Int J Hum Genet, 10(4): 231-234 (2010)
PRINT: ISSN 0972-3757 ONLINE: 2456-6360
DOI: 10.31901/24566330.2010/10.04.04

Prenatal Diagnosis of De Novo Reciprocal Translocation t(1;12)(q21.3;p11.2) with Trisomy 21 and Sperm FISH Analysis for Increased Aneuploidy Risk

Mutlu Karkucak[1]*, Sebnem Sag[1], Tahsin Yakut[1] and Yalcin Kimya[2]

[1]Department of Medical Genetics, [2]Department of Obstetrics and Gynecology, Uludag University, Medical Faculty, 16059, Bursa, Turkey

KEYWORDS Prenatal Diagnosis. Translocation. Aneuploidy. Sperm FISH. Genetic Counseling

ABSTRACT Complex rearrangements such as de novo translocations together with aneuploidy are unusual situations in prenatal diagnosis. We report a case with de novo translocation t(1;12)(q21.3;p11.2) and trisomy 21. Father's sperm was analyzed for potential of increased risk of aneuploidy. Results showed no paternal increased risk for chromosomes 13, 18, 21, X, Y. Based on our results, we suggest that possible increased maternal aneuploidy risk and other possible mechanisms should be investigated to better understand cell division errors and to give better genetic counseling.

INTRODUCTION

Structural abnormalities detected in prenatal diagnosis are mostly familial inheritances (Caron et al. 1999). De novo rearrangements may carry an increased risk of abnormal outcome in prenatal diagnosis. De novo balanced translocations can be detected in very low frequencies (1/2000) in newborns for which cytogenetic detections are carried out in amniocentesis (Park et al. 2003). The errors in meiotic repair in the continuous cell division can play a role in chromosomal rearrangements in gametogenesis throughout the reproductive process (Baarends et al. 2001; Laan et al. 2005). Some studies suggested a positive correlation between germ cell fragile site breakpoints and sites of balanced chromosome de novo rearrangements in gametes (Hecht and Hecht 1984; Hecht and Hecht 1986). However, de novo chromosomal rearrangements are sporadic and there are no certain data for recurrence risks which takes into by chance gonadal mosaicism, and somatic-gonadal mosaicism (Gardner and Sutherland 2004). The recurrence risks for de novo trisomies have been estimated to be increased 1.6- to 1.8-fold after a trisomy 21 according to current data (Röthlisberger and Kotzot 2007). Although it is a controversial subject, an increased incidence of a chromosome aneuploidy in the fetus can be the result of the possible interchromosomal effect (ICE) regarding the presence of constitutional rearrangements in the gametes (Blanco et al. 2000; Gianaroli et al. 2002). This phenomenon was supposed to be a disturbance of meiosis where structural chromosome rearrangements such as reciprocal translocations disrupt disjunction and distribution of chromosome pairs resulting in aneuploid gametes and offspring (Estop et al.2000). The studies investigated to ICE were performed commonly on sperms of the fathers carrying reciprocal or Robertsonian translocations (Douet-Guilbert et al.2005). While some studies detected positive findings supporting ICE, certain others did not (Blanco et al.2000; Oliver-Bonet M et al.2004). In our case, there was no certain evidence on which rearrangement occurred first between t(1;12) and trisomy 21. So, it can be discussed whether the de novo rearrangement may trigger another rearrangement in the same cell division process.

In order to investigate the answer to the question "if there is a relationship between de novo structural chromosomal rearrangements and aneuploidy because of paternal cell division errors", the sperms of the father were also studied for the risk of chromosomes 13, 18,21, X and Y aneuploidies.

CASE REPORT

The woman (gravida 4 parity 1, 18 weeks gestation) who had the first trimester abortion in the first pregnancy, healthy child in the second

*Correspondence to:
Dr. Mutlu Karkucak, Uludag
University Faculty of Medicine, Department of Medical Genetics, 16059, Görükle , Bursa, Turkey
Phone: +90 224 295 43 71,
*E-mail:*mutlukarkucak@hotmail.com

pregnancy and an elective curettage in the third pregnancy applied to our genetic laboratory because of the increased risk from the triple screening test. She was 33 and her husband was 37 years old. There was neither a chromosomal analysis nor an autopsy carried on the aborted fetus. History was negative for radiation and drug exposure which might cause a chromosomal breaking or aneuploidies. Amniotic fluid volume was normal. The cell culture of amniocytes was performed according to standard methods in two flasks and chromosomal analyses were performed after GTG banding. Cytogenetic analysis of peripheral blood lymphocyte culture of the parent was performed after amniocentesis result. To investigate the possible increased aneuploidy risk, FISH analysis was conducted using dual color locus specific 13/21 and tri color centromere specific 18/X/Y probes (Abbott, Vysis) on sperms of the father and control as described elsewhere (Acar et al.2000). The donors gave his signed consent prior to participation in the study. Semen samples of the carrier and controls were obtained by masturbation. In brief, the samples were washed two time in PBS and two time in 2xSSC, swelled with 0.075 M KCl, and fixed with methanol:acetic acid (3:1) for three times. The sperm nuclei were decondensed by incubation in 0.01MDTT/2xSSC at room temperature for 10–20 min. Slides were examined with an epifluorescence microscope (Nikon E600) equipped with a Quips Imaging System (Applied, UK) including filter set (triple;dapi/red/ green, dual color; red/green, single red, green, aqua).Chi square test analysis was used to compare frequencies of normal and aneuploidic signals in sperm nuclei of the father's and control.

Cytogenetic analyses of amniocytes revealed 47,XX,t(1;12)(q21.3;p11.2)+21,13s+ karyotype of the fetus (Fig.1).Ultrasonographic examination of the fetus in the present pregnancy did not show any phenotypic abnormality. Cytogenetic analysis of peripheral blood lymphocyte culture of the parent did not reveal any chromosomal abnormalities but father also had same satellite polymorphism for chromosome 13. One thousand six hundred and eighty sperm nuclei of the father were analysed for 13, 18, 21, X and Y aneuploidies. For control, one thousand eight hundred thirty sperms of one healthy person were analysed (Fig.2).Overlapping nuclei, disrupted nuclei, nuclei with indistinguishable signals were eliminated. Statistical analyses of FISH results showed no significance for increased aneuploidy

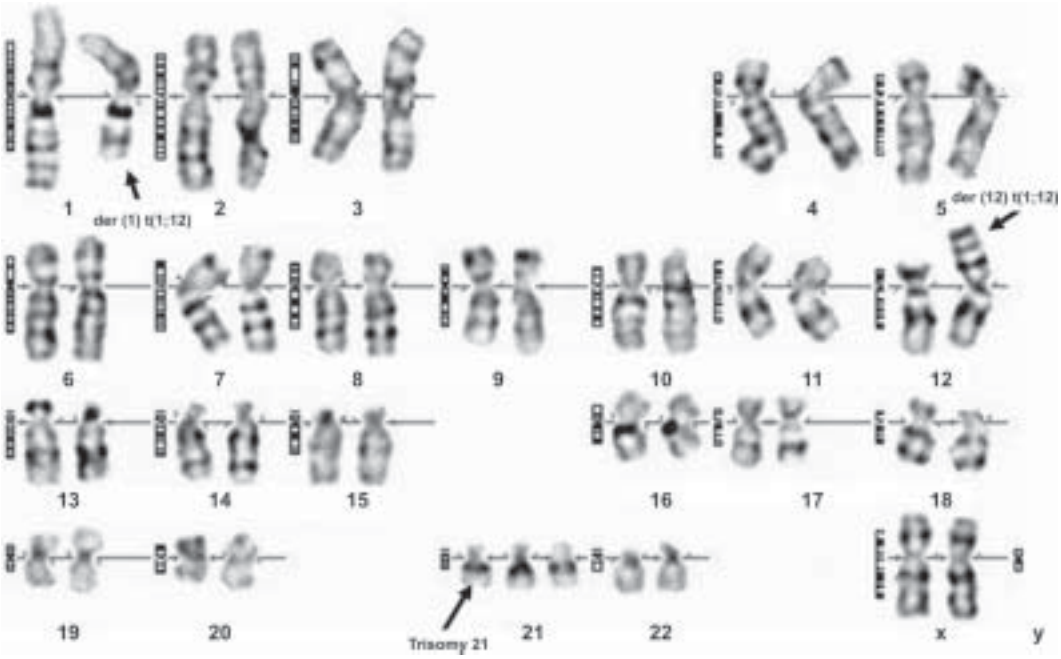

Fig.1. G-banded karyogram showing the t(1;12)(q21.3;p11.2) translocation and trisomy 21

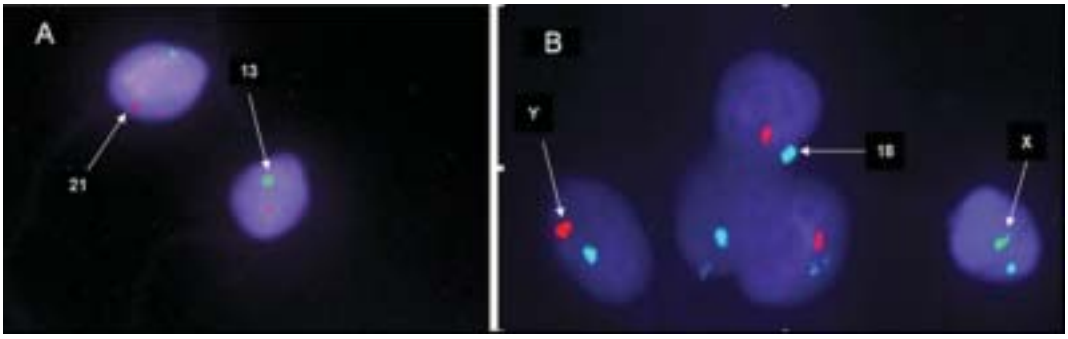

Fig. 2. Father's sperm FISH using A) 21(LSI),18(CEP), B)13(LSI), X(CEP) and Y(CEP) probes revealed one signal on each chromosomes

risk regarding chromosomes 13, 18, 21, X and Y in the case ($p > 0.05$).

DISCUSSION

The cause of de novo structural abnormalities or aneuploidies may be coincidental or there were other predisposition factors which would have to be investigated. In literature, the studies showing relationship between chromosomal breakpoints, fragile sites and chromosomal rearrangements support the occurrence of de novo chromosomal rearrangements (Brandriff et al.1988a; Brandriff et al.1988b; Chandley 1991; Estop et al.1995). Some studies support the thesis that parental chromosomal potentials may contribute to occurrence of balanced de novo rearrangements or aneuploidies (Short et al. 1988; Cannizzaro et al.1988; Warburton 1991). Some showed significant inter-chromosomal effect in chromosomal rearrangement cases (Pellestor et al.2001;Bonet et al 2002). Using FISH technique, investigating sperm nuclei in the father of the fetus with de novo reciprocal translocation is important because it allows analysis of large numbers of sperm nuclei for possible aneuploidy potential. According to our knowledge, there were limited number of studied conducted to investigate the relationship between de novo translocation and chromosomal rearrangements or germ cell line mosaicism (Brandriff et al.1988c; Colls et al.1988a; Colls et al.1988b). When occured as de novo, the phenotypic abnormality risk for reciprocal translocations is high because of gene disruption, position effect, or deletion at one of the breakpoints (Abrams and Cotter 2004). Previous abortion of the parent supports the possible chromosomal structural or numerical abnormality as a potential cause. However, there was no evidence regarding cytogenetic analysis. In our case, it cannot be detected which one of the rearrangements between t(1;12) and trisomy 21 have occurred first in the cell division process. The parent has no chromosomal rearrangement, which may trigger the de novo structural or numerical chromosomal aberrations, except the satellite polymorphism of chromosome 13 of the father. The special value of our study was to investigate if there were a potential for increased chromosomal numerical abnormality in the sperm nuclei of the father which may be triggered by de novo reciprocal translocation. Possible parental potential predisposition factors such as chromosomal breakpoints or fragile sites which need to be investigated might be the cause of the first abortion and second fetus with chromosomal rearrangements. Gonadal mosaicism including t(1;12) or trisomy 21 can be another possible predisposition factor. FISH study also showed no paternal gonadal mosaicism for trisomy 21. However paternal or maternal gonadal mosaicism for t(1;12) could not be eliminated. Statistical analysis results revealed no increased numerical abnormality risk which could be a possible interaction with de novo translocation and chromosomal aneuploidy of chromosome 21.

According to our case, we suggest that there might be other potential risks for chromosomal rearrangements, which can disrupt disjunction in meiosis and can cause a distribution of chromosome pairs resulting in aneuploid gametes and offsprings.

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