.
- One cause of Silver-Russell syndrome (SRS) is a maternally inherited duplication of chromosome 11p15.

Novel Insights

- This study is the first report of a prenatal SRS case associated with maternal 11p15.5 copy number variation gain identified by NIPT.
- This study demonstrates that great care must be taken when deciding on which test(s) to employ in revealing the underlying chromosomal structural abnormalities, considering the various benefits and limitations of each genetic technique.

Keywords
Chromosomal microarray · Non-invasive prenatal testing · Prenatal diagnosis · Silver-Russell syndrome

Abstract
Russell-Silver syndrome (SRS) is a rare condition characterized by poor growth before and after birth along with multiple physical and psychosocial characteristics such as short stature, characteristic facial features, body asymmetry, feeding difficulties, and learning disabilities. In this study, we report a family with 2 recurrent SRS pregnancies due to a derivative chromosome 15 that is the result of a maternally derived t(11;15) translocation, detected by non-invasive prenatal testing (NIPT). The 2 SRS fetuses were diagnosed by chromosomal microarray analysis, but a balanced, reciprocal translocation of the mother was disclosed by the combination of routine karyotyping and FISH. This study demonstrates that NIPT has the ability to identify submicroscopic copy number variations (CNVs) in fetuses, which in some cases may result from a parent being a balanced rearrangement carrier. Because of the differences in resolution and the various benefits and limitations of each genetic technique, great care must be taken when deciding on which test(s) to employ in family studies.

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Introduction

Silver-Russell syndrome (SRS) (OMIM #180860) is a growth disorder characterized by intrauterine and postnatal growth retardation, characteristic facial features, body asymmetry, feeding difficulties, and/or learning disabilities [Wakeling et al., 2017]. The incidence is estimated at approximately 1:30,000–100,000 live births. The genetic etiologies of SRS are complex. A hypomethylation of the imprinted region 11p15.5 occurs in nearly half of the patients, and maternal uniparental disomy of chromosome 7 is reported in 10% of patients [Eggermann et al., 2016; Ishida, 2016]. Another possible cause of SRS is a maternal copy number variation (CNV) gain of 11p15, with a ~1% frequency [Eggermann et al., 2005; Ishida, 2016].

Non-invasive prenatal testing (NIPT) for common autosomal aneuploidies has been widely applied, with both specificity and sensitivity reaching 99% [Gil et al., 2017]. Recently, many studies indicated that NIPT could also effectively detect fetal submicroscopic abnormalities beyond common aneuploidies, which will provide more testing information and show great potential clinical applications [Advani et al., 2017; Liang et al., 2019]. In this study, we report a family with 2 recurrent SRS pregnancies due to a derivative chromosome 15 that is the result of a maternal t(11;15) translocation, detected by NIPT screening.

Case Report

A 27-year-old G3P1A1 woman was seen at 20 weeks of gestation because of an abnormal NIPT result. Her unrelated husband was 29 years old and healthy. Both were of normal height (wife: 165 cm, husband: 170 cm), and their family history was unremarkable. Their first pregnancy ended in early first trimester spontaneous miscarriage. The second pregnancy ended in a late second trimester termination because of severe fetal growth retardation (FGR). Cord blood sampling showed a normal fetal karyotype (46,XX).

During this pregnancy, the mother had her prenatal care examinations at another clinic. A scan at 12 weeks showed a crown-rump length (CRL) of 55 mm with a normal nuchal translucency (1.7 mm), along with a negative screening result. An anatomy scan at 18 weeks showed normal fetal biometry with biparetal diameter (BPD) of 42 mm (50th centile), head circumference (HC) of 144 mm (50th centile), abdominal circumference (AC) of 126 mm (50th centile), and femur length (FL) of 23 mm (50th centile). However, the woman had been unduly anxious because she had endured 2 interrupted pregnancies. She required a genome-wide NIPT screening (NIFTY®, BGI, Shenzhen, China) at 19 weeks gestation. This approach reported a 12.4-Mb gain on the short arm of chromosome 11 (p15.4) with a Z-score of 5.030 (Fig. 1a). The patient was referred to our center for invasive genetic testing.

Amniocentesis was offered at 21 weeks after genetic counselling for genetic investigation using routine karyotyping and chromosomal microarray analysis (CMA) (CytoScan TM 750K Array; Affymetrix, Inc., Santa Clara, CA, USA). Cell culture revealed a normal karyotype (46,XY), but CMA reported a 7.6-Mb terminal CNV gain at 11p15.5 [arr(GRCh37)11p15.5p15.4(230,680-7,894,535)×3] with no other chromosomal aberrations involved (Fig. 1b). Both parents showed a normal CMA result. The 11p15.5 CNV gain was then regarded as de novo. Two opposite syndromes are associated with genomic duplication in the 11p15 chromosomal region. SRS is caused by maternal CNV gain of 11p15, whereas Beckwith-Wiedemann syndrome (BWS), an overgrowth syndrome with many additional clinical features such as macroglossia and organomegaly, is caused by paternal CNV gain of the same 11p15 region. A repeated ultrasound at 24 weeks showed retarded growth of AC (174 mm; 2.5th centile) and FL (38 mm; 5th centile); both BPD (60 mm; 25th centile) and HC (220 mm; 75th centile) were within normal parameters. No obvious malformations were observed, and the volume of amniotic fluid was normal. Considering the characteristic FGR, SRS was the prospective diagnosis in this case. Unfortunately, rupture of membrane occurred at 25 weeks, and the pregnancy was terminated by parental request. The delivered fetus (505 g; <5th centile) presented with a relative macrocephaly, a triangular face with a prominent forehead, and 5th finger clinodactyly of the left hand, consistent with phenotypes of SRS.

To explore the mechanism underlying the maternal chromosomal CNV gain, routine karyotyping was done in the couple although the fetal karyotype was normal. The father had a normal karyotype (46,XY). The mother had a karyotype of 46,XX,t(11;15)(p15.4;p13) (Fig. 1c). FISH analysis with a subtelomeric 11pter probe was performed in the metaphase chromosomes of the couple (Fig. 1d). This showed a signal for 11pter probe on the short arm of one chromosome 15 in the mother. Therefore, the maternal karyotype was defined as 46,XX.ish t(11;15)(p15.4;p13)(D11S2071-;D11S2071+). The fetus had a functionally trisomy of the region 11p15 and monosomy 15p which is clinically insignificant and had not been detected by CMA due to the absence of specific probes. To determine whether the first terminated pregnancy was affected with SRS, the remaining material of the abortus was retrieved and tested by CMA. As expected, the result was the same as the current one.

Discussion

At present, NIPT has been widely used in the detection of fetal common aneuploidies, usually following a positive serum screening result or mothers with advanced maternal age. As this technology improves, NIPT may also be able to identify structural chromosome abnormalities, including CNV gain/loss, particularly prior to prenatal ultrasound. For example, Liang et al. [2019] recently reported a compelling evidence that genome-wide NIPT could be used as a first-tier screening method in pregnancy. In a total of 94,085 mothers who opted for genome-NIPT, 1,128 (1.2%) were scored positive for clin-

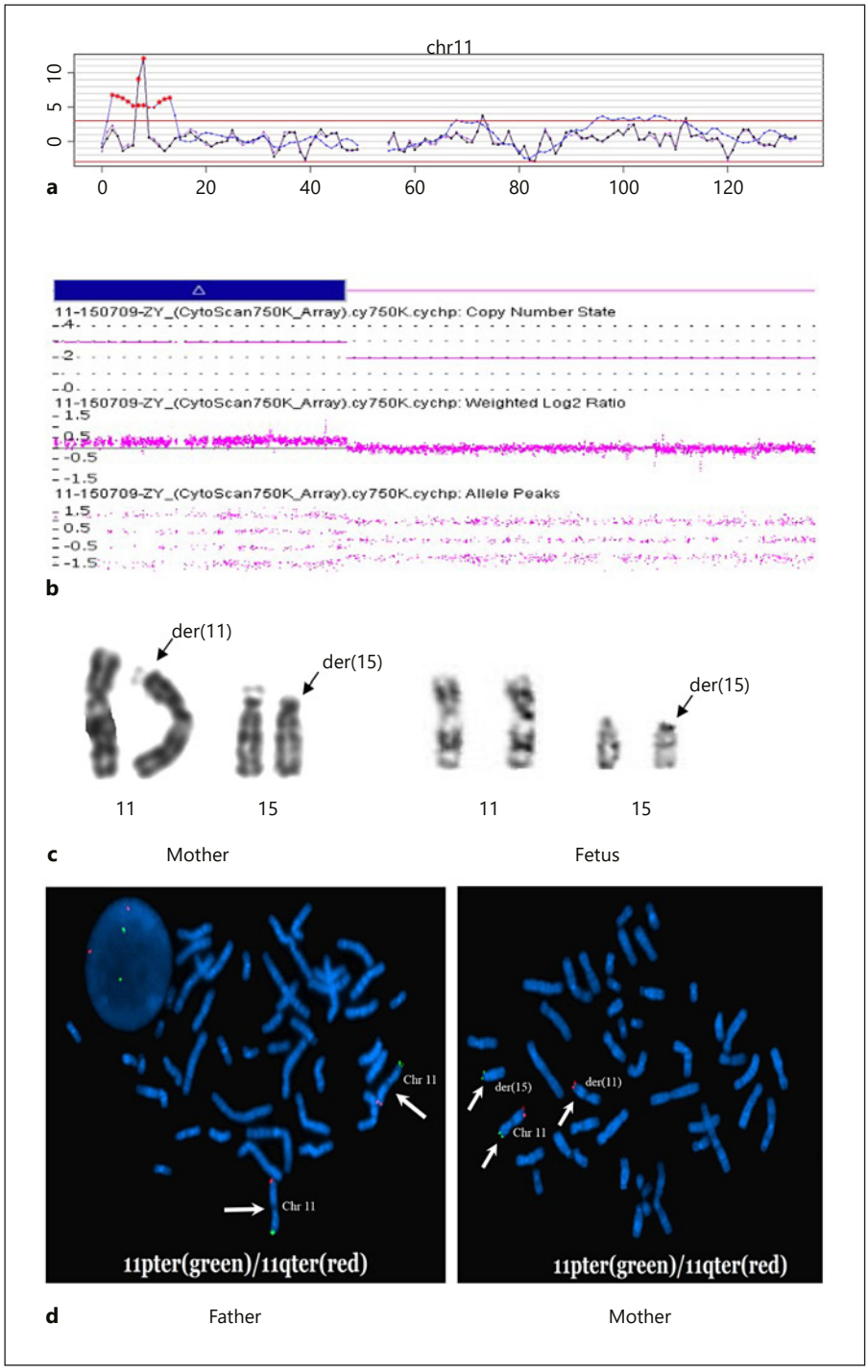

Fig. 1. Analyses of chromosomal aberrations by non-invasive prenatal testing (NIPT), conventional cytogenetics, FISH, and microarray in the family with recurrent Silver-Russell syndrome. **a** NIPT result showing a 12.4-Mb gain on the short arm of chromosome 11. The blue line is the Stuffer Z-score. The purple line and black line are the corrected Z-score. Red asterisks represent the region of gain. Vertical axis: Z-score. Horizontal axis: chromosome localization. **b** Chromosome microarray analysis result showing array plot for the 11p15.5 region in the fetus. DNA copy number change is represented by the positive log2 ratio above the baseline. The CNV gain encompasses approximately 7.6 Mb, extending from 230,680 proximally to 7,894,535 distally. **c** Representative partial karyotypes of the mother and the fetus. The abnormal chromosomes are marked by arrows. **d** FISH analysis of metaphase chromosomes with 11pter (D11S2071) and 11qter (D11S4974) probes (LBP, Guangzhou, China) in the father and mother. Two probe signals specific for 11p15.5 were seen in the maternal metaphase chromosomes, with 1 signal localized on 15p. The arrows demonstrate the targeted der(15) t(11;15) and der(11)t(11;15) with probe signals.

ically significant fetal chromosome abnormalities. Combined positive predictive values were 32% for CNV gain/loss ≥10 Mb and 19% for those <10 Mb. Flowers et al. [2020] demonstrated that genome-wide NIPT could detected fetal unbalanced chromosomal rearrangements in 95% of reciprocal translocation carriers. They proposed that this test could provide an alternative to prenatal diagnosis for such carriers. In the present study, a fetal partial CNV gain due to parental balanced translocation was initially indicated by NIPT and confirmed by CMA. Our study added the evidence that NIPT might play a role in the screening of submicroscopic chromosomal rear-

rangements due to parental balanced reciprocal translocations.

To date, there has been evidence that numerous chromosomes carry underlying genes that might be associated with SRS when mutated, including chromosomes 1, 2, 7, 8, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 22, and X, with a majority of anomalies attributed to chromosomes 7 and 11 [Ishida, 2016]. The detection of a maternal CNV gain of 11p15 in our study with the clinical diagnosis of SRS confirms the observation that gain of maternal chromosome 11p15 material belongs to the spectrum of epigenetic disturbances in this disease. Indeed, this study is the first report of a prenatal SRS case associated with maternal gain at 11p15.4 imprinting cluster. A similar 11p15 CNV gain was reported in a 2-year-old boy who was severely growth restricted. The ~8.8-Mb CNV gain resulted from a maternally derived translocation t(11;15) [Eggermann et al., 2010].

In this study, the 2 SRS fetuses were diagnosed by CMA. The identification of the relatively small 11p15.4 segment (7.6 Mb) translocation was hampered by the limited resolution of conventional karyotyping. The high resolution of CMA can provide more precise breakpoint mapping, which allows subtle chromosomal imbalances to be distinguished at a molecular level. However, CMA has some limitations [Miller et al., 2010]. One of those is that it will not detect certain chromosome rearrangements, such as balanced translocations and inversions because there is no net gain or loss of DNA, and the same is true for the 15p loss. Instead, karyotyping and FISH helped to make the precise cytogenetic diagnosis in this family. Therefore, even when CMA reveals an isolated CNV gain or loss, karyotyping and FISH should better be performed to confirm whether one of the parents carries a balanced translocation. The presence of a balanced chromosomal rearrangement in this family had resulted in 2 recurrent SRS pregnancies.

Theoretically, the woman's constitutional karyotype harbors the risk of producing 2 different types of haploid gametes that contain 11p15 gain and 11p15 loss, respectively. While a maternal 11p15 gain can lead to SRS, the clinical consequence of a maternal 11p15 loss is difficult to predict. There have been some reports of BWS associated with a maternally inherited CNV loss (~330 kb) of 11p15 [Algar et al., 2011; De Crescenzo et al., 2011; Fryssira et al., 2015; Beygo et al., 2016]. These losses only contain ICR1 and/or ICR2 regions. For this family, the phenotype of a large loss of the imprinted region (7.6 Mb) will be further influenced by haploinsufficiency of additional genes at 11p15. The outcome might be so severe that it leads to early embryonic death. However, the specimen of a first trimester miscarriage was not available for confirmation.

In this study, NIPT and CMA showed different size estimates for the same CNV gain. Indeed, CNVs identified by NIPT could be larger or smaller in size than those detected by CMA [Li et al., 2016]. NIPT can provide a good indication of chromosomal imbalances, but the detection is influenced by read counts, type of algorithm, and fetal fraction [Chen et al., 2021]. For a positive NIPT result, further diagnostic investigation is needed to identify the genomic position of chromosomal imbalances at higher precision, and CMA should be performed as a gold standard to confirm the presence of CNVs reported by NIPT.

In conclusion, NIPT has the ability to identify CNV gains and/or losses in fetuses, which in some cases may result from a parent being a balanced rearrangement carrier. This study demonstrates that great care must be taken when deciding on which test(s) to employ in prenatal diagnosis, considering the various benefits and limitations of each genetic technique. The appropriate test will depend on the clinical condition or syndrome suspected and a carefully taken family or reproductive history. Occasionally, more than one technique will be needed to make a precise diagnosis. The current family was recommended planning a future pregnancy with preimplantation genetic testing (PGT) to avoid an offspring with unbalanced chromosomal abnormality.

Statement of Ethics

This study protocol was reviewed and the need for approval was waived by Ethical Committee of Guangzhou Women and Children's Medical Center. Written informed consent was obtained from the patients for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization: Y.-L.Z., D.-Z.L. Writing and original draft preparation: Y.-L.Z. Clinical data collection: X.-Y.J., J.-H.W. Molecular genetic data: X.-Y.J., J.-H.W., M.P. Critical review: D.-Z.L. All authors analyzed and interpreted the data and approved the manuscript in its final form.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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