FACTA UNIVERSITATIS
Series: **Medicine and Biology** Vol.10, No 3, 2003, pp. 127 - 130 UC 575.113:616-007.2

BALANCED TRANSLOCATION t(5;13)(q11;q12) IN A WOMAN WITH MALFORMED CHILD

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Summary. *A balanced translocation t(5;13)(q11;q12) in a phenotypically normal woman, whose first child had multiple malformations and died 13 days after birth, was discovered.*
The GTG-banding technique was used to define the breakpoints in the translocation – 5q11 and 13q12 which were different from the translocations between chromosomes 5 and 13 described in the literature. The translocation was hereditary and was present in the grandmother of the malformed child. The type of segregation 3:1 was established using FISH with probes for 5p and 13q14 on tissue sections of the died child. The cells showed 3 signals for 13q14 and 2 signals for 5p.

Key words: *Balanced reciprocal translocations, fetal abnormality, FISH, human cytogenetics*

Introduction

Couples in which one partner is a carrier of a balanced translocation have an increased risk of infertility, recurrent abortions and delivery of chromosomally abnormal offspring (1-5).

The reproductive potential is uncertain for carriers of balanced reciprocal translocations. Unbalanced chromosomal changes are the underlying cause of fetal malformations and disturbed viability. The birth of a malformed child is an indication for cytogenetic analysis of the parents.

Case report. A couple was referred for cytogenetic analysis because of delivery of a child with multiple malformations. The child was born 15 days before the pregnancy term with intrauterine developmental retardation (weight – 1950 g; height – 43 cm). Congenital heart defect has been diagnosed in the end of VIII m.l. After birth the following congenital malformations were revealed: cleft lip and cleft palate, trigonocephaly, dysmorphic ears, upslanting and short palpebral fissures, short neck with low hair line, hypospady, finger anomalies (hexadactyly of all limbs, syndactyly of the 5th and 6th fingers). The child died on the 13th day after birth. The suspect heart malformation was proved pathologically – common arterial trunk with hypertrophy of the left ventricle. Gastrointestinal anomalies were not detected.

The parents had no chronic disorders and were not exposed to industrial or other adversities.

The family history revealed two children (brothers of the mother of the investigated woman), deceased in the first year of life and two spontaneous abortions in relatives (II degree) of the same grandmother of the malformed child (Fig.1).

Results

Cytogenetic analysis. Cytogenetic study of the couple was performed on peripheral blood lymphocytes using standard GTG-banding.

The father had a normal karyotype 46,XY. The mother was found to be a carrier of balanced reciprocal translocation between chromosomes 5 and 13 with karyotype 46,XX, t(5;13)(q11;q12) (Fig. 2). The cytogenetic study

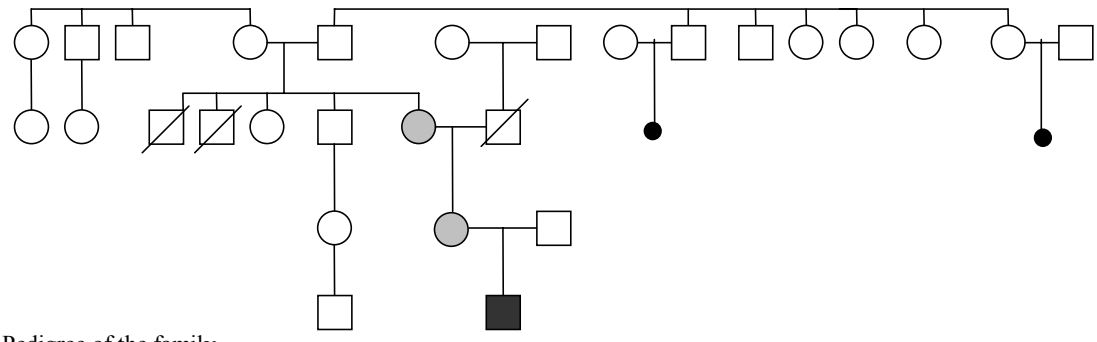

Fig. 1. Pedigree of the family
Healthy person, carrier of balanced translocation ■ Died child with malformations

revealed the same translocation t(5;13)(q11;q12) in the grandmother of the malformed child (Fig. 3). The reciprocal translocation was hereditary and meiotic imbalance was thought to be the cause for disturbed viability and mortality in the earliest period of the childhood.

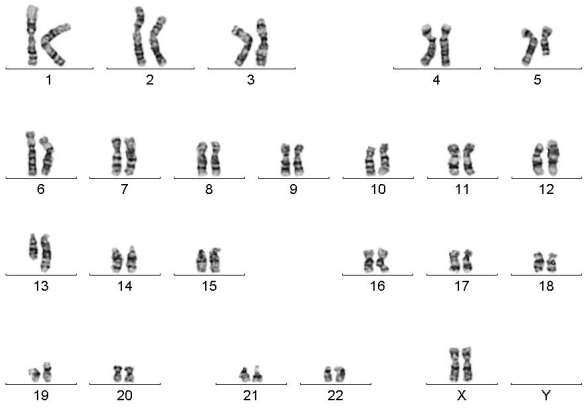

Fig. 2. Karyotype of the mother - 46,XX, t(5;13)(q11;q12)

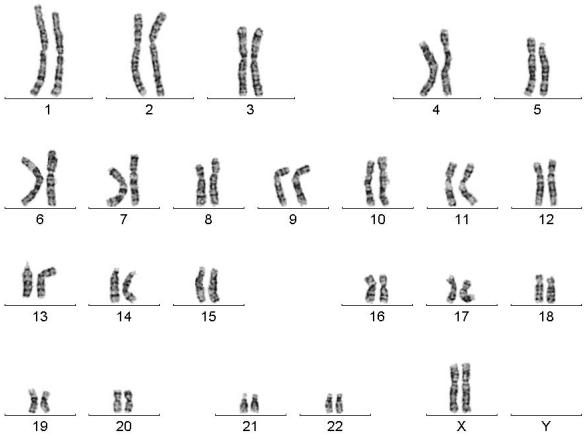

Fig. 3. Karyotype of the grandmother - 46,XX,t(5;13)(q11;q12)

A cytogenetic analysis of the malformed child was unsuccessful and no data about its karyotype was obtained.

Fluorescence in situ hybridization (FISH). We carried out a fluorescence in situ hybridization (FISH) with probes for 5p (directly labeled in Spectrum Green, Vysis) and for 13q14 (directly labeled in Spectrum Orange, Vysis) on necropsy tissue sections of the deceased child. FISH was performed separately for each probe (5p and 13q14) using standard protocol for formalin-fixed paraffin-embedded tissues. Large number of cells was analyzed to avoid confusing in charging of signals. Three signals were found for 13q14 and two - for 5p.

Discussion

Individuals who are carriers of balanced translocation usually appear completely normal and healthy but with reproductive problems: infertility, repeated miscarriages and malformative offspring (6,7). We found a carrier of balanced translocation t(5;13)(q11;q12).

The guidelines used to predict whether an aneuploid conceptus will be liveborn or aborted are just sketchy (8,9). There are findings that the size of the segments involved in interchanges is greater in couples with repetitive abortions than in couples with aneuploid liveborn infants. A review of the relevant literature has revealed few cases with participation of chromosome 5 in a reciprocal translocation with reproductive consequences (table 1) (10-17). Two cases with t(5;13) have been described so far - one with repeated spontaneous abortions – 46,XY,t(5;13)(q11;q21) and one with a liveborn girl with a less severe clinical course – 46,XX, t(5;13)(q35;q31) (16,17).

In our case new breakpoints were found, different from the ones reported in the two previous studies (16,17).

Since the karyotype of the dead child was not studied, we discuss all possible chromosomal abnormalities in it. If the egg has both translocated chromosomes the baby will be normal but will carry the same translocation as the mother – t(5;13)(q11;q12). If the egg has a

Table 1. List of balanced reciprocal translocations which involve chromosome 5, in couples who had either liveborn aneuploid child or spontaneous abortion

Couples with liveborn aneuploid Authors/Translocation	Couples with spontaneous abortions Authors/Translocation
Saadi and Moghadam (1976); t(5;7)(q35;q31)	Lucas et al. (1972); t(5;10)(q33;q11)
Bartsch-Sandhoff, Liersch (1977); t(5;8)(q33;p23)	Turleau et al. (1979); t(5;10)(q11;q26)
Zabel et al.(1978); t(5;22)(q33;q13)	Daniel (1979); t(5;15)(q13;q25), t(5;9)(q13;q33)
Georgmaneano et al. (1981); t(5;14)(q13;q23q32)	Daniel (1979); t(5;20)(q12;q11)
Fryns et al. (1986); t(5;10)(q35;q24)	Daniel (1979); t(5;19)(q12;p11)
Nakajama et al.(1993);t(5;18)(q35;q23)	Daniel (1979); t(5;6)(q22;q13)
Kurbasic et al. (2000); t(3;5)q27;q11.2)	Michels et al. (1982); t(1;5)(q21;q35)
Aviram-Goldring et al.(2000); t(5;15)(p15;q24)	Fryns et al (1984); t(5;16)(q35;q12)
Braddock et al.(2000);t(5;21)(p15.1;q22.1)	Fryns et al (1984); t(5;7)(q35;q11)
Zhu et al.(2001); t(5;10)(q35;q11)	Fryns et al (1984); t(5;16)(q15;q13)
Su et al.(2002); t(5;9)(q33.1;q13)	Fryns et al (1984); t(5;18)(q12;q11)
Wysocka et al.(2002); t(X;5)(p11;q31)	Nowichi et al. (1994); t(4;5)(p11;q14)
Uchiyama et al.(2002); t(5;13)(q35;q31)	Stana et Lungeano (1999); t(5;13)(q11;q21)

Table 2. Expected karyotypes and number of FISH signals in offspring of a carrier of balanced translocation t(5;13)(q11;q12).

Segregation	Possible chromosomal combinations in the oocyte	Expected karyotype	FISH signals
2:2	N5/N13	46,XY	2 green;2 orange
	A5/A13	46,XY,t(5;13)(q11;q12)	2 green;2 orange
	N5/A13	46,XY,dup(5)(q11;qter), del(13)(q12;qter)	2 green; 1 orange
	A5/N13	46,XY,del(5)(q11;qter), dup(13)(q12;qter)	2 green; 3 orange
	N5/A5	46,XY,+5,-13,der(5)	3 green; 2 orange
	A13/N13	46,XY, ,+13,-5,der(13)	1 green; 2 orange
3:1	N5	45,XY,-13	2 green; 1 orange
	A5	45,XY,-13,der(5)	2 green; 2 orange
	N13	45,XY,-5	1 green; 2 orange
	A13	45,XY, 5,der(13)	1 green; 1 orange
	N5/A5/N13	47,XY, +der(5)	3 green; 3 orange
	N5/A13/N13	47,XY, +der(13)	2 green; 2 orange
	A5/N13/A13	47,XY, +13,t(5;13)(q11;q12)	2 green; 3 orange
	A5/N5/A13	47,XY, +5,t(5;13)(q11;q12)	3 green; 2 orange

der(5) - del(5)(q11;qter);del(13)(p;q12)
der(13) - del(5)(p;q11);del(13)(q12;qter)
N - normal chromosome
A - derivative chromosome
Legend: N5 – normal 5th chromosome; N13 – normal 13th chromosome;
A5 – derivative chromosome containing 5pter-q11: 13q12-qter; A13- derivative chromosome containing 13pter-q12: 5q11-qter.

normal chromosome and a translocated chromosome from the same chromosomal pair (segregation 2:2), there will be an extra portion of one chromosome and a missing portion of the other chromosome. The segregation mode 3:1 produces too many unbalanced gametes and was reported in several cases with other translocations and multiple congenital anomalies (10, 11, 18-20). Every variant is occurred by chance.

In order to define the chromosomal abnormalities in the child, we used FISH analysis with probes for 5p and 13q. The possible combinations between chromosomes, involved in translocation, during meiosis as well as the respect number of signals for the FISH probes are shown in table 2. FISH may be helpful for molecular cytogenetic study of the translocations (21).

According to the results of FISH, showing 2 signals for 5p and 3 signals for 13q14, the child could be either with karyotype 46,XY,del(5)(q11;qter),dup(13)(q12;qter) or with 47,XY,+13, t(5;13)(q11;q12). Since the deficiency of such large segment as the long arm of chromosome 5 as del(5)(q11;qter) is not known to be compatible with live, we can assume that the chromosome segregation during meiosis occurred with a ratio of 3:1, including two derivative chromosomes plus an extra chromosome 13. The possible karyotype of malformed progeny would be 47, XY, t(5;13)(q11;q12),+13 – Patau syndrome. The clinical symptomes are typical for this syndrome - cleft lip and cleft palate, trigonocephaly, dysmorphic ears, low hair line, genital anomalies (hypospady), finger hexadactyly, heart defects (common arterial trunk with hypertrophy of the left ventricle).

Taking into account the risk for malformed child of the mother carrier of t(5;13)(q11;q12), the fetal karyotype for all following conceptus must be established by prenatal diagnostics, which is routinely performed in our laboratory. Another possibility is the preimplantation genetic diagnosis (PGD) (22). Unlike amniocentesis, which diagnoses chromosomal and genetic abnormalities of the fetus in utero, PGD allows such identification to occur before the embryo is even in the womb. It can help the parents to avoid the traumatic decision of ending a pregnancy and to avoid the heartache of having another child with a fatal disease or birth defect. A large advantage in non-invasive prenatal diagnosis is the study of fetal nucleated erythrocytes isolated from maternal blood using monoclonal antibody (Mab) against the zeta (z) and gamma chains of embrionic and fetal haemoglobin (23). FISH was performed with probes for X, Y and chromosomes involved in translocation to identify fetal gender.

In conclusion, a balanced karyotype t(5;13)(q11;q12) with new breakpoints (5q11 and 13q12) was found in the mother of a malformed child. The translocation was hereditary and was present in the grandmother of the malformed child. The type of segregation 3:1 was established using FISH analysis.

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BALANSIRANA TRANSLOKACIJA t(5;13)(q11;q12) KOD ŽENE SA MALFORMISANIM DETETOM

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Kratak sadržaj: *Otkrivena je balansirana translokacija t(5;13)(q11;12) kod fenotipski normalne žene, čije je prvo dete imalo multiple malformacije i umrlo 13 dana posle rodjenja.*
Korišćena je tehnika GTG-bendinga da bi se definisala prelomna mesta translokacije - 5q11 i 13q12 koja su bila različita od translokacija izmedju hromozoma 5 i 13 opisanih u literaturi. Translokacija je bila hereditarna i prisutna kod bake deteta sa malformacijom. Tip segregacije 3:1 je utvrdjen korišćenjem FISH sa probama za 5p i 13q14 na isečcima tkiva umrlog deteta. Ćelije su pokazivale 3 signala za 13q14 i 2 signala za 5p.

Ključne reči: *Balansirane recipročne translokacije, anomalije fetusa, FISH, humana citogenetika*