

De novo Balanced Robertsonian Translocation rob(22;22)(q10;q10) in a Woman with Recurrent Pregnancy Loss: A Rare Case

Nawras Alhalabi^{1*}, Walid Al-Achkar², Abdulsamad Wafa², Mazen Kenj^{3,4}, Marwan Alhalabi^{3,5}

1- Faculty of Medicine, Syrian Private University, Damascus, Syria

2- Department of Molecular Biology and Biotechnology, Human Genetics Division, Atomic Energy Commission of Syria, Damascus, Syria

3- Assisted Reproduction Unit, Orient Hospital, Damascus, Syria

4- Kenj Cytogenetics Laboratory, Damascus, Syria

5- Department of Reproductive Medicine, Genetics and Embryology, Faculty of Medicine of Damascus University, Damascus, Syria

Abstract

Background: Recurrent pregnancy loss (RPL), one of the most common complications of pregnancy, is responsible for significant emotional distress to the couple desiring to conceive. In almost 50% of the cases, the etiology remains unknown. The frequency of chromosomal structural rearrangements associated with a history of RPL in couples varies between 2% to 8%. Robertsonian translocations (ROBs) have an estimated incidence rate of 1/1000 births, making this type of rearrangement the most common structural chromosomal abnormalities seen in the general population. According to the literature, there are few RPL cases with rob (22; 22).

Case Presentation: This case is a Syrian female offered to the Orient Hospital (Damascus, Syria), having RPL in the first trimester, no fetal malformations, and/or no neonatal death. She had a balanced chromosomal translocation involved the both short arms of chromosome 22. Banding cytogenetics, refined by array-proven multi-color banding (aMCB) revealed a rob (22; 22)(q10;q10). Her husband had a normal karyotype. Interestingly, chromosomal analysis was performed for her other family members and it revealed normal karyotype for all people, which indicates that translocation is of de novo origin. However, the couple did not have any living offspring after seven years of marriage.

Conclusion: The present case was a case of RPL occurring due to rob (22;22). However, the rob(22;22)(q10;q10) is the cause of recurrent abortions. Couples with the history of RPL should be suggested to do cytogenetic analysis in order to estimate whether they have chromosomal rearrangement. This diagnostic approach is of great significance to figure out what causes RPL.

Keywords: Assisted Reproduction Techniques, Recurrent Pregnancy Loss, Robertsonian translocation, Syria.

To cite this article: Alhalabi N, Al-Achkar W, Wafa A, Kenj M, Alhalabi M. De novo Balanced Robertsonian Translocation rob(22;22)(q10;q10) in a Woman with Recurrent Pregnancy Loss: A Rare Case. *J Reprod Infertil.* 2018;19(1):61-66.

Introduction

Recurrent pregnancy loss (RPL), one of the most common complications of pregnancy is responsible for significant emotional distress to the couple desiring to conceive. RPL is defined as the occurrence of two or more consecutive abortions and it affects about 1-5% of couples trying to establish a family (1-3). About 10 to

15% of the clinically recognizable pregnancies result in pregnancy loss, with an additional pre-clinical loss of 22% (4, 5). Determining the cause of a pregnancy loss is important to determine whether further interventions are necessary, as well as to provide a sense of closure to the patient and her partner.

* Corresponding Author:
Nawras Alhalabi,
Faculty of Medicine, Syrian
Private University,
Damascus, Syria
E-mail:
nawras@me.com

Received: Aug. 25, 2017
Accepted: Dec. 3, 2017

However, in almost 50% of the cases, the etiology remains unknown. Several factors have been suggested to be involved including endocrine dysfunction, autoimmunity, genetic abnormalities, advanced maternal and paternal age, infectious diseases, environmental toxins, congenital and structural uterine anomalies and more (6, 7). Transmission of parental chromosomal abnormalities may be one of the causes for RPL in the first trimester of pregnancy (8, 9). The frequency of chromosomal structural rearrangements associated with a history of RPL in couples varies between 2% to 8% (4, 10-12), which is higher than the general population frequency of 0.7% (10). Robertsonian and reciprocal translocations are more commonly implicated compared to inversions (10, 12-14).

In this paper, a rare case of de novo balanced ROB was reported involving both short arms of chromosomes 22 in a Syrian female with a history of RPL.

Case Presentation

In Damascus, on September 2013, a 29-year-old, non-smoker Syrian female presented to the fertility clinic, Orient Hospital, due to recurrent pregnancy losses. She reported five miscarriages with the last one occurring two years ago. She had been married for 7 years, has regular menses and her first menarche was at 12 years of age. Her surgical history included two curettage aspirations and a hysteroscopy in 2010 with normal findings. BMI (body mass index) was 22.1. Physical examination was within normal limits, pelvic ultrasonography revealed normal findings which were confirmed by hysterosalpingography. Hormones profile included thyroid-stimulating hormone (TSH) 1.17 *mIU/L* (0.5-4.5 *mIU/L*), free thyroxine (free T₄) 1.30 *ng/dl* (0.80-1.80 *ng/dl*), follicle stimulating hormone (FSH) 6.5 *mmol/ml* (3.4-10 *mmol/ml*), luteinized hormone (LH) 5.4 *mmol/ml* (1.6-8.3 *mmol/ml*), prolactin (PRL) 17 *ng/ml* (3.6-20 *ng/ml*), estradiol (E2) 35 *pg/ml* (up to 50 *pg/ml*) (all within normal limits). Thrombophilia workup revealed homocysteine 9 *μmol/L* (5-12 *μmol/L*), activated protein C resistance 197 sec (120-400 sec), anticardiolipin IgG antibodies 4 *U/ml* (up to 10 *U/ml*), anticardiolipin IgM antibodies 2 *U/ml* (up to 10 *U/ml*), antithyroid peroxidase (anti-TPO) 14 *IU/ml* (up to 35 *IU/ml*), antithyroglobulin antibodies 19.8 *IU/ml* (up to 40 *IU/ml*) and lupus anti-coagulant was also negative. Immunological tests for anti-toxoplasmosis IgG antibodies

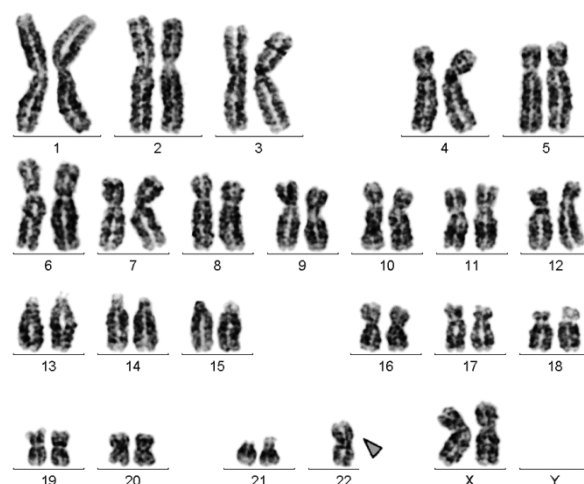


Figure 1. GTG-banding revealed a 45,XX, rob (22) (q10;q10). The derivative chromosome is marked by an arrowhead

were 199 *IU/ml* (up to 8 *IU/ml*) with an anti-toxoplasmosis IgM antibodies index of 4.1, indicating past infection with immunity. Anti-rubella IgG antibodies were 102 *IU/ml* (up to 10 *IU/ml*) and anti-rubella IgM antibodies index of 0.4 *IU/ml* (up to 10 *IU/ml*), which also signifies past infection with immunity. Although the patient was advised not to get pregnant, on December 2013, a gestational sac was noted on ultrasound. On January 2014, the conceptus was arrested at 6 weeks of pregnancy.

Her husband (38 years old), a smoker, had a BMI of 23.4. His semen analysis showed normal parameters according to world health organization criteria of 2010 (15). The couple was healthy and phenotypically normal and they were referred for chromosomal analysis based on these findings. A written informed consent was obtained from the couple before writing this report. The Institution Ethical Committee approved the report and the approval is available upon request.

Banding in conventional cytogenetics revealed a karyotype of 45,XX,rob(22;22)[20] (Figure 1). This finding was further studied by molecular cytogenetics and confirmed robertsonian translocation rob (22;22) (Figure 2). Thus, the following final karyotype was determined: 45,XX,rob(22;22)(q10;q10)[20].

The karyotype of her husband was normal 46,XY. Chromosomal analysis of the phenotypically normal parents was done to ascertain the origin of abnormal chromosome. Both parents' cytogenetics analysis revealed normal male and female karyotypes of 46,XY and 46,XX, respectively. Her

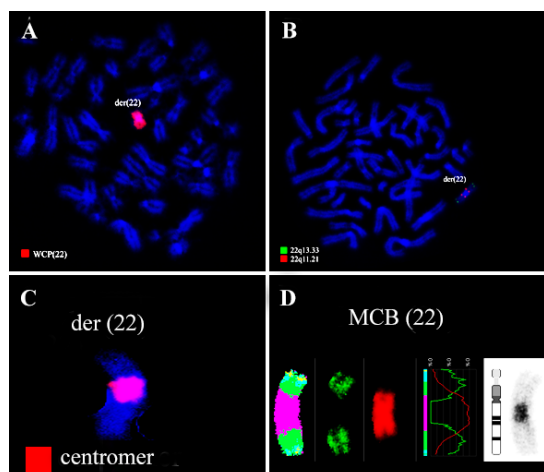


Figure 2. Karyotype and chromosomal aberrations were confirmed using molecular cytogenetic approaches. (A) A robertsonian translocation rob (22;22) was identified using the whole chromosome painting probe (B). Application of the probe Di-George probe revealed two red and two green signals on the derivative chromosome 22. (C) Application of all human centromere probe confirmed rob (22; 22). (D) The application of aMCB (22) confirmed rob (22;22)(q10;q10). Abbreviations: der = derivative chromosome

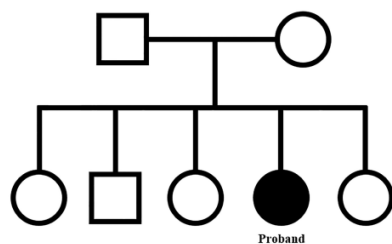


Figure 3. Pedigree of the proband

brother and three sisters had normal phenotypes as well as karyotypes (46,XY and 46,XX respectively), pedigree is shown in figure 3.

Discussion

Robertsonian translocations (ROBs) are structural chromosomal anomalies that result from the fusion of two acrocentric chromosomes (13-16, 21, 22). About 1/1000 of healthy people and 1/500 of healthy couples carry a ROB. Carriers of ROBs are often referred for reproductive counseling since they are at increased risk of spontaneous abortions, infertility and chromosomally unbalanced offsprings (12). Rob (13q14q) and rob (14q21q) are the most frequent ROBs encountered in the population (76% and 10%, respectively) (17-21). All remaining possible types of ROB constitute the remaining 15% portion of these translocations in the population.

ROBs identified in a child with an aneuploidy or through prenatal testing are more often de novo in

origin than inherited from a carrier parent (22). However, rearrangements of the acrocentric chromosomes can result in nonhomologous ROB [e.g., rob (13q14q)] or homologous rearrangements [e.g., rob (21q21q)]. In nonhomologous ROBs, the breakpoints usually occur in the short arms of the participating chromosomes, resulting in dicentric translocations (23). Although the formation of a dicentric chromosome often leads to chromosome instability through anaphase bridge formation and chromosome breakage, human dicentric ROBs usually remain stable.

Homologous rearrangements of acrocentric chromosomes can result in either isochromosomes or ROBs (24). With the technological advances of molecular genetics, including the accessibility of highly polymorphic markers, homologous rearrangements can now be distinguished as isochromosomes (both arms derived from a single parental chromosome), or true ROB (translocations composed of two different, homologous chromosomes). Of all possible ROBs, 90% occur between nonhomologous chromosomes and 10% occur between homologous chromosomes (19).

Since balanced ROBs involve loss of only short arm material, carriers have normal phenotype and impaired gametogenesis (25). The fertilization with an aneuploid gamete results in monosomy or trisomy in the fetus (26). Fetal aneuploidies are a major cause of pregnancy loss (27), hence, achieving full term pregnancy is only possible if the gemmates were fertilized with suitable aneuploid gemmates which will result in Uniparental Disomy (UPD).

Early reported literatures with similar cases were all associated with RPL. Maeda et al. (28) reported a rob (22; 22) in a woman with recurrent abortions, the karyotype was determined as 46,XX,-22,+t(22q22q) and identified after cytogenetic studies of the embryonic tissue derived from one of the spontaneous abortions. Mameli et al. (29) and Granat et al. (30) reported similar two cases of rob (22;22) identified in the husband of a woman who had early RPL. In Middle East, Ocak et al. (31) observed rob (22;22)(q10;q10) in Turkish female with RPL. Also, Kiani et al. (32) reported a rob (22;22) in Iranian female case with RPL history. Both studies were performed using conventional cytogenetics methods without confirmation by molecular cytogenetic studies. The limitations of these early cases were that further molecular cytogenetic studies were not done to confirm ROB or isochromosome (31, 33). Furthermore,

Zhao et al. (34) found 3 out of 872 cases had a similar rob (22;22), the results were also not confirmed by further cytogenetic studies. In the present study, the case of a female patient was reported with de novo rob (22;22)(q10;q10) which involved both of short arms of chromosome 22 and this result was confirmed by molecular cytogenetics analyses.

UPD associated with an isochromosome was reported in cases with i(1p) plus i(1q), i(2p) plus i(2q), i(4p) plus i(4q), i(7p) plus i(7q), psudic (8)(p23.3), i(9p) plus i(9q), i(13q), i(14q), i(15q), i(21q), and i(22q) (35, 36). In patients with maternal and paternal UPD (22), no significant clinical impact was determined (37-39). Two early cases reported suspected UPD (22) transmission for their daughters (40-42). Later, UPD (22mat) was reported in a 25 year-old healthy man investigated following RPL in his wife (43). He had a de novo balanced rob (22q;22q) which eventually appeared to be an i(22). No additional adverse phenotypic effect appeared besides causing reproductive failure with possible monosomic or trisomic conceptions for chromosome 22 (39, 42, 43).

Gamete donation (egg or sperm), surrogacy, and adoption in many countries are methods of preventing conception of an affected embryo; it is illegal and against religious beliefs in the Arab world. The choice depends upon the specific abnormality and parental preference.

Conclusion

In summary, couples with the history of RPL should be suggested to do cytogenetic analysis in order to estimate whether they have chromosomal rearrangement. However, the rob(22;22)(q10;q10) is the cause of recurrent abortions. This diagnostic approach is of great significance to figure out what causes RPL. Our results may help in enforcing genetic counseling for carriers of rare ROB.

Acknowledgement

We express gratitude to We Research Team, Faculty of Medicine of Syrian Private University, Faculty of Medicine of Damascus University and Atomic Energy Commission of SYRIA (AECS) for their support.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

1. Roman E. Fetal loss rates and their relation to pregnancy order. *J Epidemiol Community Health*. 1984; 38(1):29-35.
2. Shamsi MB, Venkatesh S, Pathak D, Deka D, Dada R. Sperm DNA damage & oxidative stress in recurrent spontaneous abortion (RSA). *Indian J Med Res*. 2011;133:550-1.
3. Practice Committee of American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. *Fertil Steril*. 2013;99(1):63.
4. Dutta UR, Rajitha P, Pidugu VK, Dalal AB. Cytogenetic abnormalities in 1162 couples with recurrent miscarriages in southern region of India: report and review. *J Assist Reprod Genet*. 2011;28(2):145-9.
5. Rull K, Nagirnaja L, Laan M. Genetics of recurrent miscarriage: challenges, current knowledge, future directions. *Front Genet* 2012;3:34.
6. Jauniaux E, Farquharson RG, Christiansen OB, Exalto N. Evidence-based guidelines for the investigation and medical treatment of recurrent miscarriage. *Hum Reprod*. 2006;21(9):2216-22.
7. Dudley DJ, Branch DW. New approaches to recurrent pregnancy loss. *Clin Obstet Gynecol*. 1989;32(3):520-32.
8. Sullivan AE, Silver RM, LaCoursiere DY, Porter TF, Branch DW. Recurrent fetal aneuploidy and recurrent miscarriage. *Obstet Gynecol*. 2004;104(4):784-8.
9. Philipp T, Philipp K, Reiner A, Beer F, Kalousek DK. Embryoscopic and cytogenetic analysis of 233 missed abortions: factors involved in the pathogenesis of developmental defects of early failed pregnancies. *Hum Reprod*. 2003;18(8):1724-32.
10. De Braekeleer M, Dao TN. Cytogenetic studies in couples experiencing repeated pregnancy losses. *Hum Reprod*. 1990;5(5):519-28.
11. Elghezal H, Hidar S, Mougou S, Khairi H, Saad A. Prevalence of chromosomal abnormalities in couples with recurrent miscarriage. *Fertil Steril*. 2007;88(3):721-3.
12. Fryns JP, Van Buggenhout G. Structural chromosome rearrangements in couples with recurrent fetal wastage. *Eur J Obstet Gynecol Reprod Biol*. 1998;81(2):171-6.
13. Reindollar RH. Contemporary issues for spontaneous abortion. Does recurrent abortion exist? *Obstet Gynecol Clin North Am*. 2000;27(3):541-54.
14. Franssen MT, Korevaar JC, Leschot NJ, Bossuyt PM, Knecht AC, Gerssen-Schoorl KB, et al. Selective chromosome analysis in couples with two or

- more miscarriages: case-control study. *BMJ*. 2005; 331(7509):137-41.
15. World Health Organization, Department of Reproductive Health and Research. WHO laboratory manual for the examination and processing of human semen. 5th ed. Geneva: World Health Organization; 2010. 287 p.
 16. Keymolen K, Van Berkel K, Vorrsselmans A, Staessen C, Liebaers I. Pregnancy outcome in carriers of Robertsonian translocations. *Am J Med Genet A*. 2011;155A(10):2381-5.
 17. Rowley JD, Pergament E. Possible non random selection of D group chromosomes involved in centric fusion translocations. *Ann Genet*. 1969;12(3):177-83.
 18. Hecht F, Kimbling WJ. Patterns of D chromosome involvement in human (DqDq) and (DqGq) Robertsonian rearrangements. *Am J Hum Genet*. 1971; 23(4):361-7.
 19. Therman E, Susman B, Deniston D. The nonrandom participation of human acrocentric chromosomes in Robertsonian translocations. *Ann Hum Genet*. 1989;(Pt 1):49-65.
 20. Choo KH, Vissel B, Brown R, Filby RG, Earle E. Homologous alpha satellite sequences on human acrocentric chromosomes with selectivity for chromosome 13, 14 and 21: implications for recombination between nonhomologous and Robertsonian translocations. *Nucleic Acids Res*. 1988;16(4): 1273-84.
 21. Choo KH, Vissel B, Earle E. Evolution of alpha-satellite DNA on human acrocentric chromosomes. *Genomics*. 1989;5(2):332-44.
 22. Shaffer LG, Jackson-Cook CK, Stasiowski BA, Spence JE, Brown JA. Parental origin determination in thirty de novo Robertsonian translocations. *Am J Med Genet*. 1992;43(6):957-63.
 23. Sullivan BA, Jenkins LS, Karson EM, Leana-Cox J, Schwartz S. Evidence for structural heterogeneity from molecular cytogenetic analysis of dicentric Robertsonian translocations. *Am J Hum Genet*. 1996;59(1):167-75.
 24. Robinson WP, Bernasconi F, Basaran S, Yüksel-Apak M, Neri G, Serille F, et al. A somatic origin of homologous Robertsonian translocations and isochromosomes. *Am J Hum Genet*. 1994;54(2): 290-302.
 25. Wang W, Lan H. Rapid and parallel chromosomal number reductions in muntjac deer inferred from mitochondrial DNA phylogeny. *Mol Biol Evol* 2000;17(9):1326-33.
 26. Causio F, Fischetto R, Sarcina E, Geusa S, Targagni M. Chromosome analysis of spontaneous abortions after in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). *Eur J Obstet Gynecol Reprod Biol*. 2002;105(1):44-8.
 27. Li TC, Makris M, Tomsu M, Tuckerman E, Laird S. Recurrent miscarriage: aetiology, management and prognosis. *Hum Reprod Update*. 2002;8(5): 463-81.
 28. Maeda T, Ohno M, Shimada N, Nishida M, Jobo T. A 22/22 translocation carrier with recurrent abortions demonstrated by a Giemsa banding technique. *Hum Genet*. 1976;31(2):243-5.
 29. Mameli M, Cardia S, Milia A, Seabright M. A further case of a 22;22 Robertsonian translocation associated with recurrent abortions. *Hum Genet*. 1978;41(3):359-61.
 30. Granat M, Aloni T, Makler A, Dar H. Autosomal translocation in an apparently normospermic male as a cause of habitual abortion. *J Reprod Med*. 1981;26(1):52-5.
 31. Ocak Z, Özlü T, Ozyurt O. Association of recurrent pregnancy loss with chromosomal abnormalities and hereditary thrombophilias. *Afr Health Sci*. 2013;13(2):447-52.
 32. Kiani MA, Shakibaie MZ, Kariminejad MH. A 22; 22 Robertsonian Translocation in a Patient with Repeated Abortions. *Arch Iran Med*. 2000;3(3):1-3.
 33. Lewis BV, Ridler MA. Recurrent abortion associated with a balanced 22;22 translocation, or isochromosome 22q in a monozygous twin. *Hum Genet*. 1977;37(1):81-5.
 34. Zhao WW, Wu M, Chen F, Jiang S, Su H, Liang J, et al. Robertsonian translocations: an overview of 872 Robertsonian translocations identified in a diagnostic laboratory in China. *PLoS One*. 2015; 10(5):e0122647.
 35. Kotzot D. Complex and segmental uniparental disomy (UPD): review and lessons from rare chromosomal complements. *J Med Genet*. 2001;38(8): 497-507.
 36. Chang LW, Lee IW, Kuo PL, Kuan LC. Maternal derivative chromosome 9 and recurrent pregnancy loss. *Fertil Steril*. 2007;88(4):968.e1-3.
 37. Liehr T. Cases with uniparental disomy [Internet]. Jena, Germany: Jena University Hospital; 2017 [cited 2017 Dec 17]. Available from: <http://www.med.uni-jena.de/fish/sSMC/00STARTUPD.htm>.
 38. McKinlay Gardner RJ, Sutherland GR, Shaffer LG. Chromosome abnormalities and genetic counseling. 4th ed. USA: Oxford University Press; 2012. 364 p.
 39. Yip MY. Uniparental disomy in Robertsonian translocations: strategies for uniparental disomy testing. *Trans Pediatr*. 2014;3(2):98-107.

40. Palmer CG, Schwartz S, Hodes M. Transmission of a balanced homologous t (22q; 22q) translocation from mother to normal daughter. Clin Genet. 1980;17(6):418-22.
41. Kirkels VG, Hustinx TW, Scheres JM. Habitual abortion and translocation (22q;22q): unexpected transmission from a mother to her phenotypically normal daughter. Clin Genet. 1980;18(6):456-61.
42. Schinzel AA, Basaran S, Bernasconi F, Karaman B, Yüksel-Apak M, Robinson W. Maternal uniparental disomy 22 has no impact on the phenotype. Am J Hum Genet 1994;54(1):21-4.
43. Donnai D. NICHD conference. Robertsonian translocations: clues to imprinting. Am J Med Genet. 1993;46(6):681-2.