

A de novo Complex Chromosomal Rearrangement of 46,XX,t(7;15;13)(p15;q21;q31) in a Female with an Adverse Obstetric History

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ABSTRACT Complex chromosomal rearrangements (CCRs) are rare structural rearrangements involving three or more chromosomes. Balanced CCRs are often seen in phenotypically normal females who may later present with fertility problems. We report a 25-year old female with an adverse obstetric history and a de novo CCR involving chromosomes 7, 13 and 15 detected after GTG-banding. The de novo origin was confirmed because the karyotypes of the proband's parents and male sibling were normal. Cytogenetic analysis of the proband revealed the following complex karyotype: 46,XX,t(7;15;13)(p15;q21;q31). This case illustrates the importance of identifying de novo, apparently balanced CCRs in patients with adverse obstetric histories. Further, offspring of female carriers of apparently balanced CCRs may be affected as a result of abnormal meiosis during gametogenesis. This makes it imperative to karyotype women with adverse obstetric histories to rule out the presence of chromosomal rearrangements and facilitate genetic counseling of the patient, family planning, and prenatal diagnosis of future pregnancies.

INTRODUCTION

Complex chromosomal rearrangements are rare structural rearrangements with three or more breakpoints and exchange of genetic material between two or more chromosomes (Kleczkowska et al. 1982). The rearrangements may be balanced or unbalanced, and are classified into type I with three to four breaks and familial origin; and type II with five or more breaks, which generally arise de novo (Kousseff et al. 1987). Unbalanced chromosomal rearrangements may lead to significant clinical consequences such as dysmorphic features, multiple congenital anomalies and mental subnormality in the progeny (Batista et al. 1994; Batanian et al. 1998). Balanced chromosomal rearrangements are often not associated with any phenotypic abnormalities and may remain undetected in family members through multiple generations. However, balanced chromosomal

rearrangements have been reported in individuals with reproductive problems including infertility, multiple miscarriages and stillbirths (Rodriguez et al. 1985; Gorski et al. 1986; Patsalis et al. 2004). Further, children born to parents with balanced chromosomal rearrangements may show congenital anomalies, dysmorphic features or mental retardation, attributed to meiotic events resulting in production of abnormal gametes. In the current report, we present a case of a de novo, complex chromosomal rearrangement involving chromosomes 7, 13 and 15, in a female patient with an adverse obstetric history.

METHODOLOGY

Case Report

A 25 year old phenotypically normal female with a clinical history of three spontaneous abortions in the first trimester between the 6th and 13th weeks of gestation, was referred for karyotyping. Ultrasonography during the three pregnancies did not reveal any apparent congenital abnormalities. Autopsies of the abortuses were declined. Peripheral blood lymphocytes of the proband, her parents, i.e., her mother (age 50 years) and father (age 51 years), male sibling (age 24 years), and husband

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(age 28 years), were subsequently karyotyped. The parents and brother were also phenotypically normal; the family history indicated no evidence of genetic disease or other inherited disorders.

Cytogenetic Studies

Metaphase spreads obtained from 72 hour PHA-stimulated peripheral blood lymphocyte cultures were GTG-banded according to standard procedures. Analysis was done on 20 metaphase spreads, images captured using Applied Imaging Cytovision software, and the karyotype was designated according to ISCN (2005) nomenclature.

RESULTS

Chromosomal analysis was initially performed on the index case with a history of three spontaneous abortions. Karyotyping of GTG-banded chromosomes (550 bands per haploid genome) from the proband revealed a complex

translocation involving chromosomes 7, 13 and 15, with the karyotype: 46, XX, t(7;15;13)(p15;q21;q31) (Fig. 1).

Analysis of the parental peripheral blood chromosomes revealed a normal karyotype, i.e., 46, XX in the mother and 46, XY in the father. Her male sibling was also karyotyped and found to be normal, 46, XY. Thus, indicating a de novo complex chromosome rearrangement in the female. Karyotyping studies of her husband demonstrated a normal male karyotype, 46, XY.

DISCUSSION

Complex chromosomal rearrangements are often undetected in individuals without associated phenotypic abnormalities. Our proband showed a three-way, type I, de novo complex chromosomal rearrangement involving chromosomes 7, 13 and 15, in a female with an adverse obstetric history including three spontaneous first trimester abortions. In the present case, the rearrangement indicated that the translocations may have arisen in a 'circular'

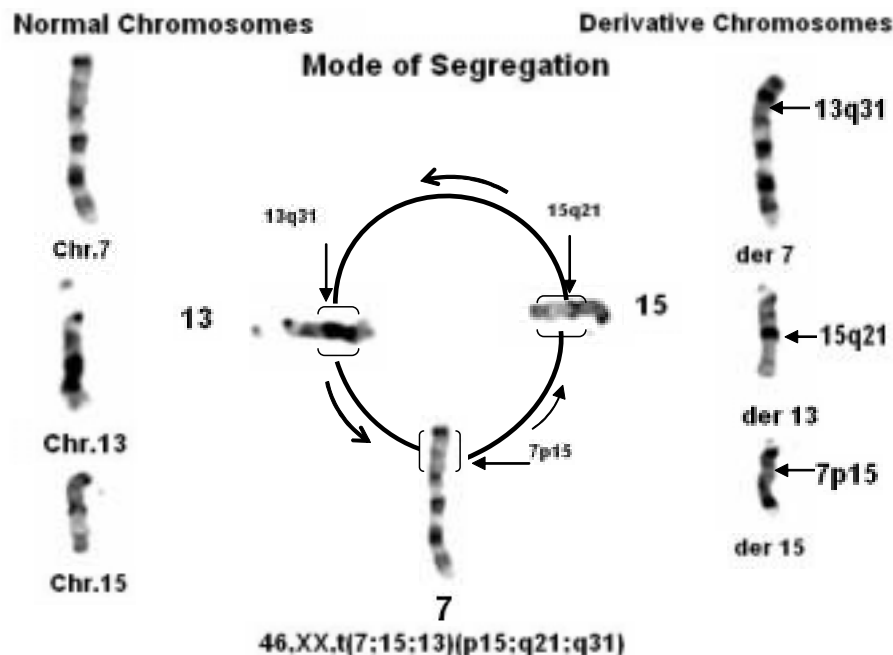


Fig. 1. Partial karyotype (GTG-banded) of the complex translocation between chromosomes 7, 13 and 15 and the resulting derivative chromosomes. The arrows indicate the breakpoints. Chr. indicates chromosome. Derivative homologue is indicated by 'der'.

fashion, with a break in chromosome 7 at band p15, chromosome 13 at band q31 and chromosome 15 at band q21. Thus, the segment of chromosome 7p distal to band 7p15 was translocated to chromosomal band 15q21; the segment of chromosome 15q distal to band 15q21 was translocated to chromosomal band 13q31; and the segment of chromosome 13q distal to band 13q31 was translocated to chromosomal band 7p15 (Fig.1).

The parents of the proband and her brother all expressed normal karyotypes. Thus, the CCR is most likely to be a type I de novo translocation. In type I translocations, theoretically, during gametogenesis, a hexavalent synaptic configuration may produce symmetric disjunction, wherein only two balanced gametes out of twenty

gametes are possible; or an asymmetric disjunction with much higher number of unbalanced gametes. Generally symmetric disjunction is favored with chances of a normal pregnancy, despite an unpredictable number of clinical and occult abortions. Whereas, in the case of type II translocations, the configuration is variable with the possibility of octavalent configurations, and due to many possible breakpoints, the rate of unbalanced gametes produced is much higher. An alternative scenario may be possible with two separate and independent quadrivalents, where different translocations produce different meiotic behavior (Gardner et al. 1984).

In the index case with a CCR and clinical history of multiple abortions, the complex karyotype may be attributed to several factors

Table 1: Literature citations of complex chromosome rearrangements in phenotypically normal females with recurrent miscarriages

References	Complex chromosome rearrangement in chromosomes	Karyotype
De Gregori et al. 2007	2,6,8	46,XX,t(2;6;8)(2pter→2q37.1:: 8q24.2→8qter;6pter→6q13:: 8q24.1:: 2q37.1→2qter;8pter→8q24.1:: 6q13→6qter)
De Gregori et al. 2007	6,12,15	46,XX,t(6;12;15)(6pter→6q21:: 12q24.33→12qter; 12pter→12q24.33:: 6q23.1→6qter; 15pter→15q26.2:: 6q21→6q23.1:: 15q26.2→15qter)
Karmous-Benailly et al. 2006	8, 10, 11,16	46,XX,ins(8;10)(q12;p12.3p14),t(10;11;16)(10qter→10p12.3:: 11p12→11pter;11qter→11p11.2:: 16q12.2→16qter;16pter→16q12.2:: 11p11.2→11p12:: 10p14→10pter)
Migliori et al. 2004	4, 10,11	46,XX,t(4;10;11)(4pter→4q13:: 10p14→10pter;10qter→10p14:: 11q21→11qter; 11pter→11q21:: 4q13→4qter)
Patsalis et al. 2004	6,8,12	46,XX,t(6;8;12)(p22.2;q24.3;q13.1)
Lee MH et al. 2002	5,16,10,18	46,XX,t(5;16;10;18)(q13;q22;q11.2;q21)
Kotzot et al. 2001	8,11,12	46,XX,t(8;11;12)(8qter→8p10:: 12p10→12pter;11pter→11q14:: 8p10→8pter;12qter→12p10:: 11q14→11qter)
Kim et al. 2001	9,14,13	46,XX,t (9;14;13)(p21.2;q21;q12.2)
Weimer et al. 2000	2, 3, 7	46,XX,rev ish t(2;3;7);(2pter→2q32:: 7q31.3→7qter; 3pter→3p21.3:: 2q32→2q34:: 7q22→7q31.3:: 3p21.3→3qter; 7pter→7q22:: 2q34→2qter)
Madan et al. 1997	2,3,8	46,XX,t(2;3;8)(2pter→2q23:: 3q13.2→3qter; 3pter→3q13.2:: 2q23→2q33:: 8q13→8qter; 8pter→8q13:: 2q33→2qter)
Wallerstein et al.1996	5,7,11	46,XX,t(5;7;11)(5qter→5p15.1:: 7q31.2→7qter;7pter→7q31.2:: 5p1 5.35p15.1:: 11q13.3→11qter;11pter →11q13.3:: 5p1 5.3→5pter)
Batista et al. 1994	7,8,13	46,XX,t(7;8;13)(7pter→7q36:: 8p11→8pter;8qter→8p11:: 13q22→13qter;13pter→13q22:: 7q36→7qter)
Kausch et al. 1988	1, 2, 5,11	46,XX,+ derl(1pter -+ p31.1:: q31.1+p31.1:: llq14.3→ llqter), + der2(5pter + p14.1:: 2p16.1 + qter), + der5(lqter →q31.1:: 5p14.1 → qter), + der11(11pter + q14.3:: 2p16.1 pter)
Barros et al. 1987	1,19,6,14	46,XX,t(1;19;6;14) (1p11; 19p11; 6q25; 14q21)
Gorski et al. 1986	7,10,21	46,XX,t(7;10;21)(7q11;10q22;21q22)
Gardner et al. 1984	2,11,18	46,XX,t(2;11;18)(2pter→2q13:: 11p15.3→11pter;11qter→11p15.3:: 18q21.1→18qter;18pter→18q21.1:: 2q13→2qter)
Iyer et al.2009 (Current Study)	7,13,15	46,XX,t(7;15;13)(p15;q21;q31)

involving genes in the vicinity of the breakpoints. These include (i) disruption of a dosage-sensitive gene at the breakpoints or expression of a recessive gene; (ii) position effect with variable expression of genes near the translocation breakpoint; (iii) uniparental disomy with structurally balanced chromosomes and a functional imbalance; and (iv) additional unbalanced submicroscopic rearrangements (Nicholls et al. 1989; Bonaglia et al. 2001; Sismani et al. 2008). Alternatively, females with balanced CCRs may produce phenotypically normal children, resulting from maternal transmission of the rearrangements. The process of oogenesis is considered a robust mechanism of gametogenesis, and hence less likely to be affected by disruptions resulting from CCRs (Gardner et al. 1986). It is interesting that male carriers with CCRs have an increased risk of primary infertility due to disturbed spermatogenesis as well as pre- and post-implantation loss (Saadallah and Hulten, 1985; Gorski et al. 1986; Madan et al. 1997). Several reports of CCRs in fertile males have been documented with associated recurrent spontaneous abortions in their partners, or birth of an abnormal offspring with multiple congenital anomalies, dysmorphic features or mental retardation (Saadallah and Hulten, 1985; Johannisson et al. 1988; Zahed et al. 1998; Cai et al. 2001; Grasshoff et al. 2003).

Similar to our report, several cases of phenotypically normal females with CCRs and an associated history of recurrent pregnancy loss are summarized in Table 1. The majority (75%) of the 16 cases reported involvement of three chromosomes, and five of the cases involved acrocentric chromosomes, as observed in our proband.

CONCLUSION AND RECOMMENDATION

In conclusion, it is imperative to record description and characterise balanced or unbalanced complex chromosome rearrangements as it would be of importance in counseling and prenatal investigations. CCRs could alter the segregation modes, result in unbalanced karyotypes in the offspring leading to genetic aberrations. In vitro fertilization (IVF) and preimplantation genetic diagnosis (PGD) may have a limited role in management of couples with CCRs, due to the high rate of unbalanced gametes and possibility of apparently balanced

gametes with functional abnormalities in the offspring of females with CCR. The alternative of donor ova or adoption may be recommended.

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