Journal of Assisted Reproduction and Genetics (2019) 36:1963–1969
https://doi.org/10.1007/s10815-019-01534-6

GENETICS

Effects of a carrier's sex and age on the segregation patterns of the trivalent of Robertsonian translocations

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Received: 5 March 2019 / Accepted: 15 July 2019 / Published online: 7 August 2019

Abstract

Purpose To investigate the effects of a carrier's sex and age on the segregation patterns of the trivalent of Robertsonian translocations.

Methods This retrospective study was designed to analyze the segregation patterns of the trivalent and euploidy rates of blastocysts. Data were collected from 154 couples with Robertsonian translocation (77 with a female carrier and 77 with a male carrier). Embryos were diagnosed via array comparative genomic hybridization between January 2013 and July 2017. The segregation patterns of the trivalent of 604 blastocysts were analyzed according to the carrier's sex and age.

Results The proportion of alternate segregation was significantly higher (82.9% vs. 55.2%) in the male carriers than in the female carriers of Robertsonian translocation, and the proportion of adjacent segregation was significantly lower (16.8% vs. 42.6%), with no difference in 3:0 segregation. The segregation patterns were similar in same-sex carriers when analyzed according to the type of translocation. The carrier's age had no influence on the segregation patterns of the trivalent.

Conclusions The proportions of the trivalent's meiotic segregation pattern differ significantly according to the carrier's sex in Robertsonian translocations and are independent of the carrier's age. A significantly higher proportion of alternate segregation for normal or balanced chromosome contents was observed in the blastocysts of the male carriers than in those of the female carriers.

Keywords Chromosomal translocation · Meiosis · Preimplantation genetic testing · Aneuploidy · Genetic counseling

Introduction

Robertsonian translocation occurs when two acrocentric chromosomes fuse at the centromere [1] and was first described in 1916 [2]. Although the short arms are absent from both involved chromosomes, the carriers are commonly phenotypically normal, but they may encounter reproductive problems such as infertility, pregnancy loss, or offspring with Down syndrome or Patau syndrome. As one type of common structural chromosomal rearrangement in human beings, Robertsonian translocations occur in 0.74 to 1.23 per 1000 newborns [3, 4] and have an incidence of 0.8% in infertile men [5] and 3.1% in couples with recurrent pregnancy loss [6].

During the pachytene stage of prophase I in the gametogenesis of Robertsonian translocation carriers, the derivative chromosome and its two normal homologs form a trivalent structure. During anaphase I, the trivalent segregates into one of the three patterns: alternate segregation, adjacent segregation, and 3:0 segregation [7]. Theoretically, eight types of gametes are produced with respect to chromosomal constitution, including two types generated from alternate segregation

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10815-019-01534-6) contains supplementary material, which is available to authorized users.

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being normal or balanced. Studies of the meiosis segregation patterns of the trivalent have been performed on the sperm cells of male carriers via in vitro fertilization of hamster oocytes with human spermatozoa [8, 9] or by fluorescence in situ hybridization (FISH) [10, 11]. The results have indicated that normal or balanced gametes are the most common products, at a mean proportion of 85.4% (range, 60 to 96.60%) [12].

Preimplantation genetic testing for structural rearrangements (PGT-SR) has been successfully applied as an alternative treatment in carriers of Robertsonian translocation. FISH was first introduced into PGT-SR for the detection of the first polar body [13] or a biopsied blastomere [14, 15]. With the aid of PGT, promising reproductive outcomes have been achieved by reducing the risk of pregnancy loss and decreasing the risk of conceiving an infant with a chromosomal abnormality [16, 17]. When the meiosis segregation patterns of the trivalent in cleavage-stage embryos were analyzed with FISH, some studies reported that the female carriers were more likely to produce embryos with an unbalanced translocation product than the male carriers [18, 19], whereas another one did not [20].

Comprehensive cytogenetic methods such as array comparative genomic hybridization (aCGH) [21], single-nucleotide polymorphism [22], and next-generation sequencing [23] have been incorporated into the PGT procedure. With the advantage of simultaneous detection of 24 chromosomes, abundant information on chromosomal abnormalities can be acquired. We previously observed a significant sex-specific segregation pattern for autosomal reciprocal translocations with acrocentric chromosome involvement, because a significantly higher proportion of alternate segregation was detected in male carriers than in female carriers [24]. In this study, we further explored the segregation patterns of the trivalent in Robertsonian translocations according to the carrier's sex and age and sought to obtain general information regarding the segregation patterns of rearrangements that involve an acrocentric chromosome. These findings may provide some clues to explain the underlying mechanisms of the meiotic segregation patterns of translocations that involve an acrocentric chromosome to estimate the reproductive risks of carriers with this type of rearrangement and to ensure that they are advised appropriately.

Materials and methods

Study population

The use and analysis of the data of Robertsonian translocation patients in this study were approved by the Institutional Review Board of Reproductive Center, Shandong University. This retrospective cohort study included 154 couples with Robertsonian translocations (77 with a female carrier and 77 with a male carrier) whose embryos were tested using aCGH microchips between January 2013 and July 2017 in the Center for Reproductive Medicine, Shandong University. Karyotype analyses of the cultured blood lymphocytes were performed with conventional G-banding. The carriers of complex chromosome rearrangements were excluded. The spouses of the translocation carriers all had normal karyotypes. Data were excluded from cycles in which the embryos were first analyzed at the blastomere stage via FISH followed by aCGH at the blastocyst stage.

Ovarian stimulation, blastocyst culture, biopsy, and aCGH procedure

The procedures for ovarian stimulation, intracytoplasmic sperm injection (ICSI), embryo culture, and biopsy were described in the literature [24]. Ovarian stimulation was performed according to the clinical routine in the Center for Reproductive Medicine, Shandong University. ICSI was performed on metaphase II oocytes after aspiration. On day 5 or 6 after fertilization, the blastocysts were graded with the Gardner and Schoolcraft grading criteria [25], and good-quality blastocysts were drilled, with 4–6 trophoblast cells being biopsied.

Whole-genome amplification (WGA, SurePlex, Illumina, Inc., San Diego, CA, USA) of biopsied trophectoderm cells and the subsequent aCGH procedures (24Sure, Illumina) were carried out in the center according to the manufacturer's protocol, as described elsewhere [24]. Briefly, Cy5-labelled SureRef (Illumina) reference male DNA WGA products were comparatively hybridized with Cy3-labelled trophoblast cell WGA products. Microarray slides were scanned by a microarray scanner (InnoScan 900), and BlueFuse Multi software (BFM, Illumina) was used to analyze the images.

Embryos with a chromosome ratio within a ±0.3 log2 ratio were defined as euploid embryos and were normal or balanced for translocated chromosomes and normal for aneuploidy of chromosomes unrelated to the rearrangement. When a ratio was higher than a +0.3 log2 ratio or lower than a −0.3 log2 ratio, aneuploid was assigned. Embryos with more than 10 Mb chromosomal segments involved in aneuploidy were defined as having segmental abnormality.

Data analysis and statistics

The segregation patterns of the trivalent chromosomes were recorded. Data with a normal distribution were reported with the mean ± standard deviation and were compared with a two-sample Student's *t* test. Data with a skewed distribution were expressed with the median and quartile range and were compared with a Mann-Whitney *U* test. Categorical data were expressed as a frequency (percentage), with comparisons made with the chi-square test or Fisher exact test. A *P* value of less than 0.05 was considered to indicate statistical

significance. All statistical analyses were performed with SPSS version 21.0 software.

Results

Clinical characteristics and pregnancy outcomes of Robertsonian translocation carriers

Supplemental Table 1 lists the number of couples with Robertsonian translocation. In our 154 couples, the female carriers and the spouses of the male carriers had similar baseline characteristics (Table 1). The male carriers had worse semen parameters than the spouses of the female carriers, with significantly lower total counts of sperm and progressive motile sperm per ejaculation (Supplemental Table 2).

This study included 172 oocyte retrieval cycles. A total of 2104 cumulus-oocyte complexes were retrieved, and 1864 metaphase II oocytes (88.6%) underwent ICSI. Overall, 673 good-quality blastocysts were formed, from which 614 biopsy specimens were taken, and 604 (98.4%) were successfully diagnosed. The number of transferable euploid embryos was significantly higher in the male carriers than in the female carriers (Table 1).

The pregnancy outcomes did not differ significantly between the male and female carriers after the transfer of euploid blastocysts. Of the 144 embryo transfer cycles, 89 live birth deliveries (61.8%) were achieved, with two ongoing pregnancies (Table 1).

Analysis of segregation patterns of trivalent chromosomes

The meiotic segregation patterns were analyzed in 604 embryos. The frequencies of alternate, adjacent, and 3:0 segregation patterns were 411 (68.0%), 185 (30.6%), and 8 (1.3%), respectively.

The meiotic segregation patterns of the trivalent differed significantly ($P < 0.001$) between the female and male carriers. Compared with the female carriers, the male carriers had a significantly higher proportion of alternate segregation (82.9% vs. 55.2%; $P < 0.001$), a significantly lower proportion of adjacent segregation (16.8% vs. 42.6%; $P < 0.001$), and no difference in 3:0 segregation (0.4% vs. 2.2%; $P = 0.074$; Table 2). An analysis stratified by the carrier's age showed a similar distribution of meiotic segregation patterns in the whole group and in the young and advanced carrier subgroups. When stratified according to the type of Robertsonian translocation, a greater incidence of alternate segregation pattern was observed in the male carriers than in the female carriers with the same type of translocation. Meanwhile, similar incidences of alternate segregation were seen in the same carrier's sex (Fig. 1).

The carrier's age did not influence the trivalent's meiotic segregation patterns. When the analysis was stratified by the carrier's sex, the results remained the same (Table 3).

Analysis of chromosome abnormalities of blastocysts

Overall, as the maternal age increased, the incidence of euploid blastocyst (i.e., normal or balanced for the translocated chromosomes and normal for aneuploidy of chromosomes not involved in the translocation) decreased significantly and the aneuploidy rates of chromosomes unrelated to parental rearrangements increased significantly (Fig. 2). In both the female and male carrier subgroups, advanced maternal age was associated with a significantly higher rate of whole chromosome aneuploidy, whereas the rates of segmental abnormality were consistent (Supplemental Fig. 1). The proportion of euploid blastocysts was significantly higher in the male carrier subgroup than that in the female carrier subgroup with a maternal age of less than 35 years. The euploidy rates of blastocysts in the male carriers were 65.5%, 59.3%, 40.4%, and 33.3% when the maternal age was less than 30 years, 30 to 35 years, 35 to 40 years, and older than 40 years, respectively. The euploidy rates of blastocysts in the female carriers were 44.5%, 40.2%, 42.3%, and 10.0%, respectively (Fig. 2).

Discussion

With the development of techniques used for PGT-SR, 24-chromosome aneuploidy could be tested in the blastocysts of carriers of Robertsonian translocation, resulting in chromosome abnormalities due to the concurrent detection of unbalanced segregation of trivalent chromosomes and other *de novo* chromosome abnormalities. The incidence of aneuploidy of blastocysts was significantly higher in the female carriers than in the male carriers.

In this study, the proportions of the trivalent's meiotic segregation pattern differed significantly according to the sex of the Robertsonian translocation carrier. The male carriers had a significantly higher proportion of alternate segregation for normal or balanced chromosome contents than the female carriers, which is consistent with the findings of other studies performed by FISH [18, 19, 26]. The most common meiotic segregation pattern was alternate segregation, which showed rates of 55.2% in the female carriers and 82.9% in the male carriers. Meanwhile, the 3:0 segregation pattern was rarely observed.

The phenomenon in which meiotic segregation patterns differ significantly according to the carrier's sex in chromosomal structural rearrangements that involve acrocentric chromosomes was not exclusive in Robertsonian translocations. Our previous study showed that the sex of the autosomal reciprocal translocation carrier interacts with the involvement of

Table 1 General characteristics and PGT-SR outcomes of Robertsonian translocation carriers

Parameters	Female carriers	No.	Male carriers	No.	*P* value
Patient number	77	–	77	–	
History of live birth, *n* (%)	6 (7.8)		11 (14.3)		0.20
BMI (kg/m^2)	22.54 ± 3.11		22.61 ± 3.24		0.89
FSH (IU/L)	6.65 ± 1.69		6.73 ± 1.70		0.77
AMH (ng/ml)	5.08 ± 3.65	74	4.53 ± 3.15	76	0.33
Cycles to OR	90	–	82	–	
Female age[a] (years)	30.27 ± 4.34		30.88 ± 4.56		0.37
Male age[a] (years)	31.37 ± 5.21		31.90 ± 4.96		0.49
Embryology					
Retrieved oocytes	11 (7–17)	1105	11 (7–16)	999	0.95
Injected oocytes	9 (5–15)	965	10 (6–15)	899	0.68
2-pronuclei zygotes	7 (4–11)	758	7 (4–10)	645	0.67
Day 3 embryos	8 (4–12)	819	7.5 (5–12)	715	0.82
Good-quality blastocysts	3 (2–6)	365	3 (2–5)	308	0.82
Biopsied embryos	3 (2–5)	329	3 (2–5)	285	0.92
Diagnosed embryos	3 (2–5)	324	3 (2–5)	280	0.86
Euploid embryos	1 (0–3)	136	2 (1–3)	162	0.023
Clinical outcomes					
Transferred embryos	66	–	80	–	
FET cycles	65	–	79	–	
Positive hCG, *n* (%)	53 (81.5)		55 (69.6)		0.10
Biochemical pregnancies, *n* (%)	4 (6.2)		6 (7.6)		0.74
Implantation rate, *n* (%)	50 (75.8)		49 (61.3)		0.062
Clinical pregnancy rate per FET cycle, *n* (%)	49 (75.4)		49 (62.0)		0.087
Clinical pregnancy losses, *n* (%)	2 (3.1)		5 (6.3)		0.37
Deliveries, *n* (%)	45[b] (69.2)		44 (55.7)		0.096

AMH, anti-Mullerian hormone; *FET*, frozen embryo transfer; *OR*, oocyte retrieval; *PGT-SR*, preimplantation genetic testing for structural rearrangements

Normally distributed data are expressed as means ± standard deviation and data with skewed distribution are expressed as median (quartile)

[a] Age is calculated by the date of OR minus the date of birth

[b] Two ongoing pregnancies that complete 12 weeks of gestational age are not included

an acrocentric chromosome in translocation to influence the meiotic segregation patterns of a quadrivalent, which is formed during meiosis by two translocated chromosomes and their corresponding homologs [24]. In cases with reciprocal translocations that involve an acrocentric chromosome, male carriers have a significantly higher proportion of alternate segregation, which produces normal or balanced gametes, than female carriers, and the proportion of 3:1 segregation was significantly lower, whereas the meiotic segregation patterns in cases with reciprocal translocations that did not involve an acrocentric chromosome do not differ significantly between female and male carriers. In this scenario, a significant disparity exists in the incidence of alternate segregation according to the carrier's sex in translocations that involve acrocentric chromosomes in both reciprocal and Robertsonian translocations. Taken together, a higher rate of normal or balanced gametes produced by an alternate segregation pattern of structural rearrangements with acrocentric chromosome involvement was observed in the male carriers than in the female carriers.

Ultrastructural studies performed in human oocytes and spermatocytes regarding the spatial relationships of acrocentric chromosomes during prophase I of meiosis [27] and the results of semen analysis of affected male carriers may provide clues regarding the underlying mechanism. In our previous study, we proposed a hypothesis in which the effects of unbalanced meiotic segregation produced by translocations that involve an acrocentric chromosome on spermatogenesis were amplified due to the distribution behavior of acrocentric chromosomes in spermatogonia, resulting in the arrest of this procedure [24]. This hypothesis is supported by evidence that a significantly lower sperm count is observed in the male carriers of Robertsonian translocation than in the spouses of the female carriers. Moreover, in a post hoc analysis of semen results in reciprocal translocation carriers, a significantly

Table 2 Analysis of meiotic segregation patterns of the trivalent according to a carrier's sex

Segregation pattern	Carrier's sex, *n* (%)			*P* value
	Total	Female	Male	
Overall	604	324	280	< 0.001
Alternate	411 (68.0)	179 (55.2)	232 (82.9)	< 0.001
Adjacent	185 (30.6)	138 (42.6)	47 (16.8)	< 0.001
3:0	8 (1.3)	7 (2.2)	1 (0.4)	0.074
Carrier's age[a] < 35				
Overall	483	288	195	< 0.001
Alternate	322 (66.7)	160 (55.6)	162 (83.1)	< 0.001
Adjacent	155 (32.1)	122 (42.4)	33 (16.9)	< 0.001
3:0	6 (1.2)	6 (2.1)	0	0.086
Carrier's age[a] ≥ 35				
Overall	121	36	85	0.003
Alternate	89 (73.6)	19 (52.8)	70 (82.4)	< 0.001
Adjacent	30 (24.8)	16 (44.4)	14 (16.5)	0.001
3:0	2 (1.7)	1 (2.8)	1 (1.2)	0.51

[a] Carrier's age is calculated by the date of oocyte retrieval minus the date of birth

Table 3 Analysis of meiotic segregation patterns of the trivalent according to a carrier's age

Segregation pattern	Carrier's age[a], *n* (%)			*P* value
	Total	< 35 years	≥ 35 years	
Overall	604	483	121	0.29
Alternate	411 (68.0)	322 (66.7)	89 (73.6)	
Adjacent	185 (30.6)	155 (32.1)	30 (24.8)	
3:0	8 (1.3)	6 (1.2)	2 (1.7)	
Female carriers				
Overall	324	288	36	0.93
Alternate	179 (55.2)	160 (55.6)	19 (52.8)	
Adjacent	138 (42.6)	122 (42.4)	16 (44.4)	
3:0	7 (2.2)	6 (2.1)	1 (2.8)	
Male carriers				
Overall	280	195	85	0.32
Alternate	232 (82.9)	162 (83.1)	70 (82.4)	
Adjacent	47 (16.8)	33 (16.9)	14 (16.5)	
3:0	1 (0.4)	0	1 (1.2)	

[a] Carrier's age is calculated by the date of oocyte retrieval minus the date of birth

lower sperm count was observed in the male carriers of translocation that involves an acrocentric chromosome than in the carriers of one that does not involve an acrocentric chromosome and in the spouses of the female carriers, whereas the latter two subgroups had comparable total sperm counts (Supplemental Table 3).

In this study, we did not observe an influence of the carrier's age on the proportion of the trivalent's segregation pattern in Robertsonian translocations, consistent with the conclusion we drew from the analysis of balanced reciprocal translocations, in which a carrier's age showed no influence on the proportion of the quadrivalent's meiotic segregation. This may be a general characteristic in which the proportions of meiotic segregation pattern of structural rearrangements, regardless of the presence or absence of acrocentric chromosome involvement, are independent of the carrier's age.

In both the female and male carrier subgroups, we observed that advanced maternal age was associated with a significantly higher aneuploidy rate in blastocysts, which is consistent with the findings of other studies [24, 28]. The effect of the maternal age on genomic abnormalities is related to an abnormality of the chromosomes that is unrelated to the translocations, especially whole-chromosomal aneuploidy.

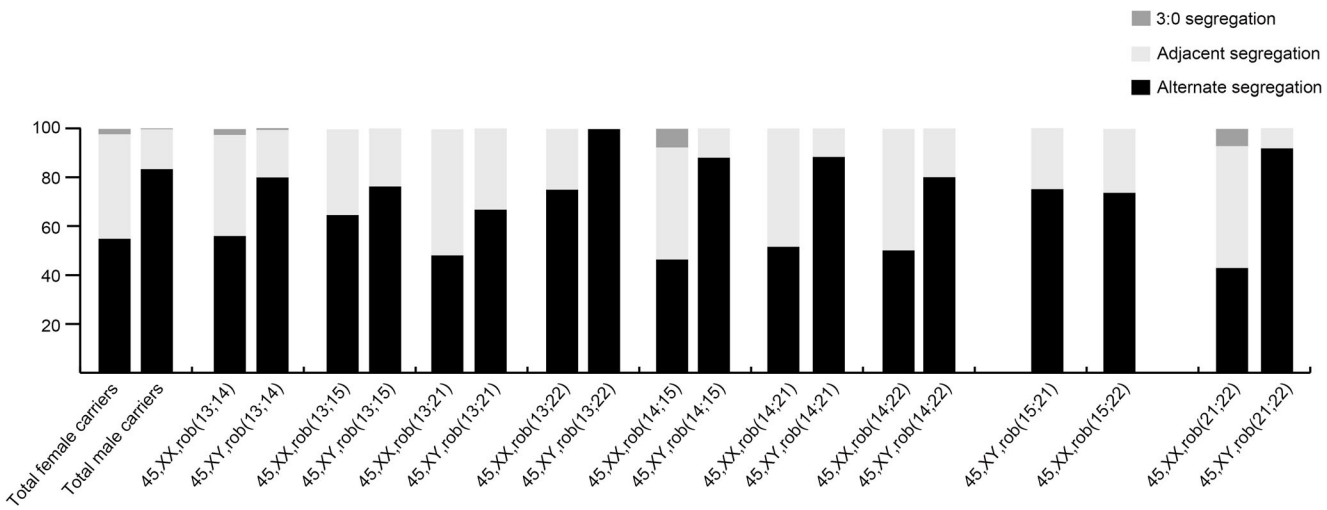

Fig. 1 Meiotic segregation patterns of female and male Robertsonian translocation carriers according to the type of the translocation

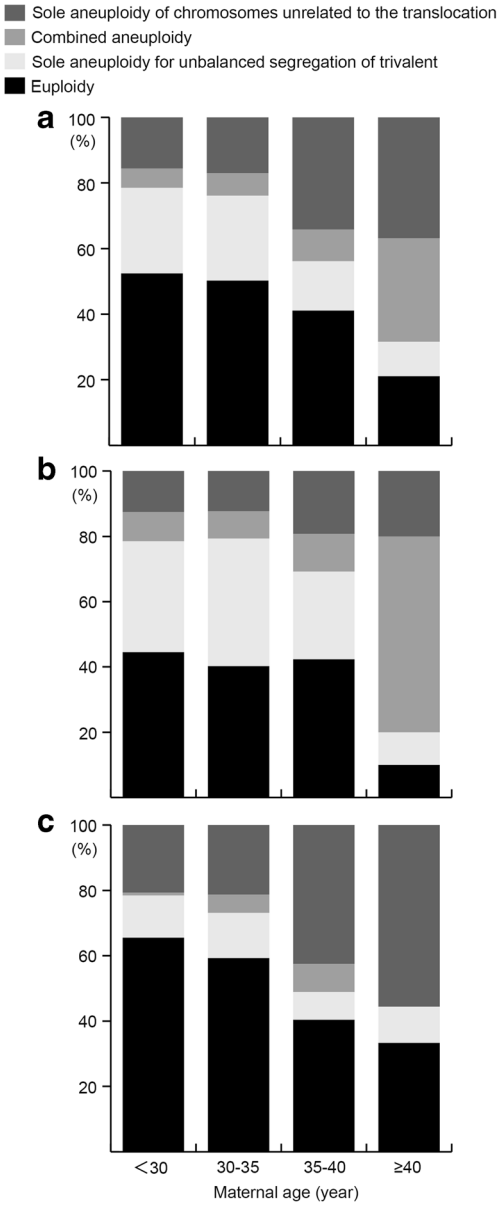

Fig. 2 Constitution of blastocyst for meiotic segregation of translocated chromosomes and aneuploidy of chromosomes unrelated to the translocation in general group independent of the sex of Robertsonian translocation carriers (**a**) and female (**b**) and male (**c**) carriers according to maternal age

PGT-SR has been recommended as an alternative to prenatal diagnosis in patients with structural rearrangements. The results of some studies showed a significantly higher rate of live births per embryo transfer cycle after the PGT procedure [29, 30], whereas one prospective cohort study concluded that the cumulative rate of live births was not higher in patients who undergo PGT than in those with natural conception [31]. Unlike the significantly lower euploidy rates of blastocysts observed in reciprocal translocation carriers [24], the euploidy rates of blastocysts observed in Robertsonian translocation carriers, especially male carriers, were considerable in this study and are comparable to that in the general population. A well-designed prospective study is needed to compare the reproductive outcomes in a subdivided population with either PGT or natural conception.

This study has several strengths. First, a joint analysis of Robertsonian translocations and reciprocal translocations provides strong support to the conclusions from our previous study [24]. From these two studies, we conclude that the proportions of meiotic segregation pattern differ significantly between the sexes in carriers with translocations that involve an acrocentric chromosome and that a significantly greater proportion of normal or balanced chromosome contents is produced in male carriers than in female carriers. In cases with translocations that do not involve an acrocentric chromosome, the proportions are similar between male and female carriers. Meanwhile, the carrier's age exerts no influence on the meiotic segregation patterns of translocated chromosomes. Furthermore, semen analysis has shown that unbalanced segregation patterns may increase the chance that spermatogenesis will be arrested in carriers of translocations that involve an acrocentric chromosome, resulting in a higher proportion of normal or balanced gametes in a significantly decreased concentration of semen. These conclusions could provide clues to explain the underlying mechanisms of meiotic segregation patterns in translocation carriers and assist with their reproductive risk assessment.

This study has some limitations. First, this was a retrospective study, so selection bias was inevitable. Second, patients with complex chromosome rearrangements were excluded, so it is inappropriate to apply these results to such couples. Third, because the parental origin of abnormal chromosome cannot be analyzed by aCGH, there is a chance that monosomies or trisomies of chromosomes involved in Robertsonian translocation at blastocyst stage were due to meiotic non-disjunction in gametes or during mitotic divisions after fertilization.

In conclusion, the proportions of the trivalent's meiotic segregation pattern in Robertsonian translocation differ significantly according to the carrier's sex and are independent of the carrier's age. A significantly higher proportion of alternate segregation for normal or balanced chromosome contents was observed in the blastocysts of the male carriers than in those of the female carriers.

Funding This study received financial support from the National Key Research and Development Program of China (2016YFC1000202); the National Natural Science Foundation of China (81671522); and the Innovative Fund of Reproductive Hospital Affiliated to Shandong University (20171114, 20171111).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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