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The inherited Robertsonian 13q14q translocation and sex chromosome aneuploidies in the same family

I. Idzelienë[1],

A. Razbadauskas[1],

I. Andriuðkevièiûtë[2],

L. Jurkënienë[2],

L. Ðalomskienë[2],

A. Sinkus[2]

[1] Rehabilitation and Nursing Department, Faculty of Health Sciences, Klaipeda University, H. Manto 84, LT-92294 Klaipëda, Lithuania
E-mal: slauga@svmf.ku.lt

[2] Department of Biology, Kaunas University of Medicine, Mickevièiaus 9, LT-44307 Kaunas, Lithuania
E-mail: sinkus@vision.kmu.lt

There is reported a large family with four healthy persons possessing Robertsonian t(13q14q) translocation. After karyotype investigation in 106 relatives, three additional individuals with sex chromosome aneuploidies were established: one carrier of translocation has a son with chromosome mosaics 45,X/46,XY/47,XYY, and in a collateral branch of the family by the woman 45,X the karyotype of her grandmother was 46,XX/45,X. The possible genetic control of aneuploidy is discussed (the role of centromere, heterochromatin, centrosome, proteolytic enzymes). In some cases the factors predetermining aneuploidy show the Mendelian inheritance. However, the familial concentration of chromosome anomalies should be evaluated as multifactorially influenced.

Key words: Robertsonian translocation, sex chromosomes, familial aneuploidy

INTRODUCTION

Starting from the first reports on human chromosomal diseases, there were observed familial cases of chromosome pathology. When one chromosomal patient is born, the risk for repeating the same or another chromosomal syndrome increases in this family. Also, in some individuals two chromosome anomalies appear independently from one another. According to the generally accepted opinion, when a family already possesses an affected individual, the genetic forecast of the birth of a chromosomal patient is at least three times more frequent than in the general population. Preimplantation analysis of chromosomal anomalies in the sperm, ovocytes, polar bodies and embryos from carriers of balanced chromosomal reorganizations allowed to recognize aneuploidy and mosaicism for the chromosomes not involved into translocations more than in 80% of cells [1, 2]. The terms usually used for the definition of such conditions – “chromosome interaction” [3] or “interchromosomal effect” [4, 5] – do ascertain the fact but do not explain its mechanism.

Analysis of references concerning complex and familial chromosome anomalies is too broad for a short review, therefore only some typical references will be provided here. Such chromosome pathology could be divided into four types:

(i) double chromosome aneuploidy in the same patient in the cases of coincidence, *e.g.*, Down syndrome and Turner syndrome [6] or Down–Klinefelter’s syndromes [7];

(ii) chromosome anomaly, different from parental or aroused additionally to that inherited from parents, *e.g.*, trisomy-21 in a baby born by the mother possessing an additionally marker [8] or reciprocal translocation in a daughter born by the mother possessing another reciprocal translocation [9];

(iii) chromosome anomalies (the same or different) found in siblings or more distant relatives, *e.g.*, simple trisomy-21 in three first cousins [10] or Klinefelter syndrome in a boy and Turner syndrome in his cousin [11].

(iv) “amplification” of the same chromosome aberration in the cells of affected patient. For example, there are known patients with more as one ring-21

chromosomes or dicentric ring chromosome 21 [12], two and more Xq isochromosomes suffering from Turner syndrome [13], duplication and triplication of chromosome segments [14].

The aim of this paper is to describe a large family with chromosome anomalies found in seven affected persons.

CASE REPORT AND FAMILIAL PEDIGREE

The karyotype of the propositus was investigated in the Klaipëda delivery house because of prenatal hypoplasia after pregnancy by a woman who had one spontaneous abortion in her anamnesis. The patient was born after a 34-week pregnancy by the 35-yrs-old mother and 39-yrs-old father. His weight at birth was 2000 g, body length 32 cm, head circumference 32 cm, chest circumference 29 cm. At the end of the first week after the birth, the patient was taken ill with pneumonia for a period of 1.5 months. While at school, his physical and mental development corresponded to the age. The chromosome investigation in umbilical blood culture showed 45 chromosomes because of Robertsonian translocation. By the G- (Fig. 1), Q- and C-staining the translocation was recognized as t(13q14q) – the most frequent condition between Group D chromosomes. The karyotype is expressed by the formula 45,XY,der(13;14)(q10;q10) [15].

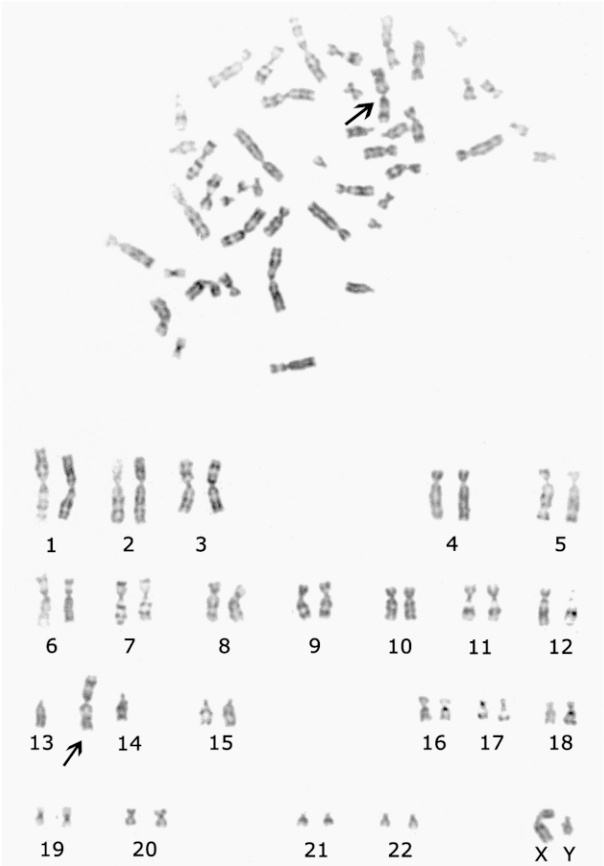

Fig. 1. Metaphase plate and karyotype of propositus 45,XY,der(13;14)(q10q10).
G-banding, ×1350

Since t(13q14q) can be inherited or appeared *de novo*, karyotype investigation was carried out in lymphocyte culture for parents and siblings of propositus IV-4 (the abbreviated familial pattern is shown in Fig. 2). The sister IV-1 with a normal female karyotype was often ill with pneumonia, and after abundant streptomycine treatment during the infancy her acoustic nerves became atrophied. She attended a school for deaf people. The same balanced translocation t (13q 14q) was found in three healthy relatives of the propositus: brother IV-3, father III-1 and aunt III-4. The only son IV-9 of the aunt III-4 has chromosome mosaics with three cell clones 45,X/46,XY/47,XYY (8%, 69% and 23% respectively in 200 examined cells). His primary chromosome constitution was 46,XY (normal male karyotype), and after mitotic nondisjunction of Y chromosome there turned up a monosomic clone without chromosome Y and a trisomic clone with double Y. His physical, mental and sexual development corresponds to the age, and he makes a good progress in the general education school.

Since the karyotype of grandfather II-4 is normal, apparently the translocation in this family was inherited from grandmother II-3. Therefore looking for other carriers of translocation the karyotype in offsprings of her (now dead) sisters II-1,2 and aunts I-2,3,4 was investigated. Chromosomes in 106 relatives and in 53 their spouses were analysed. No more translocations were found. However, the karyotype of the II-7 (female with normal gynaecological anamnesis) showed the chromosome mosaics 46,XX/45,X (the latter clone accounts for 25% of cells). Her 23-

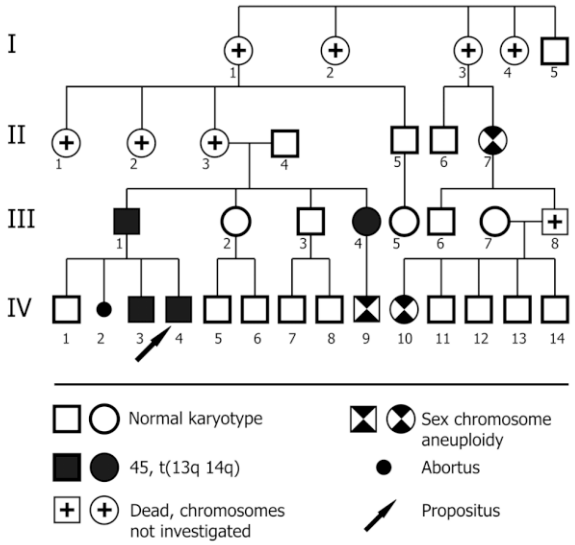

Fig. 2. Abbreviated familial pattern of inherited translocation 13q14q and sex chromosome aneuploidies (in the offsprings of individuals I–2,4 also II–1,2 no chromosome pathology was found)

yrs-old granddaughter IV–10 had the total X monosomy accompanied by the classical signs of Turner syndrome (short body and extremities, hypoplastic uterus, primary amenorrhoea, absence of breasts and pubic hair).

DISCUSSION

The incidence of chromosome anomalies is best established by the mass unselected investigation of newborn babies. The investigation, which was held in Klaipëda, happened to be the 7th one in the world. The chromosomes of 4032 unselected newborns were investigated [16]. On average, chromosome anomalies are established for 0.6% of the newborns. In the present report, among 106 relatives chromosome pathologies (inherited translocation 13q14q was taken as one event) were found in four persons, *i.e.* six times more often than in the general population. Such concentration of anomalies makes us think that in this family there is one common inherited factor which is responsible for the Robertsonian translocation and sex chromosome aneuploidies. The hypothesis that genome mutations cause gene mutations, affirmed in 1916 by C. B. Bridges, is almost as old as the negation of genetic control [17]. If chromosome patients were more often met in isolates, it would be a weighty confirmation that genes have influence on the genome and chromosome aberrations. So far, there is known only one report from Kuwait [18] where 40% of marriages are marriages between relatives. The probability to deliver a baby with Down syndrome in inbred marriages is four times higher. The authors think that there are some genes which induce mitotic nondisjunction. The genetic logic easily explains the inheritance of the t(13q14q) translocation. However, sex chromosome aneuploidy in the son of the carrier of the translocation and X-monosomy in the woman and her granddaughter makes us ask again: is there any logic in "illogical" aberrations? [19]. We think that we should look for a logical explanation of the familial chromosome nondisjunction in the cell division apparatus, *i.e.* in the structure of the chromosomes (first of all in the centromere and heterochromatine), in the kinetochochores and achromatic spindle.

The term "selective endoreduplication" was first proposed by Lejeune et al., 1966 [20]. They described the chromosome in which four chromatids possess one common centromere, while the rest 45 chromosomes as usual consist of two chromatids. Both daughter clones of this cell should have been trisomic. Also, five more chromosomes with asynchronic replication were demonstrated, not only of the whole chromosome but also a separate arm or even some fragment of a chromosome. Autonomic reduplication of the separate arm of one of the chromosomes was demonstrated for the patient who was treated with the antitumour antibiotic mitomycin [21]. Such triradial chromosomes can cause partial monosomies and partial trisomies in the daughter cells. The above-mentioned cases of selective reduplication were found in malignant tissues or after treatment with antitumour agents, therefore part of them may occur as a result of complex interchromosomal rearrangements. In the theoretic aspect, the most interesting seems to be autonome endoreplication of the long arm of the chromosome 2 in humans [22]. This chromosome was formed as a result of a fusion of two acrocentric chromosomes of primates [23], which means that philogenetically it has to be dicentric. The cytogenetic studies in mammals revealed a large variability of chromosome number and chromosome structure. The karyotype of mammals consists of only six chromosomes in *Indian muntjak*, while that in of the *black rhinoceros* contains 84 chromosomes. Comparative karyotype studies in mammals show that chromosomes wander from one biological species to another in large blocks. The fact that the number of chromosomes in different species is variable shows that the same loci in one species can exhibit centromeric activity while in other species they remain silent. Only active centromeres in multicentric chromosomes participate in the spindle checkpoint. This activity is determined by some groups of structural and motor-related centromere proteins [24]. The above-mentioned chromosome 2 in the human genome was found to be conserved in its entirety as a single chromosome arm in the *common shrew* (Sorex araneus) [25]. Reactivation of "silent" centromeres may result in aneuploid cell lines, because centromeres, which have prematurely separated and apparently cannot attach to the spindle fibers, produce nondisjunction [26].

Each new method of cytogenetics (C-blocks, Ag-impregnation, FISH) was tested for causing aneuploidy. The primary positive results are usually denied in latest investigations. The oldest history is that of associations of satellite chromosomes. It seemed that chromosome 21 more frequently takes part in chromosome association in parents of Down syndrome patients [27]. The reports that the carriers of double satellites give birth to offsprings with sex chromosome aneuploidies and with Down syndrome [28] or that chromosome variant 9qh+ increases the frequency of chromosome nondisjunction has not found their convincing confirmation in other reports. The hypotheses about the influence of heterochromatic regions upon nondisjunction are supported by the nonspecific conjugation of these during the interphase. The metaphase associations of heterochromatic regions are interpreted as the remains of interphase conjugation [29]. It was supposed that individuals with enlarged heterochromatine blocks in chromosomes 1 and 9 could induce meiotic nondisjunction after achieving "some critical activity" of hete-

rochromatin [30]. We have also tried to measure the distances between chromosomes 1, 9, 16 in human metaphases [31]. Assuming a completely random distribution of two points within a circle, these points have a mean distance of 45% of the diameter of the circle. None of the three chromosomes in question showed a significant deviation from this distribution. Current investigations show that the human genome contains numerous blocks of a highly homologous duplicated sequence [32]. There were identified 119 regions of copy–number polymorphism with segmental duplications as well as a 4 four-fold enrichment of these polymorphisms in hotspot regions. This higher order architecture provides a substrate for recombination and recurrent chromosomal rearrangement associated with genomic disease.

On the opposite end of the spindle the centrosome, a tiny organelle with a high potentiality is found. Centrosome anomalies can lead to spindle disorganization and aneuploidy. Executive duplication of ectopic assembly of centrosome proteins could lead to multipolar spindles and also create chromosome breaks [33]. It is not yet understood how the loss of function of the breast cancer susceptibility genes *BRCA1* and *BRCA2* leads to developing breast cancer. The mice embryonic fibroblasts possessing *BRCA* mutation are impaired in DNA double-strand break repair and develop chromosome aberrations. These fibroblasts frequently develop centrosome amplification and chromosome missegregation which result in aneuploidy [34]. In Alzheimer's disease a relation between centrosomes and trisomy-21 has been also shown [35]. All Down syndrome individuals develop Alzheimer's desease neuropathology by the 4th decade of life. The fibroblast cultures derived from individuals carrying familial Alzheimer's disease mutations in presenilin, exhibited a significant, approximately twofold, increase in the number of trisomy-21 cells compared to control cultures. The endogenous presenilin proteins in fibroblasts were localized to the centrosomes, the nuclear envelope, and its associated kinetochores. The results indicate that the presenilin proteins may be involved in mitosis and that their mutations may predispose to chromosome nondisjunction.

Aneuploidy can be defined by the pecularities of mitotic spindle and by the agents influencing the assemblage or disjointing of the spindle. Most discussions have been devoted to the inhibitor of alpha-1-protease (PI) (earlier called alpha-antitrypsin). PI inhibits the activity of many proteolytic enzymes and produces about 90% of antiproteolytic processes in blood. More than 40 mutantic variants have been known, each of them showing Mendelian inheritance. Because PI mutations should increase the activity of proteolytic enzymes in cells, this can injure the mitotic spindle and, therefore, cause aneuploidy. The heterozygotic carriers of PI mutations are reported in parents possessing offsprings with sex chromosome aneuploidies [36, 37]. Our investigation in Down syndrome families showed that the frequency of PI heterozygotes drastically increases in mothers aged over 35 years (10% as compared with 4.3% in control population) [38]; there exists a subpopulation in which the anomalous variants of PI increase the possibility to give birth to chromosome patients.

In conclusion, chromosome aneuploidies could be caused by numerous effects on each compound of cell division: centrosome, chromosome (especially on centromere and heterochromatine regions), and mitotic spindle. Although some of these factors show Mendelian inheritance, a larger concentration of chromosome anomalies in relatives should be evaluated as the expression of multifactorial inheritance.

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I. Idzelienë, A. Razbadauskas, I. Andriuðkevièiûtë, L. Jurkënienë, L. Ðalomskienë, A. Sinkus

PAVELDIMA ROBERTSONO TIPO TRANSLOKACIJA 13Q14Q IR LYTINIØ CHROMOSOMØ ANEUPLOIDIJOS TOJE PAÈIOJE ÐEIMOJE

S a n t r a u k a

Apraðoma didelë genealogija, kurios keturiems sveikiems asmenims nustatyta Robertsono tipo translokacija. Penkiose kartose iðtyrus 106 giminaièiø kariotipà, dar trims asmenims rastos lytiniø chromosomø aneuploidijos: translokacijos neðëjos sûnui chromosominë mozaika 45,X/46,XY/47,XYY ir kitoje giminës ðakoje moteris 45,X, kurios senelë turëjo chromosomø mozaikà 46,XX/45,X. Aptariama galima genetinë aneuploidijos kontrolë (centromera, heterochromatinas, centrosoma, làstelës proteoliziniai fermentai). Atskirais atvejais veiksnius, lemianèius chromosomø neiðsiskyrimà, gali nulemti genø mutacijos, taèiau ðeiminæ chromosomø anomalijø koncentracijà derëtø vertinti kaip paveldëtà daugiaveiksmiðkai.