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A very rare case of trisomy 4q32.3–4q35.2 and trisomy 21q11.2–21q22.11 in a patient with recombinant chromosomes 4 and 21

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ABSTRACT

We report the case of a patient with a clinical phenotype consistent with Down Syndrome (DS) who has a novel karyotypic abnormality. Karyotypic analyses were performed to investigate the cause of two spontaneous abortions. A balanced translocation between chromosomes 4 and 21 was identified, along with an additional abnormal chromosome 21. We performed high-resolution banding, comparative genomic hybridization (CGH), and FISH studies in both the patient and her mother to define the abnormality and determine its origin. CGH revealed a gain in copy number on the long arm of chromosome 4, spanning at least 24.4 Mb, and a gain in copy number on the long arm of chromosome 21, spanning at least 16.2 Mb. FISH analysis using a chromosome 21 centromere probe and chromosome 4 long arm telomere (4pter) probe confirmed the origin of the marker chromosome. It has been confirmed by the State Key Laboratory of Medical Genetics of China that this is the first reported instance of the karyotype 47,XX,t(4;21)(q31.3;q11.2),+der(21)t(4;21)mat reported in the world.

1. Introduction

Complex chromosomal rearrangements are very rare chromosomal abnormalities, and are not always associated with a clinically evident abnormality. It is believed that these rearrangements are due to either microdeletions or microduplications at the translocation breakpoints, or that they arise as a result of disruption of the genes located in the breakpoints. Patients with trisomy 4q syndrome have variable clinical features, including growth and developmental delays, intellectual disability and a dysmorphic appearance. Patients with trisomy 21 syndrome have the well-described clinical features of Down Syndrome (DS), including variable intellectual disability, characteristic facies, developmental delays and a variety of additional abnormalities in many systems.

Here, we describe a 23-year-old woman with intellectual disability who had suffered two spontaneous abortions. Using chromosomal analysis, we have been able to correlate her phenotype with trisomy 4q32.3–4q35.2 and trisomy 21q11.2–21q22.11 consequent upon recombination between chromosomes 4 and 21. All the patients consented to use their information in this study, and were aware that their information would be used in future research. Their patient information was not anonymized. All the authors have access to any identifying information. We documented the verbal consent in their files.

2. Material and methods

2.1. Clinical report

The patient was the first and only child of two healthy unrelated parents, and was born after the normal period of gestation, after an uncomplicated pregnancy and normal spontaneous delivery. Birth weight was 3500 g. Her mother and father were aged 20 and 22 at the time of her birth respectively. After her birth, her mother had one miscarriage. The time during which the patient was able to speak and walk had no difference from normal children, but her ability to study had developed slowly with age. The patient was married at 21 years old. She was examined in our institution at 23 years old because of two spontaneous abortions. Clinical examination demonstrated evidence of mental retardation, and unusual facial characteristic such as oblique mouth, wider space between the eyes, flat nasal bridge and glassy eyes.

2.2. Cytogenetic analysis

Short-term phytohemagglutinin-stimulated peripheral blood lymphocyte cultures were made from the blood of the patient and her mother. These were undertaken according to standard procedures. At

Abbreviations: DS, Down Syndrome; CGH, comparative genomic hybridization; FISH, Fluorescence in situ hybridization.

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least 30 metaphase plates were analyzed for each individual. Karyotyping was performed using an image analyzer (CW4000).

2.3. Array-CGH analysis

Genomic DNA was isolated from the patient's peripheral blood. Array CGH was performed using oligonucleotide-based custom arrays (Agilent Technologies, Santa Clara, CA) using a standard protocol. Briefly, equal amounts of test DNA and normal sex-matched DNA were digested with *Alu*I and *Rsa*I, and differentially labeled with cyanine-5 (cy5) and cyanine-3 (cy3) fluorescent dyes using a SureTag Complete DNA Labeling Kit (Agilent). Hybridizations were carried out at 65 °C for 24 h. After washing, slides were scanned using an Agilent SureScan Microarray Scanner and the images were extracted and analyzed using Feature Extraction v11.5 (Agilent) and Cytogenomics v2.5 (Agilent) software, respectively.

2.4. Fluorescence in situ hybridization (FISH) analysis

Following the results of cytogenetic analyses and array-CGH, FISH analysis was undertaken on metaphase spreads from the patient and her mother, using a chromosome 21 centromere probe, chromosome 21 long arm telomere (21pter) probe, and chromosome 4 long arm telomere (4pter) probe, according to the manufacturer's instructions. Analysis of metaphase plates for each chromosome was performed using fluorescence microscopy analysis.

3. Results

Conventional cytogenetic analysis of the patient demonstrated a chromosomal rearrangement involving chromosomes 4 and 21. In addition, we found a third additional abnormal chromosome 21. To determine the origin of these abnormalities, we also undertook cytogenetic analysis of the patient's mother. The mother's karyotype was designated as 46,XX,t(4;21)(q31.3;q11.2). In consequence of the maternal origin of this defect, the patient's karyotype was designated as 47,XX,t(4;21)(q31.3;q11.2),+der(21)t(4;21)mat (Fig. 1). It has been verified by the State Key Laboratory of Medical Genetics of China that this is the first reported case of this karyotype worldwide.

Array-CGH analysis demonstrated a gain in copy number on the long arm of chromosome 4, spanning at least 24.4 Mb, and a gain in copy number on the long arm of chromosome 21, spanning at least 16.2 Mb. Further chromosome analysis performed in another laboratory detected a marker chromosome. Based on the array-CGH analysis data and the morphology of the marker chromosome, it is most likely to represent an additional derivative chromosome 21, resulting from an unbalanced translocation between the long arms of chromosome 4 and chromosome 21. The presence of the additional derivative chromosome 21 causes trisomy for the 4q32.3–4qter segment and 21q11.2–21q22.11 segment in this individual (Table 1).

FISH analysis demonstrated that the patient's chromosomal rearrangement resulted from translocations between chromosomes 4 and 21; the marker chromosome is an additional derivative chromosome 21 resulting from an unbalanced translocation between the long arms of chromosomes 4 and 21 (Fig. 2).

4. Discussion

Balanced translocations occur in approximately 1:625 individuals, and are usually inherited (Van Dyke et al., 1983). A simple balanced reciprocal translocation is a two-way exchange in which chromosomal segments from two chromosomes break off, translocate, and unite with the other chromosome. A balanced complex chromosome translocation (CCR) has three or more breakpoints. The risk of a serious congenital phenotypic abnormality in individuals with a *de novo* apparently balanced rearrangement is estimated at 6.7%, and this risk increases as the number of breakpoints involved in the rearrangement increases (Warburton, 1991). Array-CGH analysis of clinically affected cases with

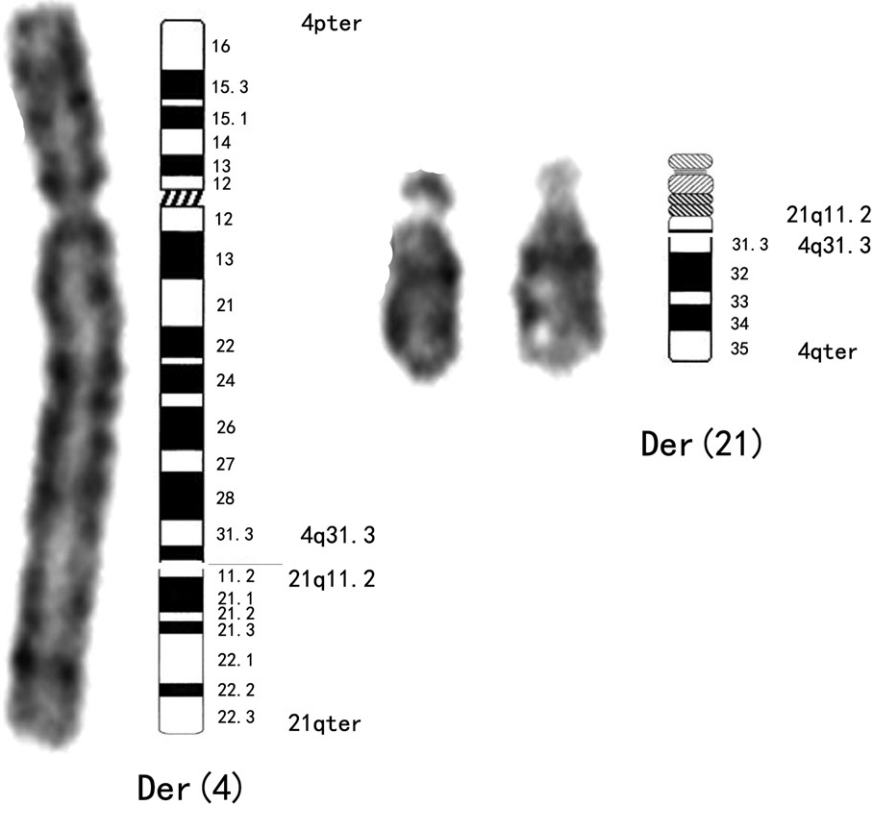

Fig. 1. Partial karyotype and ideogram of the patient's chromosomes.