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Y Chromosome CNV Attribute to the Normal Female Phenotype of a 46XX/46XY Chimerism: A Case Report

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Abstract

Background: Down's syndrome (DS) is caused by abnormal chromosome 21, which is the highest incidence of birth defect disease all the world. The phenomenon of 46XX/46XY chimeras was reported very rarely. In many cases, they were diagnosed at birth, because of the presence of ambiguous external genitalia. A case of the phenomenon of 46XX/46XY chimeras has been described in this report.

Case presentation: A 23-year-old woman at 19 weeks of gestation was transferred to our hospital due to fetal chromosomal abnormalities of antenatal diagnosis. There was no abnormality of appearance through past medical history and ultrasonic examination, and hormonal levels also were normal. The peripheral blood of the patient and umbilical cord blood of fetus were detected to analyze using karyotype analysis, it showed that abnormal 46XX/46XY chimera of patient and abnormal 46XYY karyotype of fetus observed during prenatal diagnosis performed. Then copy number variation (CNV) of her genome sequence showed the sex-determination gene SRY was completely lost on her Y chromosome, even including some other male characteristic gene also were lost. According to sequencing analysis results showed that Y chromosome CNV attribute to the normal female phenotype of 46XX/46XY chimerism.

Discussion and Conclusions: The case presented here further describe a novel, fast target-next generation sequencing method, which devotes to find gene deletion or mutation of chromosome abnormality.

Keywords: Chimerism; Normal female phenotype; Copy number variation; SRY gene

Introduction

Down's syndrome (DS) is caused by abnormal chromosome 21, which is the highest incidence of birth defect disease all the world. The child is often manifested as mental retardation, physical development deficiency, and accompany with multiple organs of the body malformation. The occurrence of DS affects seriously the social population quality and increases the burden of family at mental and economic. Prenatal diagnosis can contribute to reduce the birth rate of deformed fetuses vastly, therefore, termination of pregnancy timely is particularly essential for patients and deformed fetuses. Chromosomal mosaic is a rare type of Down's syndrome. In clinical, the phenomenon of 46XX/46XY is belonged to the chimeric genetic which is caused by having two distinct cell population with the body [1]. Most chimeric individuals have been detected due to a discrepancy in the sex chromosome configuration of the two cell lines resulting in 46XX/46XY otovestibular disorder of sexual development (DSD), previously described as true hermaphroditism. Very occasionally, the additional parental alleles of blood group and Mendelian disorders were found, which showed the detection of chimeric individuals are coincident in the sex chromosome [2,3]. A 46XX/46XY chimerism can be identified during pregnancy by prenatal screening or in early childhood through genetic testing and direct observation [4]. True sex chromosome discrepant chimerism has also been detected for routine indications on some occasions using the prenatal diagnosis performed. Whole body XX/XY chimerism already has been proven in a clinically unaffected adult male and a physically normal adult female who was being investigated for infertility [5].

Case Presentation

Here we described a 23-year-old, gravida 1, para 0 woman at 19 weeks of gestation with no abnormal symptom history was transferred to our hospital due to high-risk assessment on Down's syndrome of fetus by routine antenatal testing. There was a dissociative B-HCG at 42.4 ng/ml by peripheral blood extraction, which was more than normal range (0.000-2.500). And then, umbilical cord blood of fetus was applied to verification using karyotype analysis.

The result showed that abnormal 46XYY karyotype of fetus observed during karyotype performed, hence, the peripheral blood of the patient was extracted to show abnormal 46XX/46XY chimera. For analysis the reason, following work detection of karyotype and sequencing have been done. The all karyotypes of the patient's relatives as Table 1 showed that were all presented in this report. The target-next generation sequencing, including gene variation detection (SNP, single-nucleotide

Character	Gender	Karyotype
Fetus	Unknown	46XYY
Patient	Female	46XX/XY
Patient's father	Male	46XY
Patient's mother	Female	46XX
Patient's brother	Male	46XY
Patient's sister	Female	46XX

Table 1: Difference of chromosome karyotyping analysis.

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polymorphism; INDEL, insertion and deletion; SV, structural variation; CNV, copy number variation), which has become a strong and reliable player in molecular diagnostics. The mapped sequencing reads on X chromosome and Y chromosome were analyzed to providing basic for etiology analysis. All patients' samples were referred to the regulation of ethnic commission of Shenzhen People's Hospital; Detailed case reports are provided as online supplementary information. Informed parental consent was then collected also for this study.

The patient was normal phenotype female who was already pregnant for 19 weeks, was the main object. That was her first pregnant, the prenatal screening results showed there was a high risk of DS, the value-at-risk was highly reached to 1:250. The peripheral blood of patient was extracted to determinate hormonal levels, include of FSH (5.7 mIU/ml), LSH (8.32 mIU/ml), estradiol (267.34 pg/ml), progesterone (1.27 ng/ml), prolactin (16.37 ng/ml), testosterone (29.88 ng/dl), DHEA-S (189.00 μg/dl), all of results levels were normal. And then, the cord blood results declared that there was one more sex chromosome in the number of 47 chromosome in her fetus body. For future analysis the reason that the fetal chromosome number was unusual, patient's blood was collected for karyotyping as showed (Figure 1). Meantime, the chromosome information of her relatives including her parents, her young brother and young sister were also described for excluding the hereditary cause. Her chromosomal karyotype analysis by the peripheral blood was showed 46XX [67]/46XY [38], meaning the G-banded sex chromosome chimerism. All the clinical and prenatal diagnosis results were normal except the concentration of Alpha Fetoprotein (AFP) was 9 times higher than normal humans, which maybe because she was pregnant. And then, target-next generation sequencing was used to further testing. The original sequenced reads containing image analysis and base calling were obtained by Illumina pipeline, biological information analysis using the reference genome hg 19. Copy number variation detection was presented by control-FREEC software.

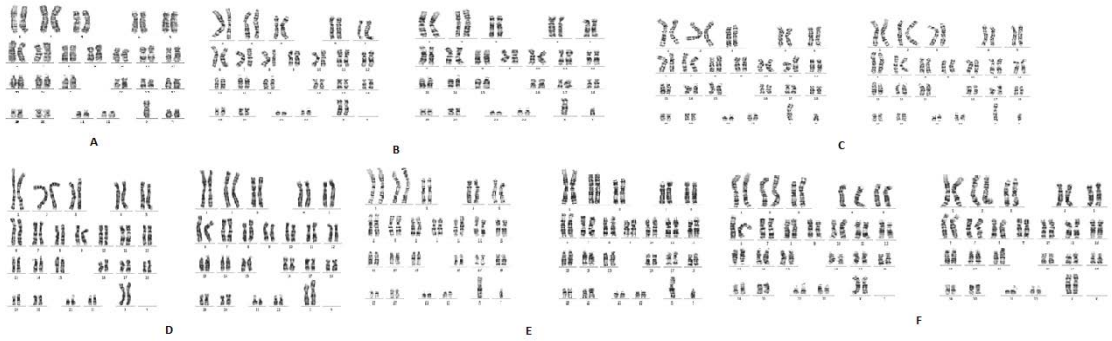

Figure 1: Chromosome karyotype analysis results where **A:** Fetus's; **B:** Patient's; **C:** Patient's father; **D:** Patient's mother; **E:** Patient's older brother; **F:** Patient's younger sister.

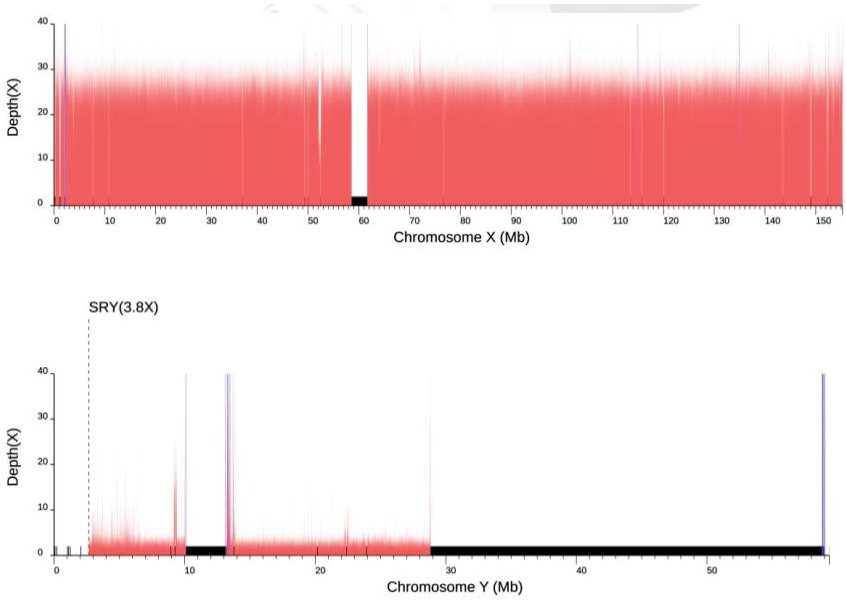

Figure 2: The distribution map of X chromosome and Y chromosome reads covered the horizontal axis represents the physical coordinates of chromosome, and the vertical axis represents the depth of the coverage; the black area means the gap(the base N area in the reference genome hg19), red area represents average depth of coverage in the nonoverlapping window of per 1000 bp, blue area means the average depth is more than 40-fold; imaginary line represents the location of SRY gene in the Y chromosome; other white area means no reads coverage.

*Chr	Gene name (part)	Gene	Cyto band	Size	CNV type
Y	LINC00278, SRY, RPS4Y1, ZFY, TGIF2LY	NM_001008, NM_001145275, NM_001145276, NM_003140, NM_003411, NM_139214	Yp11.2-Yp11.31	1014249	loss
Y	TSPY3, TSPY1, TSPY8, TSPY10	NM_001077697, NM_001320964, NM_001243721, NM_001282469	Yp11.2	3591249	loss
Y	TTTY14	NR_125734.1	Yq11.221-Yq11.222	7282749	loss
Y	DAZ3, DAZ4, DAZ	NM_020364, NM_00105375, NM_004081	Yq11.23-Yq11.223	7648249	loss

Table 2: Copy number variation on chromosome Y referring to hg19.

In Figure 2, the effective coverage of X chromosome (the length of 100% coverage of sequence reads - numbers of base N) reached to more than 99.9%, average coverage depth was 26.2-fold. The effective coverage and depth of X chromosome was comparable with autosomal. For Y chromosome, the effective coverage was 90.0% and mean coverage depth was 5.4-fold, and average coverage depth of SRY gene was 3.8-fold. The coverage depth of Y chromosome with SRY gene was lower than X chromosome with autosomal.

Sex-determining region Y (SRY) gene, as the sex-specific gene, which activates a cascade of genes that lead the embryonic gonad to develop into a testis, is attended in the Y chromosome, and was only found on the Yp11.3. For a normal phenotype female, her karyotyping showed she carried the Y chromosome. The CNV of target-next sequencing, whole SRY gene presented loss, start from 2649550bp to 3663749bp, size of loss highly reached to 1014249bp. The location of SRY gene, on the chromosome, it's sequence reads were white as showed in below Figure 2. Among this long lost fragment, as Table 2 showed that there still were LINC00278(an RNA gene), RPS4Y1(a protein coding gene, diseases associated with RPS4Y1 include Tumer Syndrome, ZFY (a candidate gene for the testis-determining factor(TDF) and was erroneously referred to as TDF), TGIF2LY(a gene encodes a member of the TALE/TGIF homeobox family of transcription factors, lies within the male specific region of chromosome Y, in a block of sequence that is thought to be the result of a large X-to-Y transposition), which all were lost on the Y chromosome. Meanwhile, the testis-specific protein Y (TSPY) family gene including TSPY8, TSPY3, TSPY1 and TSPY10 were also lost on the patient's Y chromosome. TTTY14, testis-specific transcript was lost also. The DAZ gene family containing DAZ3, DAZ4 and DAZ1 is a candidate for the human Y-chromosome azoospermia factor and codes an RNA-binding protein that is important for spermatogenesis. Fortunately, they were lost in the patient's body.

*Chr refer to chromosome; Gene Name (part) means only some important gene was showed here; Size(whole) is the all lost gene length.

Discussion

The phenomenon of 46XX/46XY chimeras was reported very rarely. In many cases, they were diagnosed at birth, because of the presence of ambiguous external genitalia [6]. The normal sperm combine rightly with egg will be form to zygote, and the original zygote cells are healthy. Whereas, the cells divide but the chromosomes do not separate when occurs mitosis in sometimes, the abnormal number of chromosomes will lead to more than one karyotypes. Generally, symptoms in clinical of patients who is chimerism depend on the rate between normal cells and abnormal cells. The more number of abnormal karyotype, the more serious influence on phenotype and function. Chimeras are caused by various types of number and structural aberrations, such a wrong number unseparated chromosome, the loss of chromosome, chromosome endoreduplication and chromosome breakage and recombination, it can also be a combination of multiple normal sperm and egg or polar body fertilization.

As far as we know, only few similar cases have been published so far. One group detected a 46XX/46XY chimerism in a female affected by mammary hypoplasia and sterility. For another case reported on a phenotypically normal women with a 46XY karyotype [6].

Copy number variation(CNV), which means the increase and decrease in the number of copies of large fragments in genome, is a significant molecular mechanism including the deletion and duplication two types. CNV can reduce to Mendelian genetic disorders and rare disease, even some complex disease associated with cancer, that's why the research in deletion and duplication of chromosome has become a research hotspot. Detection of copy number variation on chromosome has a very irreplaceable role in the diagnosis of patients with unexplained clinical symptoms and other identification of chromosome disease.

Target-next generation sequencing may serve as a useful diagnostic tool to measure the levels of disease-specific mosaicism and provide better phenotype correlations [6,7]. In addition, with the increasing use of trophectoderm blastocyst and whole-genome amplification for preimplantation genetic diagnosis, CNV sequence should also be sensitive and specific for detection of the low-level mosaicism associated with the trophectoderm cell lineage. In many developing country, prenatal diagnosis just relies heavily on fetal karyotyping, maternal serum screening and ultrasound to detect chromosome disease. The introduction of noninvasive prenatal diagnosis and the increasing rate of uptake by high- and low-risk pregnant women is beginning to change the landscape for at least the early detection of common aneuploidies [8-10].

In this case, all this significant male characteristic gene was totally or partly loss in the patient's genome sequence, which can completely explain why the patient carried the Y chromosome but presented a normal health phenotype female. Hence, the patient was a phenotype completely healthy women who presented in her pregnancy and was found to have a karyotype certifying the high level of chimerism carrying two cell lines discordant for the chromosomes present in peripheral blood. Because of the CNV of specific male determination gene, she presented a very healthy normal women even carrying Y chromosome. The case presented here further describe a novel, fast target-next generation sequencing method, which devotes to find gene deletion or mutation of chromosome abnormality. Though this tool is being developed as a strategy to more effectively and accurately to find pathogenesis, so far, there is no conclusive effective treatment, which needs more study.

Conclusions

The fast target-next generation sequencing should be considered as a detection option to apply to Down's syndrome testing in earlier of pregnancy. It plays an important role to find gene deletion or mutation of chromosome abnormality to reduce the birth rate of deformed fetuses greatly.

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Availability of Data and Materials

Data sharing is not applicable to this article, because no datasets were generated or analyzed during the present study.

Contributor Ship Statement

Huirong Zhang and Lin Gao planned the study and submitted the study. Pan Zhao and Chang Liu conducted chromosome detection test. Wei Li and Malin Hong Zhong conducted target-next generation sequencing test. Xiaoru Zhong analyzed sequencing results. Deheng Chen collected a case. Yong Dai, Jianhong Wang and Chang Zou supplied research funding.

Ethics Approval and Consent to Participate

Ethical approval was not obtained for the publication of this case report, because it does not involve sharing of the personal details of the patient.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing Interests

The authors declare no conflicts of interests.

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