Journal of Sciences, Islamic Republic of Iran 23(3): 213-217 (2012) http://jsciences.ut.ac.ir
University of Tehran, ISSN 1016-1104

Chromosomal Abnormalities in Regions 8q22 and 13q32 Associated with Different Disorders in an Iranian Family

N. Nouri,[1,2] P. Karimi,[3] N. Nouri,[4] A. Izaditabar,[1]
M. Salehi,[1,3,5,*] and M.R. Noori-Daloii[6]

[1]*Medical Genetics Laboratory, Alzahra University Hospital, Medical Sciences University of Isfahan, Isfahan, Islamic Republic of Iran*
[2]*Pediatric Inherited Disease Research Center (PIDRC), Medical Sciences University of Isfahan, Isfahan, Islamic Republic of Iran*
[3]*Division of Genetics, Department of Biomedical Sciences, Medical School, Medical Sciences University of Isfahan, Isfahan, Islamic Republic of Iran*
[4]*Tohid Genetic Counseling Center, Isfahan, Islamic Republic of Iran*
[5]*Medical Genetics Center of Genome, Isfahan, Islamic Republic of Iran*
[6]*Department of Medical Genetics, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran*

Received: 4 July 2012 / Revised: 2 September 2012 / Accepted: 11 September 2012

Abstract

Chromosomal abnormalities are major causes of infertility, miscarriage and birth of handicapped progeny. In human live births, the prevalence of a chromosome aberration is ~0.5% and, of these, 0.1–0.3% correspond to structural chromosome rearrangements such as translocations, inversions, insertions and deletions .Our proband is an infant who had died 4 hours after birth due to a variety of abnormalities. Her parents referred to counseling centerfor their next pregnancy. The parents were clinically normal but there was some noticeable history of diseases in their familial pedigree. Combination of the infant's phenotypes and the family pedigree history, made chromosomal abnormality as a possible diagnosis. Cytogenetic analysis was performed on parents of the dead infant, proceeded with the chromosomal analysis of maternal grandparents of the infant. The man had a normal karyotype but the woman's karyotype was [46, XX, t (8:13) (q22:q32), add (15) (p.s)] which had inherited from her parents. This is the first report of rearrangement in region 8q22 and 13q23. This is a novel study due to the chromosomal bands are involved in translocation between chromosome 8 and 13. Moreover, the addition in chromosome 15 is a noticeable feature that its probable role in infant's abnormalities should be considered.

Keywords: Chromosomal abnormalities; GTG-banding; karyotype; (8:13)(q22;q32) rearrangement; Reciprocal translocation

Introduction

A chromosome translocation is an abnormality caused by rearrangement of one or more parts between nonhomologous chromosomes. There are two main types including reciprocal (also known as non-

* Corresponding author, Tel.: +98(311)6287617, Fax: +98(311)6684510, E-mail: m_salehi@med.mui.ac.ir

robertsonian) and robertsonian (this rearrangement involves two acrocentric chromosomes that fuse near the centromere region with loss of the short arms). Translocations can be balanced in an even exchange of material with no genetic information extra or missing, and ideally full functionality or unbalanced where the exchange of chromosome material is unequal resulting in extra or missing gene [1, 2].

About 3% of live-born infants have genetically congenital anomalies. Over 50% of first trimester spontaneous abortions may have chromosomal abnormalities. Also congenital anomaliea are responsible for 20% to 25% of perinatal deaths [3]. Among these anomalies, reciprocal translocations incidence range from about 1 in 500 [4] to 1 in 625 human newborns [5]. Carriers of reciprocal translocations experience difficulty in achieving pregnancy. They deal with frequently spontaneous abortions and high risk of delivering phenotypically abnormal offspring [6]. Due to problems of reciprocal translocation carriers, it is important that these abnormalities can be diagnosed before infant's birth. To reach this purpose genetic consoling is the best way for detection abnormalities and prevents future difficulties.

Carriers of balanced reciprocal translocation are phenotypically normal but they can produce 32 types of gametes, just two of which would result in a chromosomally normal child, one having normal chromosomes and the other carrying the balanced form of the translocation, however other modes will lead to imbalanced forms [6,7]. It has been proven that the frequencies of alternate and adjacent-1 forms of segregations are similar but the frequencies of adjacent-2 and 3:1 products are different in male and female carriers. Also empiric data showed that 3:1 segregation has greater incidence in females than males [4] and just this form leads to viable outcomes [7]. On the other hand studies showed that adjacent-1 is the most frequent mode of segregation leads to imbalance [8] and causes partial monosomy and partial trisomy.

One type of reciprocal translocation can occur between chromosomes8 and 13, in which one form of zygotes has partial trisomy of chromosome8 and partial monosomy of chromosome13 or vice versa. In this rare chromosomal disorder there are 3 copies of part of one chromosome and the long arm or short arm of other chromosome is deleted resulting in various physical, neurological and developmental abnormalities. The type and severity of symptoms is determined by the amount and location of genetic material that is deleted and duplicated [9].

Another chromosomal rearrangement is a polymorphic variation of satellites in the 15 'p' arm (15ps+) which the satellites on one homologue of chromosome 15 were enlarged [10]. Some researchers believe that these polymorphic satellites which termed as minor variations neither produce an abnormal phenotype in the hosts nor increase their risk of producing abnormal offspring [11]. On the other hand some researchers by performing special studies conclude that there is considerable polymorphism of heterochromatic regions that appears to be dependent on sex and connected with origin of some pathologic conditions [12].

Materials and Methods

Case Report

A family with history of an infant's death was referred to our counseling center, Iran, Isfahan in 2011 for next pregnancy. Their infant, who was the first child of the family, had died 4 hours after birth because of different anomalies. The parents had a 3 degree consanguineous marriage. The father was 26years old and the mother was 25 at the time of the baby's birth. Results of three-dimensional ultrasound at 32 weeks had shown a female fetus with 1790 gr weight, which had club foot in right and left feet and shortness in left leg, cleft palate and deformity features in face, hydronephrosis in both kidneys and polyhydramnios; however the fetus heart, upper extremity and vertebral column were normal. The parents were clinically normal but there was some noticeable history in their familial pedigree. Interestingly precedent of miscarriage, stillbirth and infertility was observed in 4 generations of the proband familial pedigree (Fig. 1). Combination of the infant's phenotypes and the family pedigree history, made chromosomal abnormality as a possible diagnosis.

Unfortunately cytogenetic analysis on the infant (IV-3) was not possible because she was dead already, so cytogenetic analysis was performed on parents of the dead infant (III-3 and III-4) and after getting the result it proceeded with chromosomal analysis of maternal grandparents of the infant (II-4 and II-5).

Fresh heparinated blood from II-4, II-5, III-3 and III-4 individuals was obtained by venipuncture. Blood samples were cultured 3 days at 37°C in RPMI 1640 (Bahar Afshan, iran) medium supplemented with 20% fetal calf serum (Bioidea, iran) and Phytohemaglutinin, (invitrogen, USA). Colcemid (invitrogen, USA) was added 30 minutes prior to harvesting, cells were suspended in 0.075 M KCI (Merck, Germany) for 20 min at 37°C and finally fixed in a 3:1 methanol (Merck, Germany)/glacial acetic acid (Merck, Germany)

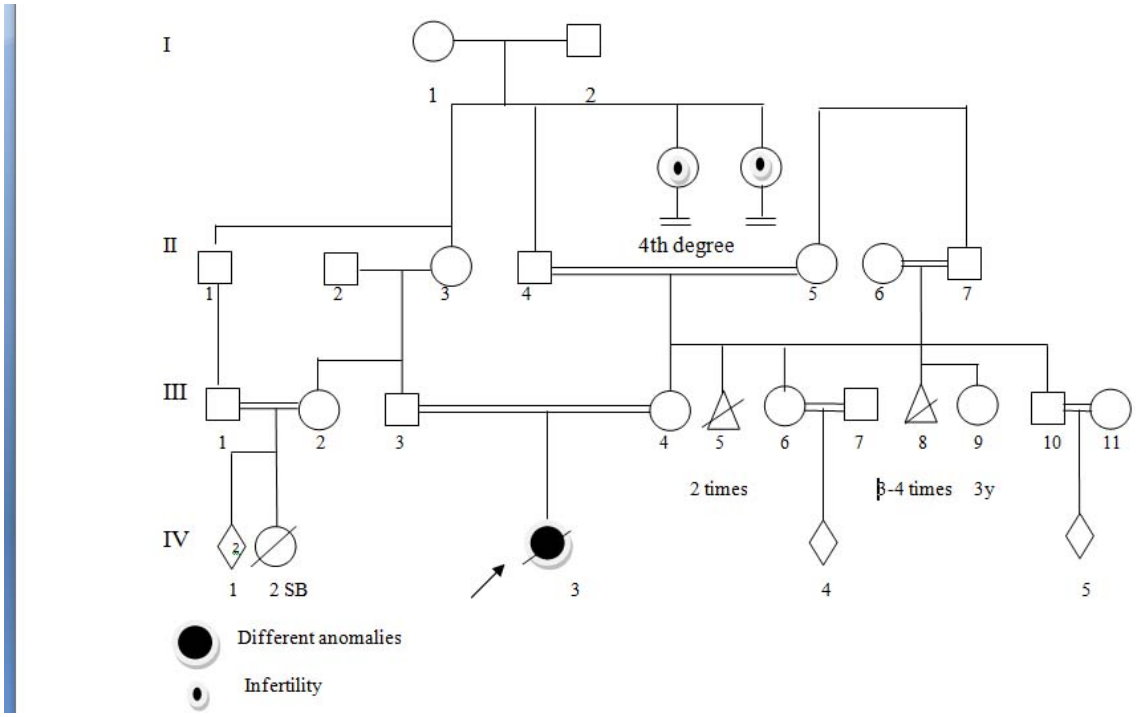


Figure 1. Family pedigree of an infant who had been affected by variety of abnormalities and died shortly after birth.

solution. Slides were prepared the following day, airdried, aged in a 60°C oven for 48 hr, and stored. The specimens were routinely analyzed with trypsin (invitrogen, USA) G-banding, in addition to conventional Giemsa (Merck, Germany) staining (solid staining).

Result

Karyotyping results of the infant father(III-3) was normal but mother (III-4) was carrier of a balanced reciprocal translocation 8/13 and a polymorphic variation of enlarged satellites in the 15 'p' arm (15ps+), so her karyotype ascertained as [46, XX, t (8; 13) (q22:q32), add (15) (p.s)].

The maternal grandmother (II-5) karyotype was [46, XX, rcp t (8; 13) (q22:q32)] and maternal grandfather (II-4) karyotype was [46, XY, add (15) (p.s)] (Fig. 2). The infant's mother has inherited both of these anomalies from her parents.

Discussion

Here we studied on a family with history of miscarriage, stillbirth and infertility in 4 generation of their familial pedigree. We found a reciprocal translocation between chromosomes8 and 13 and addition of chromosome15 in a woman in this family who had a dead infant, the translocation and addition were also seen in her mother and father respectively (Fig. 1).

There are Two opposing group of studies based on the approval and rejection of the influence of polymorphic satellites variations such as (15ps+) on phenotype abnormalities [11, 12]. Since of existence individuals in our pedigree who were carrier of (15ps+) addition with normal phenotype (II-3, III-4), it seems that polymorphic satellites variations neither produce an abnormal phenotype in the hosts (such as II-3 in pedigree) nor increase their risk of producing abnormal offspring (such as III-4 in pedigree) [11].

Different breakpoints have been reported in previous studies too [13-17] that in all of them the variety of symptoms depends on the exact location of breakpoints and the amount of genes that are disrupted. Abuelo et al. [13] studied on a 11 month-old daughter of a translocation carrier mother who was relatively indistinct and more resemble to case of dup (8) (q21 qter) rather than distal 13q deletion. Muncer et al. [14] reported a male newborn from an 8:13 translocation carrier mother died 72 hours after birth and presented unusual face, choanal atresia, a cardiac defect, hypospadias, broad thumbs and big toes and a TE fistula. This case showed dup (8q) = dup (8) (q11 qter). In another study by Brocker-Vriends [15] two members

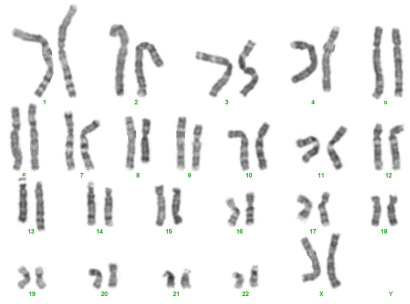
of a family with history of translocation (8: 13) (p21: q22) showed a partial trisomy 8p with partial monosomy 13q and two others had partial monosomy 8p with partial trisomy 13q. There have been some cases who had died soon after birth or at age of 3 to11 months [16,17] that all of them had dup (8) (q21 qter). Another cases with this rearrangement (dup (8) (q21 qter)) had been reported to survived up to 4 years [18] and 6 years [19]. The spectrum of symptoms which these cases showed include major heart and renal disorders, intrauterine and postnatal growth retardation, prominent occiput, hypertelorism, a broad based nose, low-set ears, cleft palate, small mandible, short neck, cryptorchidism in males, hydronephrosis, campto and clinodactyly and overriding toes.

Some people with 8/13 translocation show features of specific kinds of disorders. For example translocation between 13q12 and 8p11 is a consistent cytogenetic abnormality seen in a nonspecific myeloproliferative disorder that is associated with T-cell leukemia/ lymphoma and peripheral blood eosinophilia [20]. Another example is Pediatric lipoma with unknown etiology. A lipoma case with an apparently balanced translocation involving chromosomes 8 and 13 (t (8; 13) (q21; q22)) detected by routine cytogenetic analysis and small deletions on 5q21.1 and 8q21.11 detected by array comparative genetic hybridization has been reported [21].

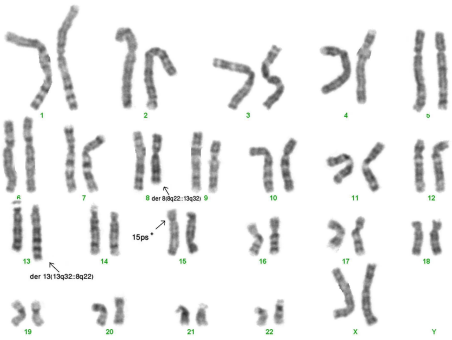
A child with 46, XY, der (13), t (8; 13) (p11.2; p12) karyotype has already been reported In Iran by Mahjoubi et al [9] that his mother had an apparently balanced translocation between chromosomes 8 and 13 and his father was normal. He had a variety of abnormalities include: facial features and development delay, cleft palate, skin laxity, congenital heart defects, aplasia of the corpus callosum and atrophy of cortex. The similarity of this study to ours is that in both of them mothers are carrier of translocation without any clinical abnormality and fathers are normal, also both of infants showed some similar abnormalities such as facial features, development delay, cleft palate, however the fetus heart, was normal in our study on contrary of the previous study, and in our study the translocation occurred between unique bands which haven't been reported before.

In our study, although there was no access to infant's sample because of her death before birth, regarding to clinical symptoms of dead infant during pregnancy and after birth and similarity of the symptoms to previous studies mentioned [9 and 13-17], her family pedigree and cytogenetic analysis results, partial trisomy of chromosome8 and partial monosomy of chromosome 13 is probable as cause of her anomalies. These monosomy

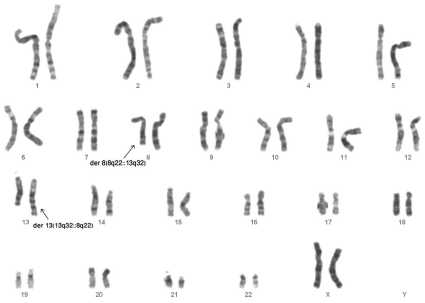
A)



B)



C)



D)

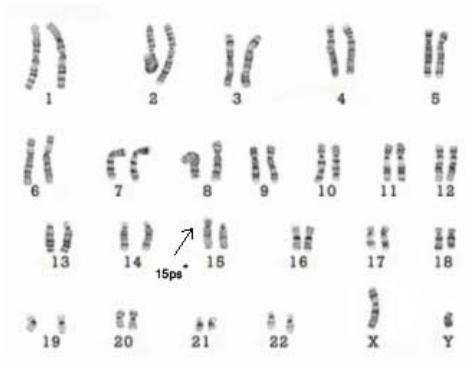


Figure 2. A) Karyotyping results of the father (III-3) that is normal. B) Karyotyping results of the mother (III-4) that is: [46, XX, t (8; 13) (q22:q32), add (15) (p.s)]. C) Karyotyping results of the maternal grandmother (II-5) karyotype was [46, XX, rcp t (8; 13) (q22:q32)] and D) Karyotyping results of the maternal grandfather (II-4) karyotype was [46, XY, add (15) (p.s)].

and trisomy disorders might be the reason of recurrent miscarriage, stillbirth and infertility in this pedigree. But again it wasn't possible to determine exactly which chromosome was partially duplicated and which one was partially deleted; although in previous studies, some similar rearrangements in chromosome 8 and 13 have been reported; this is the first time that rearrangement in region 8q22 and 13q32 has been observed [13-21].

Regarding to the infant's anomalies and her family problems, the genes are located in or around 8q22 and 13q32 chromosomal regions must be critical for maintaining the life and normal development. Studies on more individuals from different populations are necessary to understand the importance of the genes located in these areas.

References

1. Keify, F. Zhiyan, N. Mirzaei, F. Tootian, S. Ghazaey, S. and Abbaszadegan, M. R. Two Novel Familial Balanced Translocations t(8;11)(p23;q21) and t(6;16)(q26;p12) Implicated in Recurrent Spontaneous Abortion. Iranian Medicine **15**: 249-252 (2012).
2. Akbas, H. Koksal, O. Konca, C. Balkan, M. and Budak, T. Familial Balanced Reciprocal Translocation [t(16;22)(p11;q13)mat] in a Child With Constitutional Short Stature. Journal of Medical Cases **3**: 149-152 (2012).
3. Rodney-Arnold, K. M. and Self, Z. B. Genetic Screening and Counseling: Family Medicine Obstetrics. Prim Care Clin Office Pract. **39**: 55-70 (2012).
4. Ogilvie, C. M. and Scriven, P. N. Meiotic outcomes in reciprocal translocation carriers ascertained in 3-day human embryos. European Journal of Human Genetics **10**: 801-806 (2002).
5. Bonet, M. O. Navarro, J. Carrera, M. Egozcae, J. and Benet, J. Aneuploid and unbalanced translocation carriers: evaluation of the genetic risk. Mol. Hum. Reprod. **8:** 958-963 (2002).
6. Pujol, A. Benet, J. Staessen, C. Assche, E. V. Campillo, M. Egozcue, J. and Navarro, J. The importance of aneuploidy screening in reciprocal translocation carriers. Reproduction. **131**: 1025-1035 (2006).
7. Jalbert, P. Sele, B. and Jalbert, H. Reciprocal translocations: a way to predict the mode of imbalanced segregation by pachytene-diagram drawing. Hum Genet. **55**: 209-222 (1980).
8. Estop, A. M. Van Kirk, V. and Ceiply, K. Segregation analysis of four translocations, t(2;18), t(3;15), t(5;7), and t(10,12), by sperm chromosome studies and a review of the literature. Cytogenet. Cell. Genet. **70:** 60-67 (1995).
9. Mahjoubi, F. Totian, S. Kareeme, S. and Shafegatee, Y. Trisomy 8p (p11.2-pter) due to maternal translocation t (8; 13) (p11; p12) in a child with dysmorphic features. Indian J Hum. Genet. **11:** 111-113 (2005).
10. Dutta, S., Shaw, J. Sinha, S. and Mukhopadhyay, K. Chromosomal abnormalities associated with mental retardation in female subjects. Indian. J. Hum. Genet. **15**: 28–31(2009).
11. Tharapel, A. T. and Summitt, R. L. Minor chromosome variations and selected heteromorphisms in 200 unclassifiable mentally retarded patients and 200 normal controls. Hum. Genet. **41:** 121-130 (1978).
12. Mikelsaar, A. V. N. Käosaar, M. E. Tüür, S. J. Viikmaa, M. H. Talvik, T. A. and Lääts, J. Human karyotype polymorphism. Hum. Genet. **26:** 1-23 (1975).
13. Abuelo, D. Perl, D. P. Henkle, C. and Richardson, A. Partial trisomy8 (trisomy8q21 8qter). J. Med. Genet. **14:** 463-466 (1997).
14. Muncer, R. S. and Rennert, O. M. Partial trisomy 8q. Pediatr Res. **15:**566 (1981).
15. Bröcker-Vriends , A. H. van de Kamp, J. J. Geraedts, J. P. Bos, S. E. and Nijenhuis, T. A. Unbalanced karyotype with normal phenotype in a family with translocation (8; 13) (p21; q22). Clin. Genet. **27:** 487-95 (1985).
16. Sachs, E. S. and van Waveren, G. Phenotype of partial trisomy 8 (q21 qter) in two unrelated patients with de novo translocation. J. Med. Genet. **18:** 204-208 (1981).
17. Bredberg, A. Iselius, L. Lindgren, L. and Lundmark, K. M. Duplication of part of the long arm of chromosome8 due to a familial 8:13 translocation. Hereditas **96:** 105-108 (1982).
18. Soudek, D. Hunter, D. O'shaughnessy, S. Simpson, N. E. and Soudek, V. Familial translocation t(8:14) with a case of tertiary trisomy, +14q. Birth Defects OAS XIV. **6:** 309-315 (1978).
19. Fryns, J. P. Verresen, H. van den Berghe, H. van Kerckvoarde, J. and Cassiman, J. J. Partial trisomy 8: trisomy of the distal part of the long arm of chromosome No 8+ (8q2) in a severely retarded and malformed girl. Hum. Genet. **24:** 241-246 (1974).
20. Still, I. H. Chernova, O. Hurd, D. Stone, R. M. and Cowell, J. K. Molecular characterization of the t(8; 13)(p11;q12) translocation associated with an atypical myeloproliferative disorder: evidence for three discrete loci involved in myeloid leukemias on 8p11. Blood Journal **90:** 3136-3141(1997).
21. Jin, J. Niu, J. Kim, Y. M. Wang, X. Parham, D. Letton, R. Li, S. and Lee, J. Y. A novel t (8; 13) (q21; q22) translocation in a pediatric lipoma. Cancer. Genet. **204**: 629-33(2011).