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Constitutional Translocation t(11,22) in Slovak Romanies from the Prešov Region (Slovakia)

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ABSTRACT Three families with constitutional translocation t(11,22) with family occurence in balanced and unbalanced form was detected in Slovac Romanies from the Prešov region in 1990-2004. In probands and individual members of families variable fenotypical picture with different degree of mental retardation was detected. Cytogenetic examination of newborns with multiply development anomalies disclose their causal reason. It has its importance for prognosis of clinical course as well as for genetic counselling in this family. Detection of constitutional translocation t(11,22) in Romany population is part of population-genetic analysis of Romany ethnic.

INTRODUCTION

The constitutional t(11,22) translocation is the most common recurrent non-Robertsonian translocation in human (Edelmann et al., 1999). Usually has a family origin. The families most often have been ascertained through an abnormal child with the karyotype 47,XX or XY,+der(22)t (11,22)(q23,q11) (Armstrong et al., 2000). Patients with der(22) syndrome carry a supernumerary der(22) chromosome and are therefore trisomic for 11q23-qter and 22pter-q11. Clinical features of the der(22) syndrome include mental retardation, craniofacial abnormalities and congenital heart defects (Hill et al., 2000). This syndrome is due to 3:1 meiotic malsegregation of balanced translocation in meiosis (Kurahashi et al., 2000) (Fig. 1).

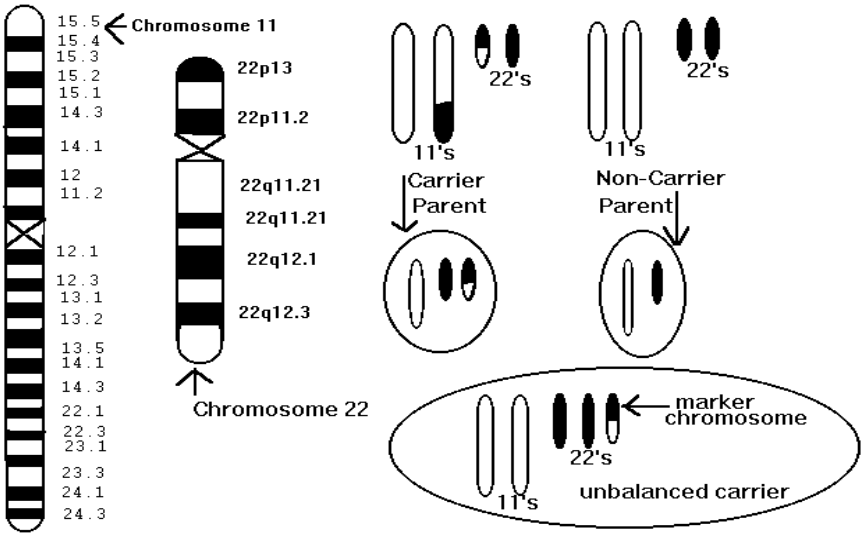

Fig. 1. Formation of supernumerary der(22) chromosome from balanced carrier of t(11,22)

Carriers of balanced translocations are in general consideration to be phenotypically normal. However, they have an increased risk of producing chromosomally unbalanced offspring. Efficient diagnostics of t(11,22) is important for children born to carriers of the translocation and for prenatal and pre-implantation diagnosis (Tapia-Paez et al., 2001).

Balanced translocations t(11,22) are hardly detecteble by conventional applied methods concernig on that chromosome analysis is routinelly performed in metaphase, translocated material on both chromosomes is G-band negative and included segments are very small.

MATERIAL AND METHODS

In the Prešov region in 1990-2004 four cases of translocation t(11,22) with family occurence in balanced and unbalanced form were detected. Three families were of Romany origin, two of them were congenial to each other. Eight carriers of the t(11,22) balanced translocation and two probands with the supernumerary der(22) syndrome were detected (Pedigree 1, Pedigree 2). Cytogenetic examination was performed from the peripheral blood samples according to standard procedures, G-banding methods, C-banding methods, cytogenetic analysis of metaphase chromosomes.

CASES REPORT

Family 1

The proband was the sixth child born to nonconsanguineous parents of Romany origin. In the time of conception father was 36 year old, mother was 34 year old. The child was born in the 40th week of gestation. The birth weight of the propositus was 2700g and length 46cm. He was noted at birth to have craniofacial stigmatization, mikropenis. Cytogenetic examination was indicated. Peripheral blood cytogenetic analysis revealed a 47,XY,+der(22)t(11,22)(q23,q12) karyotype. The karyotype of his mother showed a reciprocal translocation over the distal bands 11q23 and 22q11 and that of his father was 46,XY. Re-investigation of the proband at the age of 6 years did not show any progress in motor and mental development. Motor function was profoundly delayed and at the time of investigation he was unable to sit and walk. His anthropological parameters were on the level of the age of two.

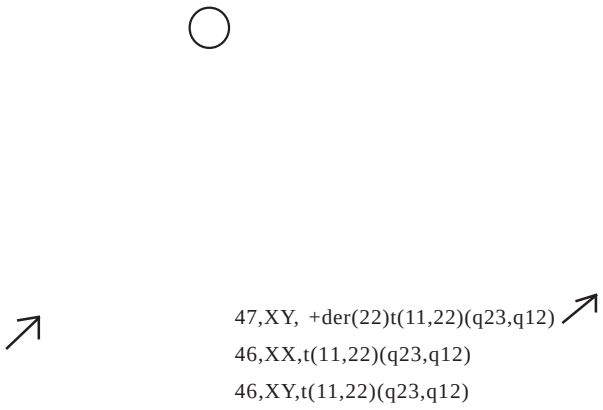

Fig. 2. Pedigree of family 3 with non balanced form of t(11,22) (q23,q13)

Fig. 3. Pedigree of family 1 and family 2 with translocation t(11,22) (q23,q12)

Family 2

The proband was a girl born in the 40th week of gestation to nonconsanguineous parents of Romany origin. In the time of conception father was 38 year old, mother was 33 year old. The proband´s birth weight was 3400g, her length was 48cm. The proband was investigated after birth, obvious of physical and mental retardation were present. She had a generalized mycosis. The head was microcephalic and dysmorphic. Clinical features included craniophacial dysmorphism, hypertonia and psychomotor retardation. Balanced translocation 46,XX,t(11,22)(q23,q12) was detected by banding studies in proband. Cytogenetic examination of proband´s father and two proband´s siblings diclosed identical findings of balanced rearrangements, in other two siblings normal karyotypes were detected. Mother´s karyotype was normal. She had two spontaneus abortions. Immunology examination of the family declosed laboratory autoimune syndrome without clinical marks of autoimune disease in the time of examination.

Family 3

The proband was born as the third child to consanguineous parents of Romany origin. Father in the time of conception was 25 year old, mother was 22 year old. Delivery was spontaneous in the 41th week of gestation, the proband´s birth weight was 2900g, birth length was 48cm, children was lived 48 hours. She was noted at birth to have evident craniophacial stigmatization, dolichocephaly, preauricular pits and tags, malformations and flexible contractions of hands and feet, congenital heart defects, aplasia kidney and hypoplasia of uterus. Cytogenetic analysis of peripheral blood cell chromosome showed an abnormal chromosome complement of 47,XX,+der(22)t(11,22)(q23,q13) in all cells analyzed. Chromosome analysis of peripheral blood in father revealed that he was a carrier of the translocation with the karyotype 46,XY,t(11,22)(q23,q11). Also in two siblings identical findings of balanced rearrangement were detected. The family was not available for immunology investigation.

DISCUSSION

The t(11,22) is the most common recurrent non-Robertsonian constitutional translocation in humans, having been reported in more than 160 unrelated families (Hill et.al., 2000).

The clinical findings in our probands with unbalanced karyotypes were variabile. Especially in the case of family 2 variable phenotypical picture of individual members with different degree of mental retardation was detected. Possible explanation is social mental retardation, submicroscopic changes or position effect. The proband from the last described family 3 had the breakpoints on the chromosome 22 located more distally and spectrum of malformations was so substantial that they were not compatible with life. The identification of the breakpoints on chromosomes 11 and 22 is therefore an important aid to our understanding the nature of these inherited defects. It is very important to know the location of moved piece of chromosomal material in order to make some general comparisions between individuals.

The translocation t(11,22) appears to occur in families with no common ancestry and a variety of racial and ethnic backgrounds and, additionally, familial heteromorphic variants of the derivative 22 have been described. The wide geographical distribution of the ascertained families suggests multifocal origin of this translocation (Koduru et al., 1988).

Common constitutional translocations, inversions and deletions indicate that there are prefereble chromosomal sites for recombination or rearragements in the human genome. Despite the fact that chromosome 22 represents only 1,9% of the haploid autosome length, numerous rearrangements of this chromosome have been associated with both a variety of malignant diseases and developmental abnormalities (Hill et al., 2000). Many clinically important diseases connected with translocations, duplications or deletions of 22q11-13 indicate that acting of this area on rearreagments and instability of chromosomes is not random. This part of chromosome 22 also harbors the site of the constitutional t(11,22)(q23,q11) translocation.

Balanced translocations, which there is not microscopically visible loss of genetic material accounting roughly 0,2% of structural abnormalities (Kurahashi et al., 2000). In cytogenetic laboratories, these anomalies are generally ascertained through unbalanced carriers or through patients attending for reproductive failure i.e. recurrent spontaneous abortions or male sterility.

Although balanced carriers for this translocation are normal it has been suggested that they may have a 10-fold increased risk of breast cancer (Hill et al., 2000). Non random chromosomal changes were described in connecting with multiple human equired and inherited diseases. Cytogenetic and molecular studies in human tumors dislosed non random equired rearrangements which have substancial account in etiology of tumorogenesis.

Geneticists have been interested in understanding the mechanisms and consequences of genomic rearrangements for a long time. Chromosomal rearrangements or translocation are the result of DNA rearrangements at the molecular level. Mechanisms by which their arrise are still unknown. To analyze the genome structure of the breakpoint the junction fragments from the der(11) and der (22) of the t(11,22) balanced carriers were cloned. The breakpoints of the t(11,22) have been identified within palindromic AT-rich repeats (PATRRs) on chromosomes 11 and 22, suggesting that hairpin cruciform structures mediate double strand breaks leading to the translocation. For futher characterizing of the mechanisms of translocation, identification of the precise location the translocation breakpoints is essential (Kurahashi et al., 2001). Several unrelated t(11,22) families demonstrate similar breakpoints on both chromosomes, indicating that their translocations are within the same palindrome. It is likely that the PATRRs produce unstable DNA structures in 22q11 and 11q23 that are responsible for the recurrent t(11,22) translocation (Kurahashi et al., 2000). Under-standing the molecular basis of this translocation may serve as a model for understanding the mechanisms involved in creating other translocations.

CONCLUSION

The t(11,22) is the only known recurrent, site specific, non-Robertsonian constitutional translocation in humans. Whereas balanced carriers have no clinical symptoms, severely affected offspring often demonstrate the supernumerary der(22)t(11,22) syndrome through 3:1 meiotic malsegregation of the balanced translocated chromosomes.

Analysis of chromosomes have wide aplication in clinical diagnostic as a specific diagnostic method of genetic examination. It is indicated especially in patients with congenital malformations, affected several organic systems, also in patients with mental retardation and accident of overall or gonadal development. In the case of finding of supernumerary chromosome likely to chromosome 22 (22q-) it is necessary always fairly examine parental´s chromosomes, especially chromosomes 11 and 22. Cytogenetic examination of newborns with multiply develovepment anomalies clarify their causal account. It has accident for prognosis of clinical course, as well as genetic counseling in these families.

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