Biomedical Research 2014; 25 (2): 233-239 *ISSN 0970-938X*
http://www.biomedres.info

Analysis of meiotic segregation patterns and interchromosomal effects in sperm from a Robertsonian translocation family

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Abstract

The objective of the present study is to provide more genetic information about meiotic segregation behavior and the possibility of interchromosomal effects (ICE) in spermatozoa from carriers of Robertsonian (Rob) translocation. Analysis of sperm chromosomes was done by fluorescence in situ hybridization (FISH). In vitro fertilization was conducted in clinic and genetics laboratory in a hospital. Two patients (men) from a Rob translocation family were included in the study. Multicolor FISH was used for probing of chromosomes 14, 15, 18, X, and Y on sperm. *Main Outcome Measure:* Frequencies of meiotic segregation products in sperm and sperm aneuploidy of chromosomes 14, 15, 18, X, and Y. To Rob Translocation heterozygote of this paper, the rate of normal/balanced spermatozoa resulting from alternate segregation is 79.9%. The frequency of unbalanced spermatozoa resulting from adjacent segregation is 20.1%. The higher frequencies of aneuploidy for sex chromosome were observed. In addition, the increased rates of diploid were found. To Rob translocation homozygosity, the rate of balanced spermatozoa is 99.7%. The frequency of unbalanced spermatozoa is 0.3%. The higher frequencies of aneuploidy for sex chromosome were not observed. Alternate segregation is dominant in the different types of Rob translocations. Carriers may be at an increased risk for ICE. Rob translocation homozygosity could be seen as a potential speciation in humans with 44 chromosomes.

Keywords: Sperm fluorescence in-situ hybridization, interchromosomal effects, meiotic segregation, Robertsonian translocation homozygosity, evolution

Accepted January 07 2014

Introduction

The frequency of Rob translocation in newborn babies is approximately one in 1,000. Rob translocation is an unusual type of chromosome rearrangement caused by two particular chromosomes joining together. In humans, it occurs in the five acrocentric chromosomes, such as chromosomes 13, 14, 15, 21, and 22. During a Rob translocation, the participating chromosomes break at their centromeres and the long arms fuse to form a single chromosome with a single centromere. The short arms also join to form a reciprocal product, which in the acrocentric chromosomes, typically contains nonessential genes and repetitive sequences such as nucleolar organizing regions, and is usually lost within a few cell divisions.

Translocation between chromosomes 13 and 14 is the most frequent one in humans, estimated to be approximately 75% of all Rob translocations. The t (14; 22) and t (13; 21) are two rare Rob translocations, comprising about only 1.2 and 2% of all detected Rob translocations, respectively [1].

Since Rob translocation carriers have a balanced chromosomal complement, they are healthy and have a normal lifespan, and may be unaware of their unusual chromosome rearrangement. A Rob translocation can be transmitted for many generations without detection.

In Rob translocations, at the end of meiosis I, segregation of the translocated and nontranslocated chromosomes from the two different chromosome pairs implicated leads to the formation of either balanced (alternate segregation mode) or unbalanced (adjacent 1, adjacent 2, and 3:1 segregation modes) gametes [2, 3], which can segregate in different ways at anaphase. Only products of alternate segregation have normal/balanced karyotype.

All other segregation modes (adjacent-1, adjacent-2, 3:0) produce unbalanced gametes with disomies and nullisomies of chromosomes involved in Rob translocations. It is well known that meiotic tetravalent configuration tends to segregate in alternate way [4], resulting in preferential production of normal/balanced spermatozoa. However, certain percentages of unbalanced gametes derived from adjacent segregation are also produced, leading to the increased risk of miscarriage and pregnancy with livebirth of chromosomally unbalanced fetus.

Analysis of the chromosomal constitution in sperm of Rob translocation carriers is of great interest for assessing the risk of unbalanced offspring and adapting genetic counseling. Sperm fluorescence in situ hybridization (FISH) using appropriate probes is a useful technique for predicting the rate of each class of segregation modes in sperm from translocation carriers. During the last decade, meiotic segregation in spermatozoa has been repeatedly studied in male carriers of Rob translocations [5 - 9]. Although it may vary from one translocation to the other, the rate of unbalanced gametes is generally not conclusive enough for genetic counseling, but most of these studies showed strong prevalence of alternate segregation in gametes. However, one recent study gave conflicting results, showing a high percentage of unbalanced spermatozoa in two Rob translocation carriers [10].

More recently, interchromosomal effects (ICE) have been described for several chromosome pairs in Rob translocations. The interchromosomal effect (ICE) refers to a disturbance of meiosis where rearranged chromosomes disrupt disjunction and distribution of chromosome pairs not involved in the rearrangement. This effect was first postulated by Lejeune [11], who noticed an excess of carriers of balanced reciprocal translocations among the fathers of children with Down syndrome. Contradictory data have been reported on the analysis of spermatozoa. Several studies have found such an ICE in male carriers of Rob translocations [12, 13], but others did not [14, 15].

In this study, we report results of chromosome segregation studies in sperm of a Rob translocation family.

Case report

This case report was occasioned by the ascertainment of a 25-year-old Chinese man (IV-1) married to a non-consanguineous woman with normal chromosomes (IV-2).

This couple had a son who died at the age of 6 months, buried without an autopsy, but had a chromosome study because of cerebral palsy. The karyotyping analysis of IV-1 was authenticated by the Chinese Academic Committee of the state key laboratory of medical genetics with previously undescribed balanced human karyotype 44XY, der(14;15)(q10;q10), der(14;15)(q10;q10) (see ***Figure 2.***).

The parents of the propositus are phenotypically normal first consins, each a carrier of the same Rob translocation (Ⅲ-1, Ⅲ-2). Their parents, a mutual uncle, and both grandparents are deceased, thus it is not possible to determine whether I-1 or I-2 was the carrier of the translocation (Figure 1).

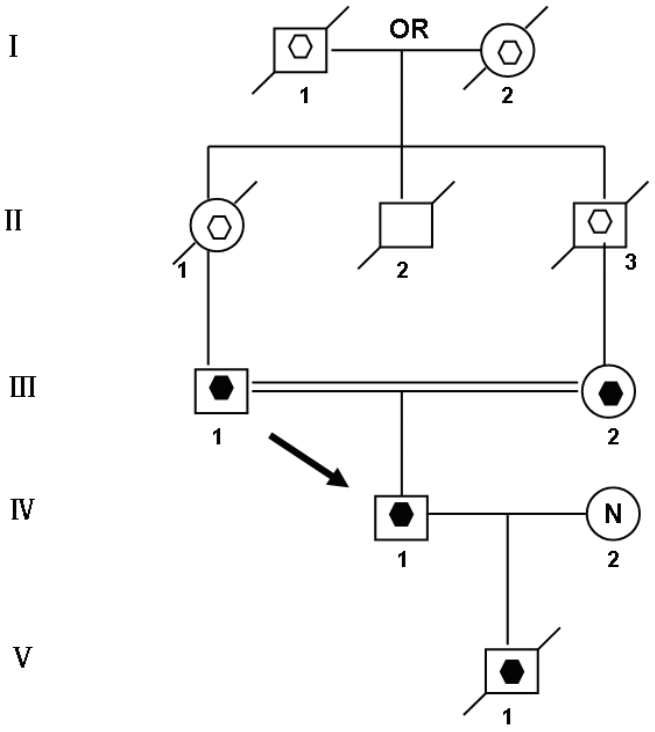

Figure 1: *Pedigree of the family transmitting Rob translocation chromosome t(14; 15)(q10;q10). Open hexagon designates a presumed carrier of t(14; 15)(q10;q10). Filled hexagon designates a known carrier of t(14;15)(q10;q10). The proband, IV-1 (arrow), has disomy t(14;15)(q10;q10). The proband's wife, IV-2, had a normal karyotype. Their deceased son, V-1, was a carrier with karyotype 45,XY,der(14;15)(q10;q10).*

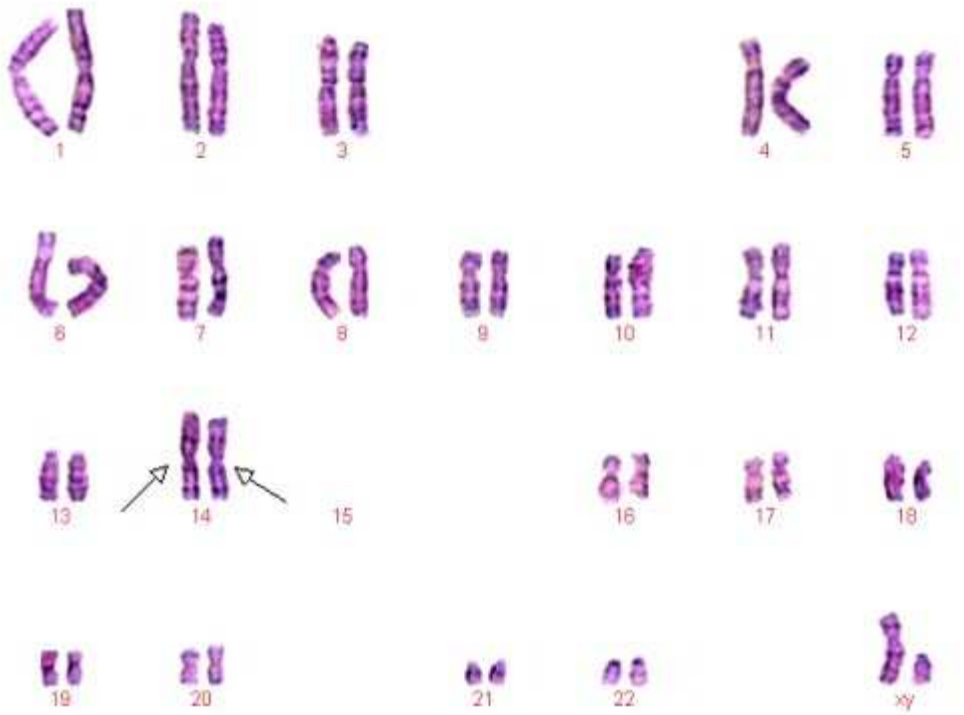

Figure 2: *Karyotype of the proband of the study, 44,XY,der(14;15)(q10;q10),der(14;15)(q10;q10), having disomy for the Rob translocation chromosome (arrows).*

Materials and Methods

Patients

Two men were included in the study.

IV-1: 25-year-old, Karyotype is 44,XY, der (14;15) (q10;q10), der(14;15)(q10;q10) and Ⅲ-1: 48-year-old, Karyotype is 45,XY,der(14;15)(q10;q10)

Sperm preparation, FISH and scoring

All semen samples were first analyzed to evaluate volume, concentration and motility (***Table. 1.***), according to the World Health Organization criteria [16]. After semen analysis, sperm with progressive motility was isolated and washed twice in phosphate buffered saline (pH 7.4) by centrifugation at 1500 rpm for 11 min. Final pellets were fixed with 5 ml of acetic acid/methanol mixture (1:3) for at least 30 min at 4 °C. Aliquots (40–50µl) of the resulting suspension of nuclei were smeared on cold pre-cleaned slides. Nuclei decondensation was performed in 1 N NaOH for 2 min. After dehydration in ethanol series (70 %, 90 %, 100 %), denaturation was performed in 0.25 % formamide in 2xSSC followed by overnight hybridization with a combination of commercially available probes.

Two sets of probe mixtures were used in this study: Firstly, for the detection of normal/balanced or unbalanced sperm, dual-color FISH was carried out using locusspecific probes (LSP) and Tel probes from Vysis (Vysis, Downers Grove, IL, USA). For IV-1 and Ⅲ-1，14/15 two fluorescent probes were used: TelVysion Probe 14q (D14S1420, Spectrum Red) for 14q32.33 and TelVysion Probe 15q(D15S120, Spectrum Green) for 15q26.3.

Secondly, to investigate the presence of ICE, triple-color FISH was performed using the second probe mixture which consist of commercial satellite (DNA) probes from Vysis, including chromosomes 18, X and Y (CEP 18, Spectrum Blue/CEP X, Spectrum Green/CEP Y, Spectrum Red).

Post-hybridization washes included 2 min in 0.4xSSC/ 0.3%NP-40 (pH=7) at 72 °C, followed by 1 min in 2xSSC/ 0.1%NP-40 (pH=7) at room temperature. Slides were covered with DAPI II (Vysis). Only intact spermatozoa bearing a similar degree of decondensation and clear hybridization signals were scored; disrupted or overlapping spermatozoa were excluded from analysis. Only slides with hybridization efficiency of 99% and more were analyzed. 1,000 sperm nuclei per patient were analyzed.

Statistical analysis

Chi-squared test was used to compare frequencies of segregation products. A probability value of less than 0.05 was considered to be statistically significant.

Table 1. *Cytogenetic and spermiologic results of IV-1 and □-1*

Patient	Age (years)	Sperm concentration ($\times 10^6$/ml)	Mobility (a+b)\ (%)
III-1	48	13	22
IV-1	25	56	53

Table 2. *The number of spermatozoa scored, the alternate mode of segregation, incidence of sperm nullisomy, disomy and 3:0/diploid for the chromosomes involved in the Rob translocation in two Rob translocation carriers*

Segregation modes	III-1	IV-1
normal or balanced	799	997
nullisomy 14	41	2
disomy 14	49	0
nullisomy 15	55	0
disomy 15	45	0
3:0 or diploid	11	1
Total	1000	1000

Table 3. *Incidence of sperm nullisomy, disomy and diploid for chromosomes 18, X and Y in two Rob translocation carriers*

Segregation modes	III-1	IV-1
normal or balanced	949	994
nullisomy 18	3	0
disomy 18	2	1
nullisomy Sex chromosome	15	2
disomy Sex chromosome	10	3
3:0 or diploid	21	0
Total	1000	1000

Results

A total of 4,000 sperm nuclei from the two translocation carriers were analyzed for this study. The results of the segregation analysis are detailed in Table 2 and Table 3.

To Rob translocation heterozygote of this paper(□-1), the rate of normal/balanced spermatozoa resulting from alternate segregation is 79.9%. The frequency of unbalanced spermatozoa resulting from adjacent segregation is 20.1%. To Rob translocation homozygosity (IV-1), the rate of balanced spermatozoa is 99.7%. The frequency of unbalanced spermatozoa is 0.3% (see Table 2). In Ⅲ-1, the frequency of unbalanced spermatozoa was significantly higher compared to that of IV-1 ($P<0.05$). In IV-1, the frequency of unbalanced spermatozoa was similarity to some controls [17-21].

The nullisomy, disomy and diploid rates for chromosomes 18, X and Y in Ⅲ-1 and IV-1 are summarized in Table 3. In Ⅲ-1, the higher frequencies of aneuploidy for sex chromosome were observed. In addition, the increased rates of diploid were found. The incidence of spermatozoa with nullisomy、disomy and diploid for the sex chromosomes of Ⅲ-1 was significantly higher compared to that of IV-1 ($P<0.05$). But, compared IV-1 with controls, the incidence was not significant [17 - 21].

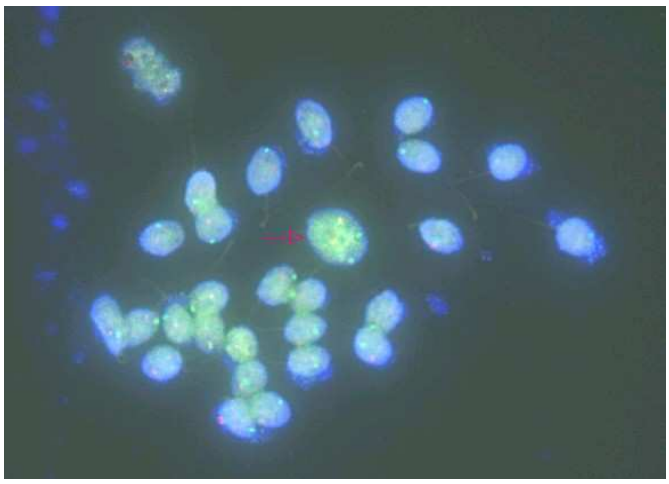

Figure 3. *Sperm cells after hybridization with TelVysion 14q32.33 (Spectrum Red) and TelVysion 15q26.3 (Spectrum Green).The sperm with red arrow may be a diploid sperm.*

Discussion

Fusion of human spermatozoa with zona-free hamster egg has been the only available method for the study of structural chromosomal aberrations in human sperm until the occurrence of FISH [22]. Multicolor FISH on decondensed sperm nuclei allows for a rapid analysis (less than 1 hour) of meiotic segregation in sperm of translocation carriers, providing information on the exact amount of normal/balanced sperm.

Accumulation of such information is undoubtedly important not only for basic cytogenetic research but also for reproductive counseling of Rob translocation carriers.
The t(14;15) are rare Rob translocations. Our data showed that alternate segregation was largely dominant over adjacent segregations in the uncommon Rob translocations carriers. This finding is consistent with results from previous studies [20, 21].

To Rob translocation heterozygote of this paper (Ⅲ-1), the rate of normal/balanced spermatozoa resulting from alternate segregation is 79.9%. The frequency of unbalanced spermatozoa resulting from adjacent segregation is 20.1%. To Rob translocation homozygosity (IV-1), the rate of balanced spermatozoa is 99.7%. The frequency of unbalanced spermatozoa is 0.3% (Table 2). In Ⅲ-1, the

frequency of unbalanced spermatozoa was significantly higher compared to that of IV-1 ($P<0.05$). In IV-1, the frequency of unbalanced spermatozoa had similarity to some controls. This finding is consistent with previously published data [5 - 7]. The high prevalence of the alternate segregation had been presumed to occur because cis-configuration of the trivalent during meiosis favored an alternate segregation in all Rob translocations [23, 24].

Variability in frequencies of unbalanced sperm in different studies can be related to technical aspects, such as FISH protocols, probes or scoring criteria used [25].

ICE first described by Lejeune [11], but the hypothesis of an ICE associated with carriers of Rob translocations has always been a controversial issue [26]. Some reports supported the possibility of ICE in Rob translocations [12, 13]. However, others demonstrated no evidence of this phenomenon [9, 18].

The interchromosomal effect could be explained by the formation of heterosynapses between chromosomes involved in the translocation and the sex vesicle, which could also involve other chromosomes [11, 26].

In the present study, the significant increased rates of nullisomy for the sex chromosomes were observed. In Ⅲ-1, the higher frequencies of aneuploidy for sex chromosome were observed. In addition, the increased rates of diploid were found. The incidence of spermatozoa with nullisomy、disomy and diploid for the sex chromosomes of Ⅲ-1 was significantly higher compared to that of IV-1 ($P < 0.05$). But, compared IV-1 with controls [17 - 21], the incidence was not significant.

The propositus (IV-1) is healthy and has a balanced chromosomal complement. Assessment of a semen sample from the propositus (IV-1) showed normal sperm number and morphology. Given his karyotype of 44,XY,der(14;15)(q10;q10),der(14;15)(q10;q10), we assumed that the person's sperm karyotype to be consistently 22,X ,der(14;15)and 22,Y,der(14;15), then, our assumption was proved by this research. From Table 2 and 3, we can see most of sperms of IV-1 are balanced haploid (not normal haploid). From Figure 3, we can see a sperm (with arrow) has four fluorescence signals (two red and two green). This means the sperm has two derivative chromosomes of der(14;15), but we can not tell the sperm is disomy of derivative chromosome or diploid. In our future research, we will employ tripl-color FISH (for example: the probe mixture consist of chromosomes 14、15 and 18) for the detection of normal/balanced or unbalanced sperm to distinguish between disomy and diploid.

Rob rearrangements are common chromosomal changes that can lead to rapid and efficient reproductive isolation between karyotypically similar populations, especially when many rob metacentric chromosomes display monobrachial homologies [27]. In the case of *Muntjac*, little or no measurable genetic or morphological differences have been found [28].

Homozygosity for Rob translocations in man has been described before. A fetus with two t(14;21) chromosomes was found by Dallapiccola et al. [29]. The related parents were heterozygous for the same translocation. Martinez et al. [30] described three adult sibs homozygous for t(13;14). Their parents were first-cousins and both were heterozygous carriers. Rajangam et al. [31] found a unique DS karyotype 45, XY, der(14;21)pat, der(14;21)-mat, +21mat. Whereas translocation heterozygosity is associated with meiotic disturbances that cause infertility and subfecundity. Translocation homozygosity should not have any effect on meiosis, at least in theory [30].

In conclusion, this present work supports that alternate segregation is largely dominant over adjacent segregations in spermatozoa from Rob translocation carriers. Furthermore, the higher incidences of aneuploidy for sex chromosomes in spermatozoa found in Rob translocation carriers indicated that the ICE on sex chromosome is likely in some male carriers of Rob translocations.

Taking into consideration relatively high levels of unbalanced sperm and unbalanced embryos, PGD is justified for Rob translocation carriers to reduce the risk of miscarriage and to increase the chances of pregnancy achievement [32 - 35].

Since the propositus is phenotypically normal with normal fertility, we consider the chromosomal rearrangement of the person to be a balanced polymorphism [36].The aberration can provide material for evolution. The establishment of a new human subspecies with a diploid complement of 44 chromosomes could occur if a small population with the karyotype of the propositus undergoes long-term reproductive isolation [37].

Acknowledgments

We thank Barry Starr and John M. Opitz for their help. This work was supported by a grant 81102141 from National Science Foundation of China

These authors contributed equally to this work.

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