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Case Report

Prenatal diagnosis of the maternal derivative chromosome der(15)t(Y;15)(q12;p13) in a dizygotic twin pregnancy

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ABSTRACT

Sex chromosome translocations are unique and must be considered separately from translocations between autosomes. Here, we describe the first prenatal case of one twin fetus with an unbalanced translocation between chromosome Y and chromosome 15, presenting a 46,XY,der(15)t(Y;15) karyotype. The other twin had a normal 46,XY karyotype. Cytogenetic analysis of the parental chromosomes revealed that the father had a normal 46,XY karyotype, whereas the mother exhibited a 46,XX,der(15)t(Y;15) karyotype. Thus, the proband inherited this translocation from the mother. Fluorescence *in situ* hybridization analyses demonstrated that the breakpoint on chromosome Y involved a heterochromatin region (Yq12), while that on chromosome 15 involved a p-arm region (15p13). At 37 gestational weeks, healthy twins were delivered vaginally. We conclude that accurate identification of der(15) chromosomal content can facilitate not only prenatal diagnosis of a chromosomal aberration in one twin, but also prediction of the fetal phenotype.

1. Introduction

The incidence of translocations involving the Y chromosome and an autosome in the general population is ~1 in 2000 [1]. There are two major types of Y-autosome translocations. The most prevalent type is a translocation between the distal part of Yq and the p-arm of an acrocentric chromosome, most commonly t(Y;15). This translocation is considered to be a prototype of the Y-autosome translocations that result in chromosome 15 carrying some heterochromatin from Yq, having an appearance similar to a long p-arm [2]. The breakpoints are frequently located in the chromosome 15p11–15p13 region and the chromosome Yq11.23–Yq12 region. It has been reported that carriers of this type are equally male and female, and these carriers of t(Y;15) usually have a normal phenotype [3–5]. The other type is balanced reciprocal translocation between the Y chromosome and an autosome in a region other than an acrocentric p-arm. There are associated abnormalities in some carriers of this type, which may be due to a disruption or deletion effect at the breakpoints [6].

We report a rare case of one of a pair of twins with a maternal-derived chromosome, der(15)t(Y;15)(q12;p13). Through fluorescence *in situ* hybridization (FISH) analysis, the breakpoints were found to involve a translocation of the Yq12 heterochromatic region to the p-arm of chromosome 15p13. To the best of our knowledge, this is the first prenatal report of one of a pair of twins with t(Y;15) and the fourth report of a family inheriting t(Y;15) from a maternal carrier.

2. Case Report

A 34-year-old mother was referred for amniocentesis at 16 weeks of gestation due to advanced maternal age. This was her

Conflict of interest: none.

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first pregnancy and she conceived twins. She did not have an abnormal family history. Cytogenetic analysis of 15 colonies showed that one of the twins, the proband, had additional material on the p-arm of one chromosome 15, whereas the second twin exhibited a normal chromosome 15 (Figs. 1A and 1B). To determine whether this atypical chromosome 15 was *de novo* or inherited, the karyotypes of the proband's parents were examined. The cytogenetic analysis of the parents based on blood samples showed that the proband's mother had the same der(15), while the father exhibited a normal chromosome 15. This finding revealed that the der(15) of the proband was maternally inherited. Dark G-banding observed on the p-arm structure of the der(15) was likely to correspond to heterochromatin. Further C-banding confirmed that the 15p regions of both the mother and the proband exhibited dark staining, mainly indicating heterochromatic content (Fig. 1C).

We subsequently performed FISH analysis to characterize the der(15) chromosome. Metaphase spreads from the proband were first hybridized with probes for the acro p-arm and centromere 15 (Fig. 2A). We found that the der(15) chromosome clearly contained the chromosome 15 centromere but showed a loss of 15p. This result indicated that the original translocation breakpoint was located on the p-arm of chromosome 15. To further investigate whether the Y chromosome was involved in the translocation, FISH analysis was performed through the hybridization of combined probes targeting chromosome Y (DYZ1 and DYZ3) and centromere 15 (Fig. 2B). Our results showed that the proband had one normal Y chromosome (DYZ1+/DYZ3+). In addition, his der(15) chromosome contained the Yq12 heterochromatic region (DYZ1+), but not the Yp11.1-q11.1 region (DYZ3−). FISH analysis was also performed using the blood lymphocytes of his mother. Our data showed that she carried a der(15)t(Y;15) translocation similar to that of the proband (Figs. 2C and 2D). Thus, our findings indicated the following der(15) chromosome: ish der(15)t(Y;15)11 (D15Z4+,DYZ1+,DYZ3−,acro-p-). This rearrangement involving Yq and 15p was a nonreciprocal translocation, and the obtained ideograms are shown in Fig. 3.

After genetic counseling, the mother provided her informed consent for an evaluation of uniparental disomy 15 (UPD15) and microdeletion within the Prader–Willi syndrome (PWS) critical region. Five microsatellite markers (D15S11, D15S122, D15S113, GABRB3, and D15S131) within the critical region were amplified in a multiplex polymerase chain reaction, and the proband showed heterozygosity for all markers. We did not find maternal UPD15 or

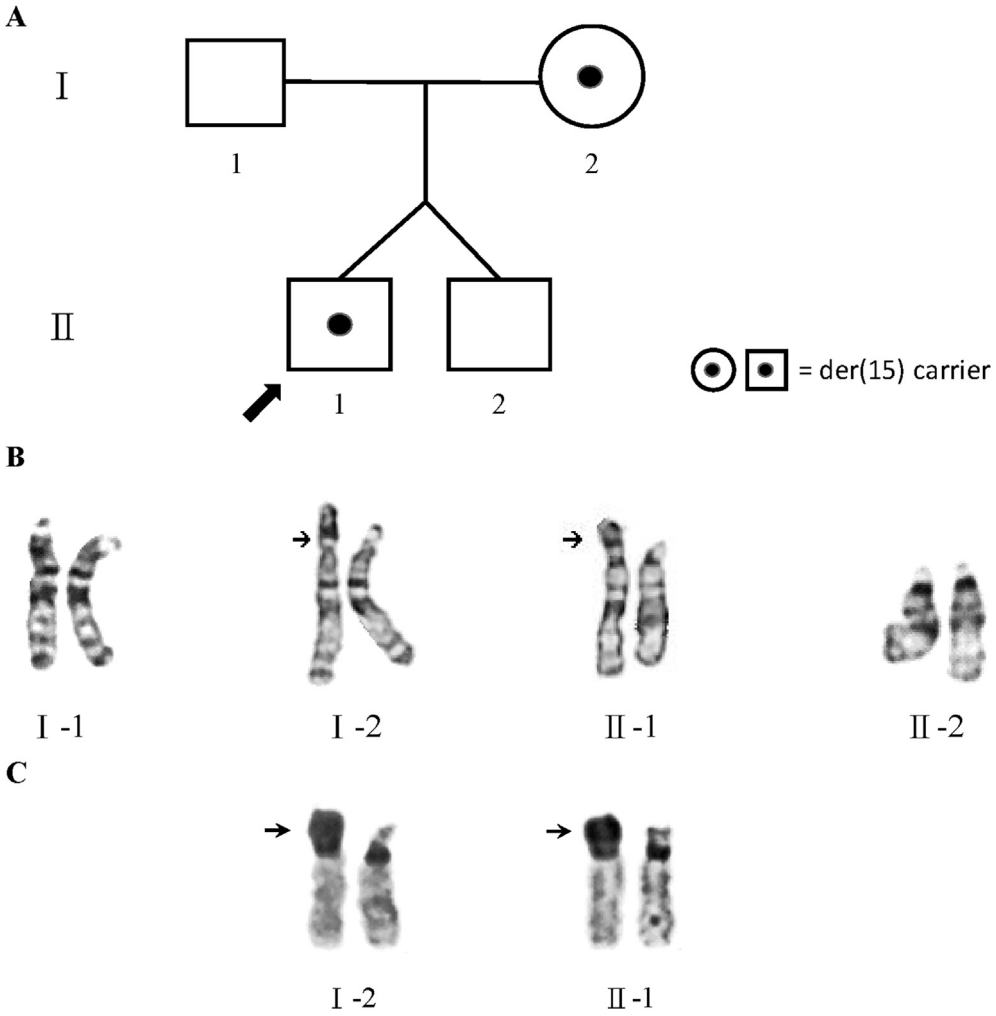

Fig. 1. Cytogenetic characterization of the der(15) translocation. (A) Pedigree data for the family. The father (I-1) has a normal karyotype, and the mother (I-2) is the der(15) translocation carrier. The arrow represents the proband II-1, who harbors the same translocation as his mother. His twin brother II-2 has a normal karyotype. (B) GTG-banded partial karyotypes show chromosome 15 in the family compared with the pedigree; the arrows indicate that the proband and his mother carry additional material on the p-arm of chromosome 15. (C) CTG-banded partial karyotypes show that both the proband (II-1) and his mother (I-2) exhibit dark staining on the p-arm of chromosome 15, mainly indicating a heterochromatic content.

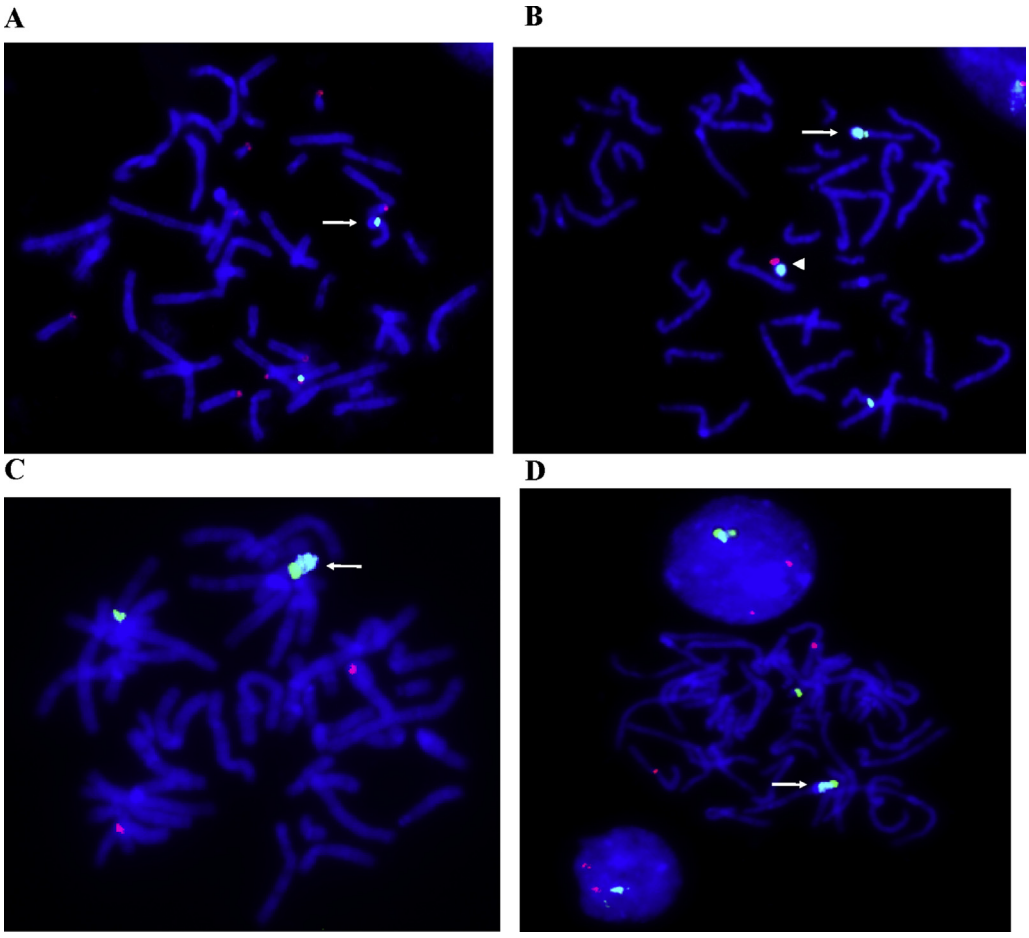

Fig. 2. FISH characterization of the breakpoints between chromosome 15 and chromosome Y. Commercially available alpha-DNA satellite probes for the X and Y chromosomes (DXZ1 and DYZ3), a centromere 15 probe (D15Z4), an acro p-arm probe (acro-p), and a Y-specific probe (DYZ1) were used. (A) FISH analysis was carried out on metaphase spreads from amniotic fluid cells. All acrocentric chromosomes including chromosomes #13, #14, #15, #21, and #22 were stained red on the p-arm by an acro-p probe. The arrow shows that the der(15) chromosome from the proband contains the chromosome 15 centromere (D15Z4/green +), but exhibits loss of 15p (acro-p/red −), indicating that the original translocation breakpoint on chromosome 15 was in the p-arm. (B) Analysis of the proband's cells using the Y chromosome-specific probes DYZ1 and DYZ3 revealed that the Y chromosome is normal, indicated by an arrowhead (DYZ1/aqua + and DYZ3/red +). The der(15) chromosome contains the chromosome 15 centromere and Yq12 heterochromatic region, but not the Yp11.1-q11.1 region, indicated by an arrow (D15Z4/green +, DYZ1/aqua +, and DYZ3/red −). (C,D) FISH analysis was carried out on the blood lymphocytes of the proband's mother. D15Z4, DYZ1, and DYZ3 probes were used. The arrow indicates that her der(15) chromosome contains the chromosome 15 centromere and Yq12 heterochromatic region, but not the Yp11.1-q11.1 region (D15Z4/green +, DYZ1/aqua +, and DYZ3/red −), results similar to those of the proband. With the X chromosome-specific probe DXZ1, FISH results show a normal female with two X chromosomes (DXZ1/red +). FISH = fluorescence *in situ* hybridization.

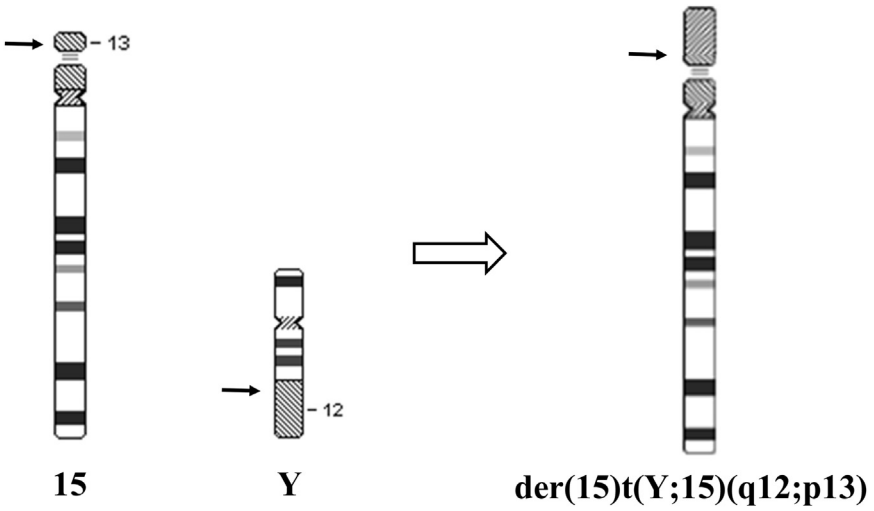

Fig. 3. Ideograms for the der(15) structural rearrangement. Ideograms of a normal chromosome 15, Y chromosome, and the derivative chromosome 15; the breakpoints are indicated with black arrows.

microdeletion within the PWS critical region (data not shown). The mother preferred to continue the pregnancy. At 37 weeks of gestation, a pair of phenotypically normal twins was delivered. The proband (2650 g) and his twin brother (2,750 g) appeared as normal boys with Apgar scores of 10 after 5 minutes. Both neonates were well developed at the age of 10 months.

3. Discussion

In this study, we described a prenatal diagnosis of twins, one of whom harbored a maternally inherited der(15) chromosome, while the other exhibited normal chromosomes. Through a combination of cytogenetic and FISH analyses, the fetal karyotype was shown to be 46,XY,der(15)t(Y;15)(q12;p13)mat. To our knowledge, this study constitutes (1) the first reported case of a der(15)t(Y;15)(q12;p13) rearrangement in a dizygotic twin pregnancy and (2) the fourth report of the t(Y;15) inherited from maternal origin to date. In contrast with previously reported t(Y;15) translocations, which were mostly of paternal origin [7–9], (3) we determined the precise breakpoints on both chromosomes and provided more comprehensive genetic information about der(15)t(Y;15) translocation to the parents in the prenatal stage.

It has been proposed that the der(15)t(Y;15)(q12;p13) of the mother may have been inherited from a paternal origin, resulting in Y material on chromosome 15p. However, we cannot complete the cytogenetic analysis on her family due to discontinuation of genetic counseling. It remains to be proven and further investigated.

The breakpoints were determined through FISH using centromeric 15-, acro p-arm-, and Y-specific probes that map to 15p13 and Yq12. Our results demonstrated that standard karyotyping in combination with the FISH technique is useful for the detection of rare chromosomal rearrangements. Some patients with PWS exhibit translocations involving chromosome 15 with deletion of the PWS region. Although the t(Y;15)(q12;p13) translocation was not involved in the PWS critical region (15q11–q13), two rare reports indicated that familial t(Y;15)(q12;p13) may result in predisposition to the generation of microdeletions within the PWS region or trisomy 15 [10,11]. These studies suggested the possibility of an increased risk for abnormal offspring. However, the association of familial t(Y;15)(q12;p13) with *de novo* PWS deletion is not clear. Using microsatellite analysis, we did not find maternal UPD15 or microdeletion within the PWS critical region. Previous reports examining a large number of cases also indicated that this translocation is likely to be a normal variant [1,3,5,12,13]. Thus, additional studies will help validate the predisposition of familial t(Y;15) in generation of microdeletions within the PWS region.

The present case illustrates the importance of characterizing variant chromosomes using FISH, especially in prenatal diagnosis. The presence of additional material on the p-arm of chromosome 15 is common and can come from Y chromosome, X chromosome, or other autosomes. For prenatal cytogenetic analysis, accurate identification of der(15) chromosomal content may facilitate the prediction of the fetal phenotype. Therefore, characterizing the der(15) chromosome via FISH is recommended. The der(15) t(Y;15)(q12;p13) translocation identified in the present work is the most common form of Y-autosome translocation; the karyotype appears unbalanced, but the phenotype is normal.

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