

Diversity of human chromosome structural rearrangements identified at the Center for Medical Genetics in 2002–2007

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Chromosome structure rearrangements could cause various human health problems. Even Down's or Turner's syndromes, which usually are determined by chromosome number change, in some cases could be caused by chromosome structure abnormalities. Here we present chromosome structure rearrangements which have been identified at Vilnius University Hospital “Santariškių Clinics” Centre for Medical Genetics in 2002–2007. In total, 106 persons with chromosome structure rearrangements were detected, including marker and derivative chromosomes, mosaic and familial cases. Chromosome 14 was most often mentioned among the detected abnormalities, meanwhile chromosomes 19 and Y had not been involved in any chromosome structure rearrangement. Translocation was the most frequent chromosome structure rearrangement type, comprising 44.3% of all our cases. Chromosome structure rearrangements most often described in literature, such as rob(13;14), t(13;20), del(18), inv(2) have been detected among our cases, too.

Key words: human cytogenetics, chromosome rearrangements, structure diversity, population incidence

INTRODUCTION

Chromosome number abnormalities in humans are the main cause of some diseases such as Down's syndrome or Turner's syndrome. However, not all cases are determined by the chromosome number abnormalities. Turner's syndrome is caused by chromosome X monosomy only in part of the cases [1, 2]. Other reasons are various structure abnormalities of chromosome X. Chromosome structure rearrangements of autosomes, depending on whether it is balanced or not, are responsible for various dysmorphic abnormalities or fertility problems [3]. Chromosome breakpoints can occur in any part of chromosome and form any type of rearrangement, but only part of them could be compatible with vital functions and postnatally detected. Therefore, chromosome structure rearrangements are unique, and only few of them are more common. Here, we would like to present the diversity of chromosome structure rearrangements that have been detected at Centre for Medical Genetics (CMG) Laboratory of Cytogenetics and to compare our findings with the literature data.

MATERIALS AND METHODS

Samples have been collected at the Centre for Medical Genetics Laboratory of Cytogenetics in 2002–2007.

Karyotyping

Proband's chromosome slides were prepared from peripheral blood cultivated lymphocytes. The lymphocytes were cultivated in RPMI 1640 medium with foetal bovine serum and phytohemagglutinin for 72 hours; thymidine was added after 48 hours and washed after 16 hours. Cell proliferation was terminated with colchicine solution. The cells were treated with hypotonic solution and Carnoy's fixative. The chromosome slides were heated at 65 °C in a chamber overnight, treated with trypsin and stained with Giemsa dye. The slides were analysed with a Nikon Eclipse 600 microscope supplied with a CCD camera. Karyotyping was performed with MacKtype software, version 4.3 (Applied Imaging).

RESULTS

In total, 106 chromosome rearrangements were collected, including marker, derivative chromosomes, mosaic and familial cases (Table 1). The most common chromosome rearrangement was translocation (44.3% of all the cases).

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The pericentric inversion chromosome 9 was excluded from the study since it had been construed as a heteromorphic variation. The inverted part of chromosome 9 is heterochromatin, and there are no undeniable data about how it could affect human development or fertility, although various considerations persist [4].

Twenty-four different reciprocal translocations were detected. Most often, into four different reciprocal translocations, four chromosomes – 10, 13, 14 and 21 – were involved. Chromosome 19 and sex chromosomes were not involved into translocations. Among all reciprocal and Robertsonian translocations their number being 29, chromosome 14 is most often mentioned (in seven translocations). Most often detected translocation was rob(13;14)(q10;q10) (six cases). This translocation is most common in humans [5].

Analysing all chromosome structure rearrangements (Table 2), most chromosome breakpoints were detected in chromosome 14 which was involved into 21 chromosome rearrangements. Chromosomes 21 and X were involved in 18 and 17 chromosome rearrangements respectively. Chromosomes 19 and Y have not been observed in any chromosome rearrangement.

Table 1. Number of chromosome structure rearrangement cases detected in CMG in 2002–2007

Chromosome rearrangement type	Number of cases
Robertsonian translocation	16
Reciprocal translocation	31
Deletion	17
Isochromosome	4
Marker chromosome	5
Ring chromosome	6
Inversion*	11
Add / duplication	8
Derivative chromosome **	8
Total	106

* Excluding pericentric inversion chromosome 9.

** Chromosome of unknown rearrangement origin or exact location, also inherited unbalanced derivative chromosomes from balanced chromosome rearrangement carrier parents.

Table 2. Number of chromosome breakpoints involved into chromosome rearrangement including mosaic karyotypes

Chromosome	1	2	3	4	5	6	7	8	9	10	11	12
Number of breakpoints	4	7	4	2	6	8	3	6	7	9	5	2
Chromosome	13	14	15	16	17	18	19	20	21	22	X	Y
Number of breakpoints	15	21	4	1	1	8	0	5	18	6	17	0

DISCUSSION

The most common chromosome structure rearrangement is reciprocal translocation. Most reciprocal chromosome translocations are unique in every single case. There is very little probability that chromosome breakpoint will occur in the same region in two separate cases. A much higher probability is that individuals carrying exactly the same translocation are relatives and have a common ancestor. In our investigation, the same translocations had only close relatives, although some non-Robertsonian translocations with breakpoints in the centromere region could not be related. We detected translocation t(13;20)(p11.1;p11.1) in two apparently nonconsanguineous genealogies; the same translocation has been described in literature [6] and it is not the only described recurrent reciprocal translocation – translocation t(11;22) (Fig. 1) [7, 8], which has also detected at our laboratory, could occur in different persons independently.

Robertsonian translocations occur between acrocentric chromosomes. Translocation (13;14) (Fig. 2) is the most common and usually is associated with fertility problems. Chromosome 21 is also frequently involved in Robertsonian translocations – four cases of translocation t(14;21)(q10;q10) and four cases of t(21;21)(q10;q10) have been detected. All of them were associated with Down syndrome. Although trisomy 21 could be detected by different methods (QF-PCR, interphase FISH), only conventional karyotyping was able to determine the type of trisomy, therefore chromosome G-banded chromosome analysis is a preferable method for genetic counseling.

Some chromosome rearrangements are detected more common in humans. Chromosome breakpoints differ in different cases, but the outcome is the same – chromosome 18 deletion has been determined to be the most common deletion among our cases (23.5%). These results match the literature data which state that deletion of chromosome 18q arm is one of the most common chromosome deletions in humans [9]. This phenomenon could be explained by the low number of genes located in chromosome 18 [10] and this might be the reason why chromosome 18 deletions as well as deletions of chromosome 9 short arm, which is also gene-poor, are common [11]. We detected deletion chromosome 9p in three cases, and this rearrangement had been described in literature too [12]. As McKinlay Gardner and Sutherland [13] state, deletions could not encompass more than 2% of human genome in liveborns, therefore fetuses with chromosome deletions in gene-poor regions are more likely to survive to term and be diagnosed.

In isochromosomes, loss of one chromosome arm is complicated by a duplication of the other arm, therefore this malformation rarely affects autosomes, but isochromosome X is common, and all isochromosomes detected by us were of i(X)(q) origin. All these cases were associated with Turner's syndrome features. As already mentioned, the cytogenetic origin of Turner's syndrome is very heterogenic, and not only isochromosomes but also deletions of chromosome X, usually of p arm, cause Turner's syndrome. Deletions could eliminate different parts of a chromosome, but if the centromere remains, it may be transmitted during cell division. In this

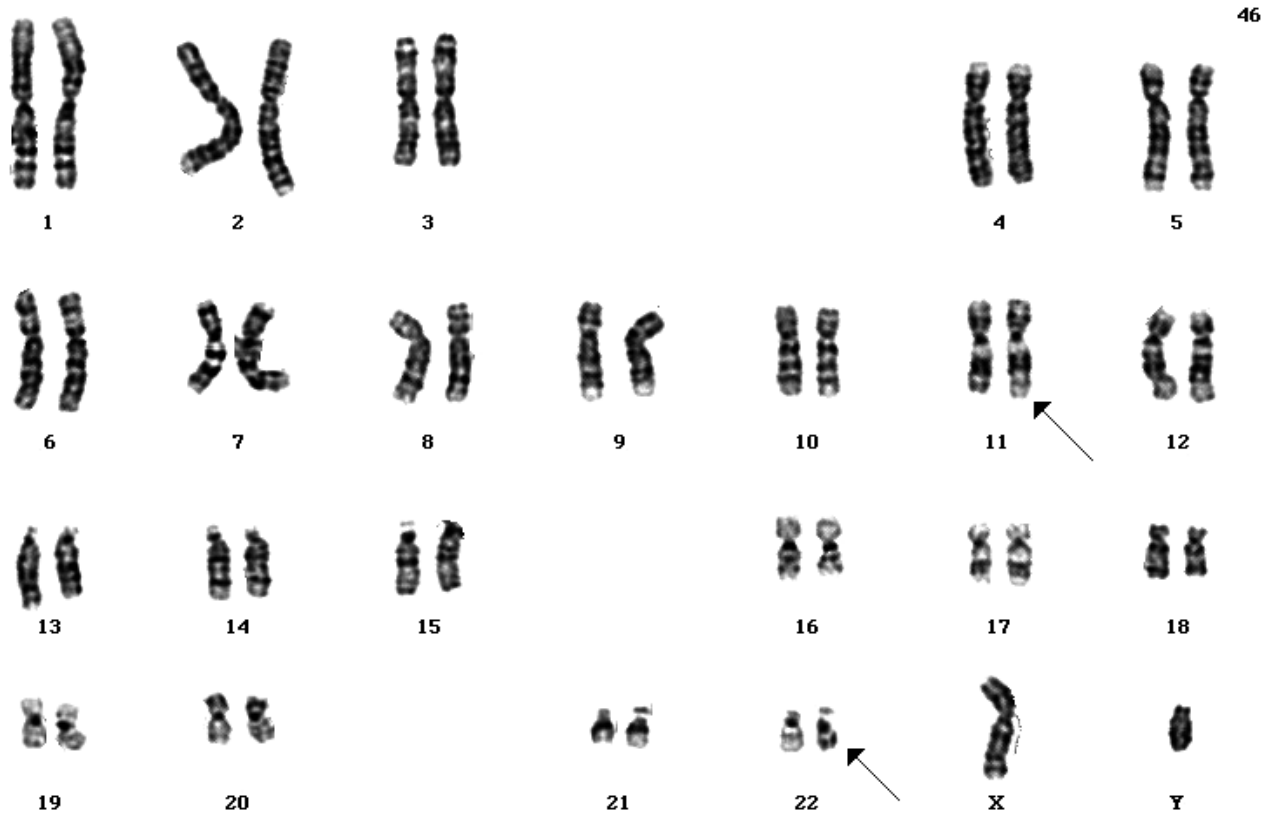


Fig. 1. Human karyotype with reciprocal translocation 46,XY,t(11;22)(q23.3;q11.2), translocated chromosomes indicated with arrows



Fig. 2. Human karyotype with Robertsonian translocation 45,XX,t(13;14)(q10;q10)

way, a marker chromosome could be formed, and four out of five marker chromosomes in our study have been associated with Turner's syndrome. Marker chromosomes are often mentioned in patients with features of this syndrome [15], and they usually consist of a small pericentric part of the lost chromosome X. The fifth case of marker chromosomes is an additional marker chromosome of unknown origin, which most likely has been transmitted due to 3:1 segregation of translocated chromosomes quadrivalent in meiosis. Such chromosome segregation is common when a very small chromosome is formed [13]. Partial chromosome deletion is formed also in the formation of the ring chromosome, and again the most commonly detected ring chromosome was chromosome X. Ring chromosome 5 (Fig. 3) is another example of the heterogeneity of chromosome syndrome origin since this malformation presents features of Cri du chat syndrome which is usually caused by chromosome 5p deletion.

Small pericentric chromosome inversions are usually of balanced origin. Nowadays, not only inversion of chromosome 9 but also inversions of chromosome 2 and 10 have been interpreted as a heteromorphic variation [16]. Assessment of the impact of such chromosome inversion on the human genome is complicated since gene position effect could be

expressed in a very different way in every single case. Moreover, the incidence of a particular rearrangement should be high to consider it as a heteromorphism. In our investigation, the pericentric inversion $inv(10)(p11.2;q21.2)$ has not been detected, but three cases of $inv(2)(p11.2;q12\sim13)$ (Fig. 4) could indicate that this inversion is common also in our population and could be a heteromorphic variant [17].

To determine the origin of some of the chromosome rearrangements is impossible without applying molecular cytogenetic methods. The origin of additional material attached to the terminal part of a chromosome arm is difficult to determine without the analysis of parental karyotypes, which helps in some cases if one of the parents is detected to be a balanced chromosome rearrangement carrier. Parental karyotype analysis helped in one of our cases when additional material— $add(14)(p11.2)$ was detected and the mother was revealed to be an $inv(14)(p11.2;q32.1)$ inversion carrier. The abnormal chromosome had been formed due to a recombinant chromosome formation. An abnormal chromosome of unknown rearrangement origin is indicated as a derivative. These chromosomes most often include partial chromosome deletion with a partial duplication which forms during gametogenesis or is an inherited abnormal chromosome from the balanced rearrangement carrier parent.

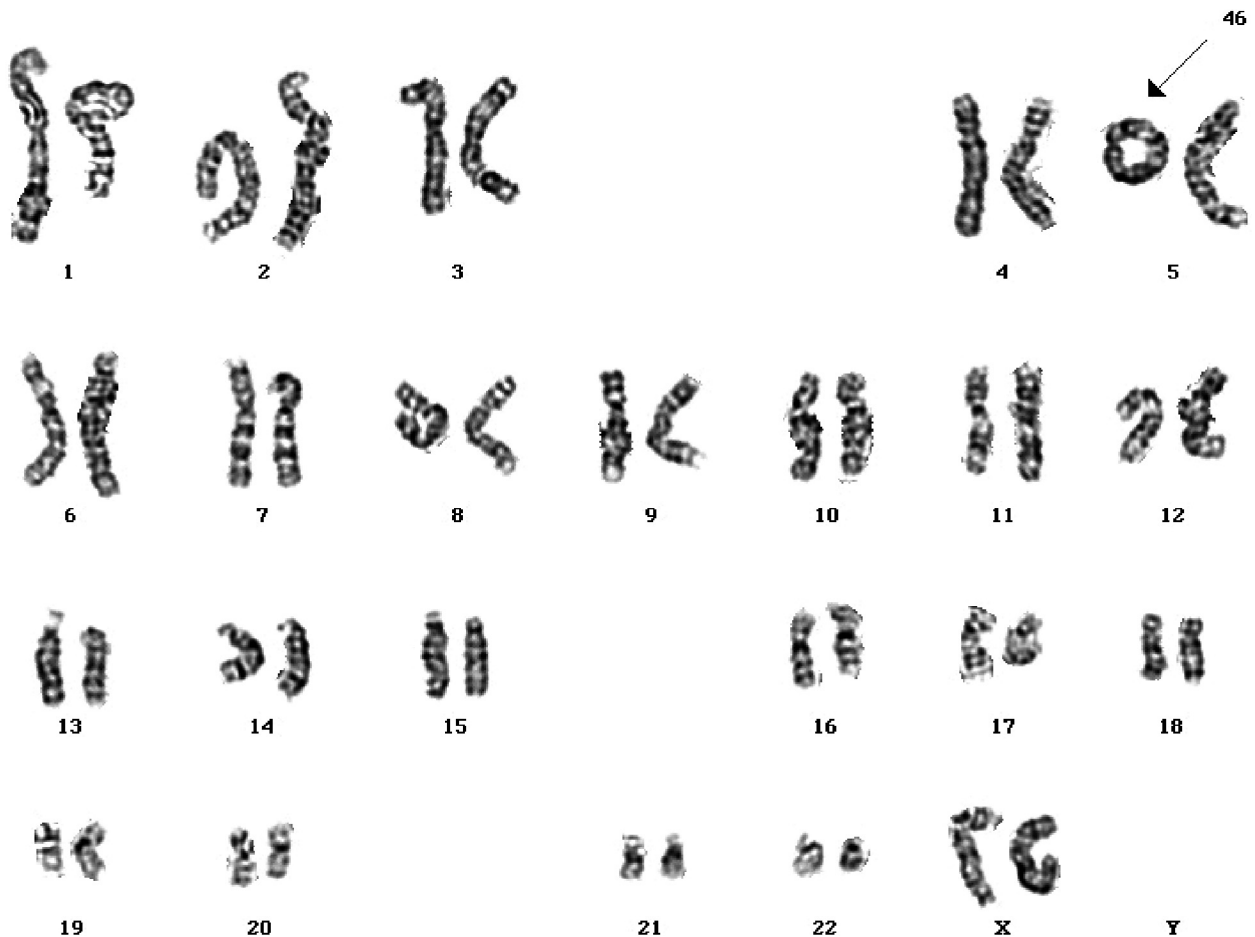


Fig. 3. Human karyotype with ring chromosome 5 – 46,XX,r(5)(p15.3q35) (arrow)



Fig. 4. Human karyotype with pericentric inversion chromosome 2 – 46,XY,inv(2)(p11.2q12), inverted chromosome indicated with arrow

We have detected five cases with abnormal chromosomes without a clear rearrangement type. The rest three identified derivative chromosomes were of known translocation origin.

Chromosome rearrangement incidence could not be counted according to our data since the study subjects were selected non-randomly, but it provides a general overview on rearrangement diversity. According to our data, chromosome 14 is the most “vulnerable” chromosome because it has been mentioned in chromosome rearrangements most often. Conversely, chromosome 19 seems not to be involved in any rearrangement; this might be a coincidence because different chromosome 19 rearrangements are described in the literature. Concerning chromosome rearrangement types, the deletion most frequently described in the literature, del(18)(q), has been the most common also in our investigation, along with Robertsonian translocation t(13;14) which is the most common translocation both in our study and in the population [18]. Genetic differences among the populations appear on the cytogenetic level too: the pericentric inversion chromosome 2 seems to be natural in our population, meanwhile the inversion chromosome 10 is not.

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**ŽMOGAUS CHROMOSOMŲ STRUKTŪROS
PERSITVARKYMŲ ĮVAIROVĖ, NUSTATYTA
MEDICININĖS GENETIKOS CENTRO CITOGENETIKOS
LABORATORIJOJE 2002–2007 m.**

Santrauka

Chromosomų struktūriniai persitvarkymai gali lemti įvairius žmogaus sveikatos sutrikimus. Netgi chromosominės ligos, pvz., Dauno ar Turnerio sindromai, gali būti nulemtos ne chromosomų skaičiaus, bet chromosomų struktūros persitvarkymų. Šiame straipsnyje apžvelgiami chromosomų struktūriniai persitvarkymai, kurie buvo nustatyti Vilniaus universiteto ligoninės Santariškių klinikų Medicininės genetikos centro citogenetikos laboratorijoje 2002–2007 metais. Iš viso buvo identifikuoti 106 persitvarkymai, tarp kurių buvo ženklinės ir išvestinės chromosomos, mozaikiniai ir šeiminiai chromosomų struktūros persitvarkymų variantai. Dažniausiai tarp chromosomų struktūros persitvarkymų buvo minima 14 chromosoma, tuo tarpu struktūros persitvarkymų, susijusių su 19-a ir Y chromosomomis, nebuvo nustatyta. Dažniausias chromosomų struktūrinis persitvarkymas buvo translokacija – 44,3% visų atvejų. Dažniausi chromosomų struktūros persitvarkymai rob(13;14), t(13;20), del(18), inv(2), aprašyti literatūroje, buvo nustatyti ir Lietuvoje.