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Association of Pericentric Inversion of Chromosome 9 (inv[9][p11q13]) and Genetic Diseases: Case Report

Etem Akbas, PhD,[1] Hicran Senli, MSc,[1] Olgu Hallioglu, MD, PhD,[2] Selim Batmaz, MD,[2] Nazan Eras Erdogan, MD[1]

([1]Department of Medical Biology and Genetics, and [2]Department of Child Health and Diseases, Faculty of Medicine, University of Mersin, Mersin, Turkey)

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Abstract

Pericentric inversion in heterochromatic region of chromosome 9 (inv[9]) is a common (1–3%) heteromorphism in the general population. It has probably evolved through breakage and reunion and is retained through mendelian inheritance without any apparent phenotypic consequences. Despite being categorized as a minor chromosomal rearrangement, which does not correlate with abnormal phenotypes, many reports in the literature raised conflicting views regarding the association with subfertility and recurrent abortions, abnormal clinical conditions, as well as chromosomal abnormalities due to the possession of this inversion. In our study, the significance of the inv(9) and the genetic counseling process was discussed in view of the literature. The possible significance of this inversion is interviewed.

Chromosome inversions are a relatively common structural alteration. There are 2 types of inversions. If both breakpoints are on the same side of the centromere, the inversion is paracentric; if they are on both sides of the centromere, then it is pericentric inversion.[1] Pericentric inversion in the heterochromatic region of chromosome 9 has been recognized as a normal variant, generally without phenotypic effect.[1] It is not clear whether inv(9) is a normal variant or an abnormal karyotype.[2] Nevertheless, this heterochromatic variant is sometimes associated with increased chromosomal instability, congenital abnormalities, and cancer proneness.[1] Pericentric inversion of chromosome 9 (inv[9] [p11q13]) is the most common (1–3%) type of inversion in the general population.[3] Although inv(9)(p11–q13) has been regarded as a normal familial karyotype variant, it has also been reported in various human diseases, such as couples with congenital genital malformation, habitual abortus, mild growth retardation, malformations of the skull and facial (craniofacial) region, undescended testis, skeletal malformations, mental retardation, hermaphroditism, and/or cardiac defects.[4,5] In this study, we aimed to investigate the contribution of inv(9) (p11q13) to various human disease conditions.

Material and Methods

Case Presentation

The male proband was the first-born child of nonconsanguineous parents. The patient was a 17-month-old mentally retarded male. His physical examination showed a height of 76 cm and a weight of 7,000 g. His remarkable clinical findings were growth retardation, small head, synophrys, long philtrum, micrognathia, hypospadias, low hairline, high arched palate, micropenis, and cryptorchidism (**Image 1**).

Cytogenetic Study

For karyotyping of the patient, 5 mL peripheral blood sample was drawn into heparinized injector. Cytogenetic analysis of 72-hour PHA-stimulated cultures of peripheral blood lymphocytes and GTG-banding was performed using standard protocols.[6,7] The preparations were examined using light microscopes. Twenty metaphase plaques were evaluated. The chromosomal abnormalities were reported according to the International System for Human Cytogenetic Nomenclature (ISCN) 2005. Cytogenetic analysis of the proband revealed inversion 9 homozyosity and the karyotype was 46,XY, inv (9) (p11q13) (**Figure 1 and 2**).

Discussion

Chromosome abnormalities are responsible for at least half of spontaneous abortions or miscarriages and are an important cause of congenital malformations.[8–10]

The prevalence of chromosomal abnormalities is 13.8% in the general population.[11] In different studies, the rates varied between 5.2% and 13.4%.[12-14]

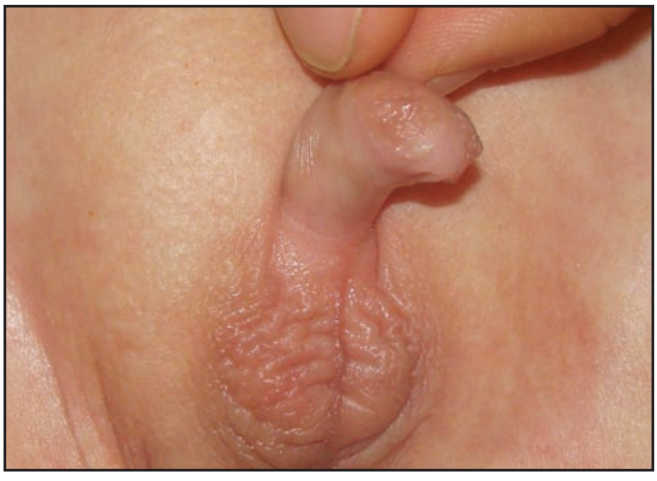

Image 1_Micropenis and cryptorchidism.

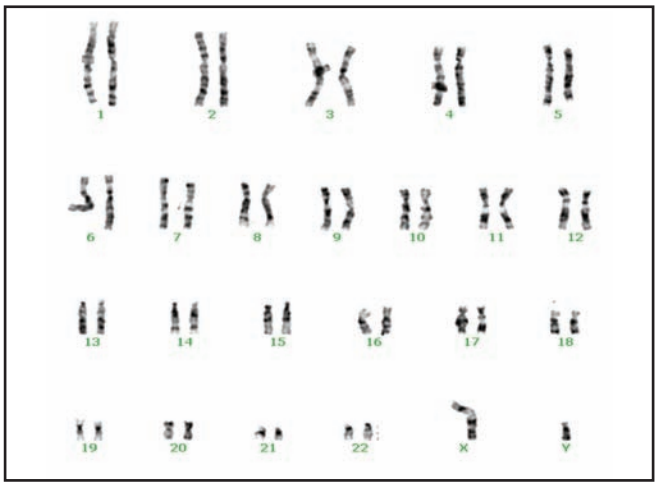

Figure 1_Karyotype of child with inv (9) (p11q13).

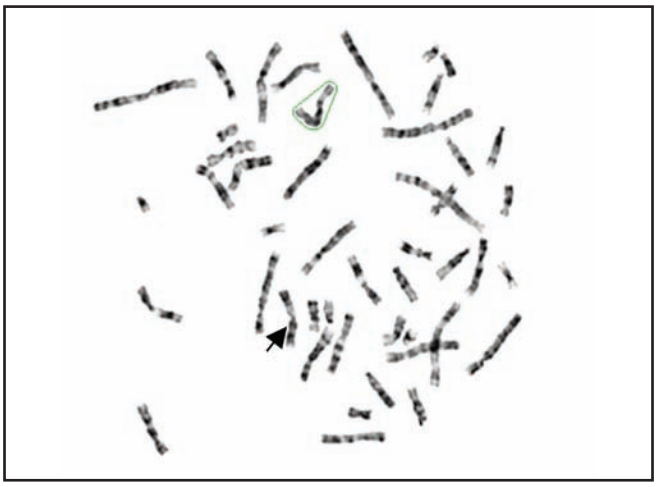

Figure 2_Metaphase plaque of child with inv (9) (p11q13).

More than 0.5% of newborns have significant abnormalities of autosomes or sex chromosomes.[15] Among these, the most common and best known chromosomal alteration is inversion 9. Chromosome 9 represents with the highest degree of morphological varations. The mechanisms of origin of inversions 9 are highly complex.[16] The inv(9) is believed to be a frequent occurrence in the general population and inherited in a Mendelian fashion.[17] Pericentric inversion of chromosome 9 in a heterozygous condition is a commonly observed structural variation in the human population. The clinical features of the case with pericentric inv (9) were variable from the normal to the multiple malformations.[18] Also, the inv(9) reported to be associated with infertility and congenital anomalies.[19-21] The correlation of inv(9) with clinical features of children with dysmorphic features (**Image 2**) revealed that most of the children had facial dysmorphism, abnormal phenotype, and delayed milestones. This suggests the unbalanced inversions at different breakpoint regions might have a role in the abnormal phenotype development. In the present study, our patient had several abnormal features as described in the clinical findings.

It has been reported that various abnormalities appeared in individuals who have pericentric inversion 9. In 2.3% of the couples with a history of recurrent spontaneous miscarriages, pericentric inversion of chromosome 9 was detected.[22] Nevertheless, most of the cytogeneticists believe there is only 1 kind of breakpoint (p11q12) on the inversions of chromosome 9, which has no known deteriorated effect on carriers and does not appear to be associated with a significant risk of miscarriage or unbalanced offspring. It is, therefore, generally considered as a normal chromosome variant. It has been suggested that phenotypes of inversion 9 may vary depending on the location of breakpoints.[23]

During the breakage reunion process there may be a change of suppression or deletion of euchromatic sequences, which might cause abnormal development. Hence, there is a need to study each breakpoint region of inv (9) using molecular cytogenetic probes and molecular biology methods to understand the disease association.

Conclusion

The parental chromosomal analysis is important for appropriate genetic counseling. Further investigations of inv(9) with sufficient samples are necessary in order to assess the certain correlation. LM

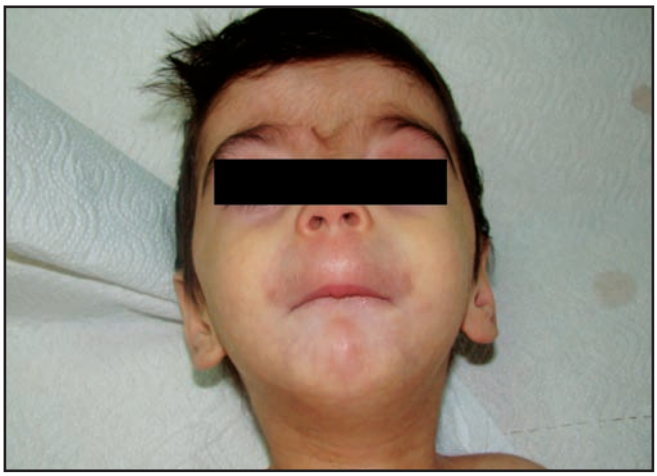

Image 2_Dysmorphic face appearance.

1. Ait-Allah AS, Ming PML, Salem HT, et al. The clinical importance of pericentric inversion of chromosome 9 in prenatal diagnosis. *J Matern Fetal Invest.* 1997;7:126–128.
2. Ceylan G, Ceylan C, Yuce H. A rare seen case with homozygosity for pericentric inversion of chromosome 9 and primary infertility. *The American Journal of Case Report.* 2008;9:385–388.
3. Tural S, Günes S, Kara N, et al. A case of habitual abortus karyotyped 46, XX, Inv (9) (p11q13) X2 with Inv 9 (p11q13) in both of homolog chromosome pairs. *Turkiye Klinikleri J Gynecol Obst.* 2007;17:331–333.
4. Lourenço GJ, Silva PMR, Bognone RAV, et al. Inherited pericentric inversion of chromosome 9 in acquired hematological disorders. *Ann Hematol.* 2007;86:465–467.
5. Ramegowda S, Savitha MR, Krishnamurthy B, et al. Association between pericentric inversion in chromosome 9 and congenital heart defects. *Int J Hum Genet.* 2007;7:241–248.
6. Akbas E, Mutluhan H, Savasoglu K, et al. Turner syndrome and 45,X/47,XXX mosaicism. *Genet Couns.* 2009;20:141–6.
7. Akbas E, Soylemez F, Savasoglu K, et al. A male case with double aneuploidy (48,XXY,+21). *Genet Couns.* 2008;19(1):59–63.

8. Rimoni DL, Connor JM, Pyeritz RE, et al. *Principles and Medical Genetics*. Vol. 1. 6th ed. Edinburgh, Scotland: Churchill Livingstone; 2002.
9. Hook EB. Prevalence risks and recurrence. In: Brock DJ, Rodeck CH, Ferguson-Smith, eds. *Prenatal Diagnosis and Screening.* Edinburgh, Scotland: Churchill Livingstone; 1992:351.
10. Tolmie JL. Chromosome disorders. In: Whittle MJ, Conner JM, eds. *Prenatal Diagnosis in Obstetric Practice.* Oxford, UK: Blackwell Scientific; 1995:34.
11. Düzcan F, Atmaca M, Cetin GO, et al. Cytogenetic studies in patients with reproductive failure. *Acta Obstet Gynecol Scand.* 2003;82:53–56.
12. Lissitsina J, Mikelsaar R, Punab M. Cytogenetic analyses in infertile men. *Arch Androl.* 2006;52:91–95.
13. Pina-Neto JM, Carrara RC, Bisinella R, et al. Somatic cytogenetic and azoospermi a factor gene micro deletion studies in infertile men. *Braz J Med Biol Res.* 2006;39:555–561.
14. Nagvenkar P, Desai K, Hinduja I, et al. Chromosomal studies in infertile men with oligozoospermi a and non-obstructive azoospermia. *Indian J Med Res.* 2005;122:34–42.
15. Queisser-Luft A, Stolz G, Wiesel A, et al. Malformations in newborn: Results based on 30,940 infants and fetuses from Mainz congenital birth defect monitoring system. *Arch Gynecol Obstet.* 2002;266:163–167.
16. Verma RS. A reply: Pericentric inversion of chromosome 9qh are real but the mechanisms of their origin are highly complex. 1999;105:183–184.
17. Luke S, Verma RS, Conte RA, et al. Molecular characterization of the secondary constriction region (qh) of human chromosome 9 with pericentric inversion. *J Cell Sci.* 1992;103:919–923.
18. Sudha T, Jayam S. Pericentric inversion in homologues of chromosome 9. *Jpn J Hum Genet.* 1993;38(3):341–343.
19. Thomas IM. Cytogenetic basis of recurrent abortions. *Perinatology.* 1999;1:181–187.
20. Davolos IP, Rivas F, Ramos AL, et al. Inv(9)(p24q13) in three sterile brothers. *Ann Genet.* 2000;43:51–54.
21. Nagvenkar P, Desai K, Hinduja I, et al. Comparison of the sperm aneuploidy rate in severe oligozoospermic and oligozoospermic men and its relation to intracytoplasmic sperm injection outcome. *Indian J Med Res.* 2005;122:34–42.
22. Sasiadek M, Haus O, Lukasik-Majchrowska M, et al. Cytogenetic analysis in couples with spontaneous abortions. *Ginekol Pol.* 1997;68:248–252.
23. Lee KB, Kunugi H, Nanko S. Familial schizophrenia with pericentric inversion of chromosome 9: A case report. *Schizophr Res.* 1998;32:123–126.