Prenatal diagnosis of de novo pericentric inversion INV(2)(p11.2z13)

Article *in* Genetic counseling (Geneva, Switzerland) · September 2015

CITATIONS
0

READS
597

6 authors, including:

Sezin Yakut
Akdeniz University
34 PUBLICATIONS **156** CITATIONS
SEE PROFILE

Zafer Cetin
SANKO University Faculty of Medicine
59 PUBLICATIONS **343** CITATIONS
SEE PROFILE

Cem Sanhal
Akdeniz University
64 PUBLICATIONS **244** CITATIONS
SEE PROFILE

Busra Karaman
Fairleigh Dickinson University
2 PUBLICATIONS **6** CITATIONS
SEE PROFILE

PRENATAL DIAGNOSIS OF *DE NOVO* PERICENTRIC INVERSION INV(2)(p11.2z13)

BY S. YAKUT [1], Z. CETIN [2], C. SANHAL [3], B. KARAMAN [4], I. MENDILCIOGLU [3] AND S.B. KARAUZUM [1]

Summary: *Prenatal diagnosis of de novo pericentric inversion inv(2)(p11.2q13):* We here report a prenatal case with *de novo* pericentric inversion inv(2)(p11.2q13). A 20-years-old G1P0 woman was referred for amniocentesis at 17 weeks of gestation, because of a positive second trimester screening test for aneuploidy. A *de novo* pericentric inversion inv(2)(p11.2q13) was detected during conventional cytogenetic analysis. Array-CGH analysis of the fetus showed no subtle chromosomal imbalances at the breakpoints. Genetic counseling was given to the family and the family decided to continue the pregnancy. To our knowledge, our case is the third prenatally detected *de novo* case with inv(2)(p11.2q13), and also the first case in which molecular karyotyping analysis were also applied.

Key-words: Pericentric inversion 2 – inv(2)(p11.2q13) – *De novo* – Prenatal diagnosis – Genetic counseling.

INTRODUCTION

Pericentric inversion is a chromosomal rearrangement in which the breakpoints occur on both arms of a chromosome resulting an inverted segment spans the centromere. Pericentric inversions of chromosome 2 are common, accounting for 14% of all pericentric inversions and in over half of the breakpoints located at the p11.2 and q13 (7). The incidence is 1/11, 680 in newborn infants (6). Familial inv(2)(p11.2q13) inversion is not associated with particular problems including mental retardation and/or congenital abnormalities but increased risk for carriers of pericentric inv(2)(p11.2q13) inversion for spontaneous abortions twice that of the general population (3). *De novo* inversion inv(2)(p11.2q13) is a very rare chromosomal rearrangement and has an empiric risk of multiple congenital abnormalities and mental problems of 6.7% (19).
In this report, we present a prenatal case with *de novo* inv(2)(p11.2q13) in which breakpoints were analysed for a possible microdeletion at these regions by array-CGH analysis.

(1) Akdeniz University, School of Medicine, Department of Medical Biology and Genetics, Antalya, Turkey.

(2) SANKO University, School of Medicine, Department of Medical Biology, Gaziantep, Turkey.

(3) Akdeniz University, School of Medicine, Department of Obstetrics and Gynaecology, Antalya, Turkey.

(4) Istanbul University, Pediatric Health Institute, Department of Medical Genetics, Istanbul, Turkey.

CASE REPORT

A 20-years-old G1P0 woman was referred for amniocentesis at 17 weeks of gestation, because of a positive second trimester screening test for aneuploidy. The patient's and her husband's personal and family histories were unremarkable, and the marriage was non-consanguineous. After amniocentesis, metaphase plates of amniocytes were obtained using standard, long-term cell culture procedures in two different flasks each containing different media. The chromosomes of the parents were obtained from standard, short-term cultures of lymphocytes. Metaphase chromosomes of the fetus, mother and father were banded with GTG banding. At least 20 GTG banded metaphases were analyzed at 550 band level from each subject. Cytogenetic analyses of the fetal chromosomes revealed a female karyotype with pericentric inversion inv(2)(p11.2q13) (Fig. 1). Parental karyotypes were found to be normal which suggested that chromosomal rearrangement is *de novo*. Array-CGH analysis of DNA samples extracted from amniocytes, excluded possible copy number alterations at inversion breakpoints. Sample was labelled with Cy3 and Cy5 using a NimbleGen Dual Colour DNA Labelling kit (Roche NimbleGen, Madison, WI, USA) according to the manufacturer's instructions. Genomic DNA was hybridised to NimbleGen human CGH 3x1.4MWG arrays (Roche NimbleGen) and this array was washed post hybridisation according to the manufacturer's instructions. Array was scanned using a NimbleGen MS 200 scanner and analyzed in a Nexus Copy Number v7.0 (BioDiscovery,

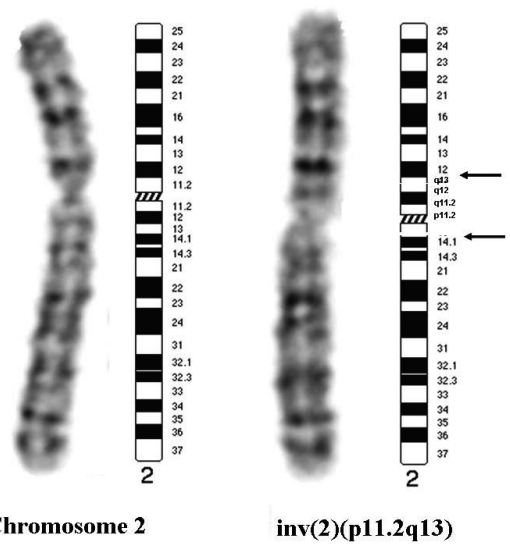

Figure 1:
GTG- banding and figure profile partial karyotype of the fetus.

Inc., El Segundo, CA, USA), using the Rank Segmentation algorithm at default settings. Changes in test DNA copy number at a specific locus were observed as the deviation of the $\log_2$ ratio value from the value of +/- 0.5 of at least three consecutive probes. Copy number changes identified in the samples were compared with the Database of Genomic Variants (http://projects.tcag.ca/variation/) and also visualized using the UCSC Genome Browser website (http://genome.ucsc.edu/). The positions of oligomers referred to the Human Genome April 2009 assembly (hg19). Array-CGH analysis of the fetus showed no subtle chromosomal changes. In addition, second trimester ultrasound for abnormality screening revealed normal findings. The couple decided to continue the pregnancy after our genetic counselling. Finally, a term healthy 3230 gr female baby was born and doing well without any congenital and neurologic abnormalities at the fourth month of age.

DISCUSSION

The pericentric inversions including chromosomes 1, 9 and 16 which have the breakpoints in repetitive, non-coding centromeric sequences, are considered as insignificant heteromorphisms (12, 14, 17). Also, some pericentric inversions with euchromatic breakpoints including inv(2)(p11.2q13) are often thought to be clinically insignificant, or it is believed that this chromosomal rearrangement does not cause an abnormal phenotype because they are considered balanced chromosomal rearrangements. This inversion is commonly inherited and is clinically benign when segregating within pedigrees (11).

However, it has been hypothesized that there could be a possible risk of an abnormal phenotype arising from the disruption of a dosage sensitive or regulatory gene(s) at the breakpoints (9). There are two published cases which have unbalanced chromosomal abnormalities raising from parental inversion carrier. One had interstitial deletion of chromosome 2p12 (10), the other one had direct duplication of chromosome 2p12p21 (13). These subtle chromosomal imbalances at breakpoints may not be detected by conventional chromosome analysis due to the low resolutions of the chromosomes (15). Recently, array-CGH analysis which detect chromosomal imbalances explain the molecular etiology of a large portion of individuals who are phenotypically abnormal but have apparently balanced chromosome rearrangements by conventional cytogenetic analysis (1, 2, 4, 8, 16).

The *de novo* pericentric inv(2)(p11.2q13) is very rare and to our knowledge, only two prenatal cases were published. One of them was delivered vaginally at 39.2 weeks and was apparently normal at birth and at

a routine six-week follow-up. The other case was an aborted fetus without abnormalities at autopsy (5, 18). Both of these cases with *de novo* inv(2)(p11.2q13) were detected by only conventional cytogenetic analysis. Our case is the third prenatal case with *de novo* inv(2)(p11.2q13) detected by conventional cytogenetic analysis. Inversion breakpoints were not evaluated by molecular karyotyping in previously reported *de novo* cases with inv(2)(p11.2q13). Our case is the first instance with prenatally detected *de novo* case with inv(2)(p11.2q13) in which molecular karyotyping analysis were applied.

According to our results; these analyses illustrate the value and importance of the array-CGH technique in delineating subtle chromosome rearrangements that are beyond the resolution of conventional karyotype analysis. Results from this type of analysis will assist family counseling in clinical genetics practice. Array-CGH analysis should be considered in cases with a *de novo* apparently balanced chromosome rearrangement by conventional cytogenetic analysis.

ACKNOWLEDGEMENTS

This study was supported by the Akdeniz University Scientific Research Project Management Foundation and by Scientific Research Project Management Foundation of SANKO University.

REFERENCES

1. *BAPTISTA J., PRIGMORE E., GRIBBLE S.M., JACOBS P.A., CARTER N.P., CROLLA J.A.:* Molecular cytogenetic analyses of breakpoints in apparently balanced reciprocal translocations carried by phenotypically normal individuals. *Eur. J. Hum. Genet.,* 2005, *13,* 1205-1212.
2. *DE GREGORI M., PRAMPARO T., MEMO L., GIMELLI G., MESSA J., ROCCHI M., PATRICELLI M.G., CICCONE R., GIORDA R., ZUFFARDI O.:* Direct duplication 12p11.21-p13.31 mediated by segmental duplications: a new recurrent rearrangement? *Hum. Genet.,* 2005, *118,* 207-213.
3. *DJALALI M., STEINBACH P., BULLERDIEK J., HOLMES-SIEDLE M., VERSCHRAEGEN-SPAE M.R., SMITH A.:* The significance of pericentric inversions of chromosome 2. *Hum. Genet.,* 1986, *72,* 32-36.
4. *GRIBBLE S.M., PRIGMORE E., BURFORD D.C., PORTER K.M., NG B.L., DOUGLAS E.J., FIEGLER H., CARR P., KALAITZOPOULOS D., CLEGG S., SANDSTROM R., TEMPLE I.K., YOUINGS S.A., THOMAS N.S., DENNIS N.R., JACOBS P.A., CROLLA J.A., CARTER N.P.:* The complex nature of constitutional de novo apparently balanced translocations in patients presenting with abnormal phenotypes. *J. Med. Genet.,* 2005, *42,* 8-16.
5. *HYSERT M., BRUYÈRE H., CÔTÉ G.B., DAWSON A.J., DOLLING J.A., FETNI R., HRYNCHAK M., LAVOIE J., MCGOWAN-JORDAN J., TIHY F., DUNCAN A.M.:* Prenatal cytogenetic assessment and inv(2)(p11.2q13). *Prenat. Diagn.,* 2006, *26,* 810-813.
6. *JACOBS P.A., MELVILLE M., RATCLIFFE S., KEAY A.J., SYME J.:* A cytogenetic survey of 11,680 newborn infants. *Ann. Hum. Genet.,* 1974, *37,* 359-376.

7. *KAISER P.:* Pericentric inversions. Problems and significance for clinical genetics. *Hum. Genet.,* 1984, *68,* 1-47.

8. *KITSIOU-TZELI S., SISMANI C., KOUMBARIS G., IOANNIDES M., KANAVAKIS E., KOLIALEXI A., MAVROU A., TOULIATOU V., PATSALIS P.C.:* Distal del(4) (q33) syndrome: detailed clinical presentation and molecular description with array-CGH. *Eur. J. Med. Genet.,* 2008, *51,* 61-67.

9. *KURAHASHI H., EMANUEL B.S.:* Long AT-rich palindromes and the constitutional t(11;22) breakpoint. *Hum. Mol. Genet.,* 2001, *10,* 2605-2617.

10. *LACBAWAN F.L., WHITE B.J., ANGUIANO A., RIGDON D.T., BALL K.D., BROMAGE G.B., YANG X., DIFAZIO M.P., LEVIN S.W.:* Rare interstitial deletion (2)(p11.2p13) in a child with pericentric inversion (2)(p11.2q13) of paternal origin. *Am. J. Med. Genet.,* 1999, *87,* 139-142.

11. *MACDONALD I.M., COX D.M.:* Inversion of chromosome 2 (p11p13): frequency and implications for genetic counselling. *Hum. Genet.,* 1985, *69,* 281-283.

12. *MADAN K., BOBROW M.:* Structural variation in chromosome No 9. *Ann. Genet.,* 1974, *17,* 81-86.

13. *MAGEE A.C., HUMPHREYS M.W., MCKEE S., STEWART M., NEVIN N.C.:* De novo direct duplication 2 (p12->p21) with paternally inherited pericentric inversion 2p11.2 2q12.2. *Clin. Genet.,* 1998, *54,* 65-69.

14. *MULLER H., KLINGER H.P., GLASSER M.:* Chromosome polymorphism in a human newborn population. II. Potentials of polymorphic chromosome variants for characterizing the idiogram of an individual. *Cytogenet. Cell Genet.*, 1975, *15,* 239-255.

15. *PATSALIS P.C., EVANGELIDOU P., CHARALAMBOUS S., SISMANI C.:* Fluorescence in situ hybridization characterization of apparently balanced translocation reveals cryptic complex chromosomal rearrangements with unexpected level of complexity. *Eur. J. Hum. Genet.,* 2004, *12,* 647-653.

16. *ROSENBERG C., KNIJNENBURG J., BAKKER E., VIANNA-MORGANTE A.M., SLOOS W., OTTO P.A., KRIEK M., HANSSON K., KREPISCHI-SANTOS A.C., FIEGLER H., CARTER N.P., BIJLSMA E.K., VAN HAERINGEN A., SZUHAI K., TANKE H.J.:* Array-CGH detection of micro rearrangements in mentally retarded individuals: clinical significance of imbalances present both in affected children and normal parents. *J. Med. Genet.,* 2006, *43,* 180-186.

17. *TUUR S., KÄOSAAR M., MIKELSAAR A.V.:* 1q plus variants in a normal adult population (one with a pericentric inversion). *Humangenetik*, 1974, *24,* 217-220.

18. *VEJERSLEV L.O., FRIEDRICH U.:* Experiences with unexpected structural chromosome aberrations in prenatal diagnosis in a Danish series. *Prenat. Diagn.,* 1984, *4*, 181-186.

19. *WARBURTON D.:* De novo balanced chromosome rearrangements and extra marker chromosomes identified at prenatal diagnosis: clinical significance and distribution of breakpoints. *Am. J. Hum. Genet.*, 1991, *49,* 995-1013.

ADDRESS FOR CORRESPONDENCE:

Ass. Prof. Dr. Sezin Yakut
Akdeniz University
Faculty of Medicine
Department of Medical Biology and Genetics
07070, Antalya, Turkey.
Tel: +90 242 249 69 70; Fax : +90 242 227 44 82
E-mail: sezinyakut@yahoo.com