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ORIGINAL ARTICLE

Exploration of the interchromosomal effects in preimplantation genetic testing for structural rearrangements based on next-generation sequencing

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Abstract

Background: To investigate the interchromosomal effect (ICE) in chromosome translocation carriers.

Methods: Data on preimplantation genetic testing aneuploidy and structural rearrangements (translocation) were retrospectively collected and classified into a reciprocal translocation group, a Robertsonian translocation group and a control group. According to the carrier's gender and age, all cases underwent further subgroup difference analysis of de novo abnormal embryo rates and the number of chromosomes involved in de novo abnormal embryos.

Results: Among the 283 couples who participated in this study, 1076 blastocysts from 352 cycles were collected, and 246 de novo abnormal embryos were included. There was a significant difference in the rate of de novo abnormal embryos among the three groups ($p < .05$) but no significant difference in the number of de novo abnormal chromosomes in the abnormal embryos ($p > .05$). Gender and age (classified by 35 years old) had no effect on the de novo abnormal embryo ratios among the translocation carriers ($p > .05$). However, the de novo abnormal ratio increased with age. The embryo constitution reflected no significant difference between the translocation groups ($p > .05$).

Conclusion: The ICE was detected for the translocation carriers. The de novo abnormal embryo ratio increased with age. Gender had no effect on the de novo abnormal embryo ratio. Translocation status played a more important role than age and gender.

Junmei Fan, Xueluo Zhang, Yanhua Chen contributed equally to this study.

KEYWORDS

age, gender, interchromosomal effect, next-generation sequencing, preimplantation genetic testing, translocation

1 | INTRODUCTION

Chromosomal structural rearrangement is the most common chromosome abnormality in the population with an incidence rate of 0.4% (Mateu-Brull et al., 2019); chromosomal reciprocal translocation, Robertsonian translocation and inversion are the most common types. Reciprocal translocation is the most common structural chromosome abnormality and is caused by the exchange of terminal fragments of different chromosomes (Morin et al., 2017). A change of position without an increase or decrease of visible chromosome segments is called balanced translocation, which typically has no obvious genetic effect. Robertsonian translocation is a special type of reciprocal translocation that involves the chromosome D and/or G groups that are fused at the centromere. Although the short arms of translocated chromosomes are also fused, aspect frequently tends to be absent during early cell division; thus, there is little impact on cell function due to the absence of unique genes in these areas (Morin et al., 2017). However, a high proportion of unbalanced gametes are produced due to chromosomal translocation and the interchromosomal effect (ICE) during meiosis (Zhang et al., 2016), resulting in a high risk of embryonic abnormalities, such as infertility, abortions, foetal retardation and neonatal congenital abnormalities (Mateu-Brull et al., 2019).

The ICE refers to parental chromosomal differences, such as translocation or inversion, which may increase the frequency of meiotic chromosome nondisjunction. Recently, whether the ICE exists has become a controversial argument. Some scholars believe that the ICE is only obvious during the cleavage stage of Robertsonian translocation carriers and that there is no ICE in polar bodies (oocytes) or during the blastocyst stage (Alfarawati et al., 2012). The ICE leads to a marked increase in aneuploidy in Robertson transmutation carriers. Other studies posited that the ICE also exists in reciprocal translocation carriers, or in both reciprocal translocation and Robertsonian translocation carriers (Piomboni et al., 2014). Additionally, scholars have posited that the ICE does not exist in chromosomal translocation carriers (Tulay et al., 2015). Existing studies have indicated the possibility of chromosome translocation affecting pregnancy to be between 10% and 15% and reported a relation to the carriers' gender (Zhang et al., 2019), as well as the type of chromosomal translocation and age (Zhang et al., 2018). Previous studies have indicated that an advanced age among pregnant women was an important factor that affected the chromosomal status of embryos and was closely related to embryonic aneuploidy (Xie et al., 2018). Age also has an impact on the meiotic segregation pattern of translocation carriers, which can increase genomic instability during meiosis. In addition, carrier gender affects the segregation pattern of gametes, and the meiotic segregation pattern and incidence of unbalanced gametes differ among different gender carriers. Male carriers of chromosomal translocations have normal phenotypes but may produce genetically unbalanced sperm, resulting in unbalanced embryos and miscarriages. How translocation chromosomes interfere with other non-participating chromosomes during embryogenesis remains unclear.

Preimplantation genetic testing (PGT) is a method for embryonic genetic evaluation before implantation. This process includes a PGT for monogenic disease (PGT-M), a PGT for aneuploidy (PGT-A) and a PGT for structural rearrangements (PGT-SR). The biopsy samples of a PGT can include the polar body, blastomere or trophectoderm cells. Currently, a trophoblast cell biopsy is recommended due to its minimal impact on the embryo's potential development, and the test results are more accurate compared with using polar and blastomere cells (Kokkali et al., 2007). The blastocyst stage is the best stage for conducting a biopsy, because it can provide more reliable test results as compared with the cleavage stage. Furthermore, considering the possible influence on embryo development potential, research in recent years has had a larger focus on non-invasive PGT (Farra et al., 2018).

During the past few decades, fluorescence in situ hybridisation has gradually been superseded by a single-nucleotide polymorphism array, a comparative genomic hybridisation array and next-generation sequencing (NGS). Among these methods, NGS is the most widely used technique for conducting a PGT and can simultaneously evaluate monogenic disease, chromosome translocation and mitochondrial genome abnormalities from the same biopsy sample, as well as analyse the deoxyribonucleic acid (DNA) sequences of embryos from different patients.

Based on the controversy involving the ICE and the age and gender of the embryonic chromosomes of couples with chromosome translocation, this study retrospectively collected PGT-A and PGT-SR data derived by NGS from our hospital's reproductive records to explore the

possibility of the presence of an ICE and the relationship between de novo abnormal embryos, age and gender to provide evidence for genetic consultation for translocation carriers.

2 | MATERIALS AND METHODS

2.1 | Patients

Couples who completed PGT-A and PGT-SR in our hospital from 1 January 2017 to 30 December 2019 were included in this study. The PGT-SR included only Robertsonian and reciprocal translocation carriers. All participants had received adequate genetic consultation and had signed the required informed consent forms for undergoing the PGT. According to the chromosomal status of the couples, the patients were divided into three groups: the reciprocal translocation carriers (the reciprocal translocation group), the Robertsonian translocation carriers (the Robertsonian translocation group) and the chromosome polymorphism carriers and/or normal chromosome patients (the control group).

2.2 | Ethical compliance

This study was a retrospective analysis and was approved by the medical ethics committee of our hospital (IRB-KYYN-2020-001).

2.3 | Inclusion and exclusion criteria

The inclusion criteria were as follows: (Mateu-Brull et al., 2019) Both the husband and the wife had normal and/or polymorphic chromosomes accompanied by recurrent abortions (two or more early spontaneous abortions) (Morin et al., 2017). Both the husband and the wife had normal and/or polymorphic chromosomes accompanied by repeated implantation failure (three or more transplantations with one to two high-quality embryos at a time) (Zhang et al., 2016). The husband or the wife was a translocation carrier. The first two groups were the control groups, and the third group was the experimental group.

The exclusion criteria were as follows: (Mateu-Brull et al., 2019) Both the husband and the wife were translocation carriers, leading to the bivariate, which was not conducive to the analysis of the effect of gender on the ICE (Morin et al., 2017). The husband or the wife had complex translocations including more than two chromosomes or translocation referring to sex chromosomes, which affected the assemblage and segregation of gametes (Zhang et al., 2016). The patients had incomplete data (Alfarawati et al., 2012). Both the husband and the wife had normal and/or polymorphic chromosomes, and the maternal age was older than 38 years old, as an advanced age would have affected chromosomal stability (Piomboni et al., 2014). The husband had undergone PGT-A cycles due to severe oligoasthenozoospermia; this would have affected chromosomal stability.

2.4 | The trophoblast cell biopsy and the NGS procedure

According to the patients' ovarian response, a personalised controlled superovulation plan was adopted and follicle growth was monitored by transvaginal ultrasound. When the average diameter of three follicles was ≥18 mm, an 8000–10,000 IU human chorionic gonadotropin intramuscular injection (Livzon, CN) was administered. After 34–36 h, the eggs were retrieved under the guidance of a transvaginal ultrasound and preserved in a G-GAMETE solution (Vitrolife, SE). The granulosa cells around the eggs were removed under a microscope, and the mature eggs were observed before performing the intracytoplasmic sperm injection, then washed, cultured and inseminated in a G-IVF solution (Vitrolife, SE). The embryos were sequentially cultured in a G1 and G2 culture media to the blastocyst stage (D5–D6). Next, 20% human serum albumin (Vitrolife, SE) was added to the culture medium. The embryos were cryopreserved by vitrification following the trophectoderm biopsy. The biopsy samples were loaded into a 0.2 ml ribonucleic acid (RNA)-free PCR tube filled with a 2.5 μl phosphate buffered saline solution and transported to the Shenzhen Genomics Institute Co., Ltd. In this study, the NGS technique was used to detect the copy number variations. SurePlex DNA Amplification (Illumina, US) was adopted for whole genome amplification; the DNA quality evaluation, the construction of a sequencing library and its quality evaluation, and sample sequencing and data analysis according to the standard processes were performed. The BGI-Seq500 high-throughput sequencing instrument was adopted; however, it was unable to detect high chromosome repetition, high pyknosis regions (chromosome abnormalities in or near the centromere and telomere regions and Robertsonian translocation), additional polyploid variations except for triploid, gains or losses smaller than 4 Mb, translocation, inversion, low proportion mosaicism and uniparental disomy. The sequence that was obtained by bioinformatics analysis was compared with the human reference genome RCh37/hg19, and the number of

unique corresponding sequences of each chromosome was counted to infer the copy number variation of the entire chromosome. The final results were obtained by consulting the gene variation database (DGV, http://dgv.tcag.ca/dgv/app/home), the online human Mendelian genetic database (OMIM, http://www.omim.org), the human chromosome imbalance and phenotype database (DECIPHER, http://decipher.sanger.ac.uk/), the human genome database (GeneCards, http://www.genecards.org/) and the International Standard for Cell Genome Microarray Analysis (ISCA, http://dbsearch.clinicalgenome.org/search/). Genetic advice was then provided.

2.5 | Outcomes analysis standard

The embryos with no gains or losses that were larger than 4 Mb were regarded as normal/balanced embryos; others were regarded as abnormal embryos. The abnormal parental translocation chromosomes were related to abnormal embryos, otherwise, these were de novo chromosome abnormal embryos, while the embryos with unbalanced translocation chromosomes resulting from parents and de novo abnormalities simultaneously were related to de novo abnormal embryos. Mosaic chromosomes in abnormal embryos were classified as reflecting aneuploidy. Aneuploid chromosomes that were involved in the translocation of parents go in related abnormal winter, and aneuploid chromosomes that were not involved in the translocation of parents go in de novo abnormal winters.

2.6 | Statistical analysis

We used the SPSS 24.0 (IBM, Chicago, USA) software to conduct the statistical analysis. The continuous variables of normal distribution were expressed as the mean ± standard deviation; the continuous variables of non-normal distribution were expressed as a median (interquartile range), and the categorical variables were expressed as a frequency (percentage). For multiple comparisons, each value was compared by a one-way analysis of variance following a Dunnett's test when each datum conformed to a normal distribution, while non-normally distributed continuous data were compared using non-parametric tests. The counting data were tested using a chi-square test. A p value $< .05$ was considered statistically significant.

3 | RESULTS

3.1 | General information

In this study, 283 couples were included, with a total of 352 cycles. There were 1076 blastocysts, and there were 246 de novo abnormal embryos. The reciprocal translocation carriers included 144 cycles from 102 cases. The Robertsonian translocation carriers included 61 cycles from 46 cases, and the chromosome polymorphism/normal chromosomes comprised 147 cycles from 135 cases. The results showed that a difference in maternal age was not significant in the three groups ($p > .05$), and differences in the paternal age in the three groups were not significant ($p > .05$) (Table 1). There was no significant difference in the proportion of different gender carriers between the reciprocal translocation and the Robertsonian translocation groups ($p > .05$).

3.2 | The influence of ICE on de novo abnormal embryos in the PGT-SR of translocation carriers

The difference in the de novo abnormal embryo ratios was significant among the three groups ($p < .05$). We conducted additional subgroup comparisons that indicated the presence of a significant difference in the de novo abnormal ratios between the control and the reciprocal translocation groups ($p < .05$); there was also a significant difference in the de novo abnormal ratios between the control and the Robertsonian translocation groups ($p < .05$). There was no significant difference between the reciprocal translocation and the Robertsonian translocation groups ($p > .05$) (Table 2). Upon further comparison of the number of de novo abnormal chromosomes of embryos among the reciprocal translocation, the Robertsonian translocation, and the polymorphism/normal chromosome groups, no

TABLE 1 The difference of couples age in three groups [median (interquartile range)]

Group	Maternal age (*n*/%)	*F*	*p*	Paternal age (*n*/%)	*F*	*p*
Control group	30/4.00	5.651	.059	32/4.00	2.694	.260
Robertsonian translocation	30/4.00			31/4.25		
Reciprocal translocation	29/4.25			31/5.25		

TABLE 2 Comparison of de novo abnormal embryos ratio in different chromosome state

Group	De novo abnormal embryo (*n*/%)	Non de novo embryo (*n*/%)	χ^2	*p*
Control group	74/16.3	379/83.7	19.675	.000#
Robertsonian translocation	38/25.0	114/75.0	5.664	.017#
Reciprocal translocation	134/28.5	337/71.5	19.428	.000#

Notes: The de novo chromosomal abnormal embryos in reciprocal translocation and Robertsonian translocation groups referred to completely de novo abnormal embryos + de novo and unbalanced translocation abnormal embryos. "#" representing the difference was significant. The ratio of de novo abnormal embryos was no significant between reciprocal translocation group and Robertsonian translocation group ($\chi^2 = 0.648$, $p = .408$).

TABLE 3 Comparison of referring abnormal chromosomes number in de novo abnormal chromosomes in three groups

Group	1 chromosome (*n*/%)	2 chromosomes (*n*/%)	≥3 chromosomes (*n*/%)	Total	χ^2	*p*
Control group	48/64.9	20/27.0	6/8.1	74	2.798*	.592
Robertsonian translocation	28/73.7	8/21.1	2/5.3	38		
Reciprocal translocation	99/73.9	24/17.9	11/8.2	134		

Note: "*" representing correction for continuity of chi-square test was used.

significant difference was found in the rate of abnormal embryos, respectively, with one, two and three or more de novo abnormal chromosomes ($p > .05$) (Table 3).

3.3 | The effect of different carrier ages on the de novo abnormal embryo ratios among translocation carriers

An age subgroup analysis was conducted according to different gender carrier ages. In the reciprocal translocation group, there was no significant difference in the de novo abnormal embryo ratios between the <35- and ≥35-year-old groups, regardless of maternal or paternal age grouping ($p > .05$). In the Robertsonian translocation group, there was no significant difference in the de novo abnormal embryo ratios between the <35- and ≥35-year-old groups, regardless of maternal or paternal age grouping ($p > .05$) (Table 4).

3.4 | The influence of different gender translocation carriers on de novo abnormal embryos in the PGT-SR

Comparing the effect of translocation carrier gender on the de novo abnormal embryo rate of the reciprocal translocation and the Robertsonian translocation groups, no significant difference was found in de novo abnormal embryo ratios ($p > .05$) (Table 5). Furthermore, there was no significant difference for the testing of embryo chromosome types between different gender carriers in the reciprocal translocation group ($p > .05$) (Table 6), and no significant differences for the tested embryo chromosome types between different gender carriers in the Robertsonian translocation group ($p > .05$) (Table 6).

4 | DISCUSSION

The ICE was first described by Lejeune (1963) and referred to the chromosomes that interfere with the correct segregation of other chromosomes by disturbing the arrangement of chromosomes on the spindle during the meiosis stage. During this stage, the location and pairing of rearranged chromosomes may affect embryogenesis and impact the location and pairing of non-translocation chromosomes and may even alter their separation pattern. The segregation error of translocation chromosomes in meiosis may lead to a deviation in mitosis and cause centrosome amplification, abnormal chromosome segregation and genomic instability, thereby resulting in the aneuploidy of unrelated chromosomes (Xie et al., 2018); specifically, de novo abnormal chromosomes will occur. Differences in the ICE incidence among couples may be related to the size of rearranged fragments and the specific chromosomes involved in these rearrangements. Other factors may also contribute in this regard, such as maternal age and semen abnormalities; however, the data are conflicting as to whether an ICE truly exists in humans (Miller, 2020). Some studies have suggested that an ICE exists in PGT embryos, while others have indicated this effect to be negligible or even absent (Alfarawati et al., 2011; Anton et al., 2008).

In this study, we conducted trophectoderm biopsies at the blastocyst stage and found the difference in the de novo abnormal embryo ratios among the three groups to be significant. This indicated that the ICE did exist in patients

TABLE 4 Analysis of difference gender carrier age influence on de novo abnormal embryo rate of translocation carrier couples

	Maternal (year) (*n*/%)				Paternal (year) (*n*/%)			
Group	**<35**	**≥35**	χ^2	***p***	**<35**	**≥35**	χ^2	***p***
Robertsonian translocation								
De novo abnormal embryo	17/20.5	3/37.5	0.440*	.507	12/24.5	6/50.0	1.914*	.167
Non de novo embryo	66/79.5	5/62.5			37/75.5	6/50.0		
Reciprocal translocation								
De novo abnormal embryo	61/28.5	8/30.8	0.058	.810	55/27.1	10/35.7	0.904	.342
Non de novo embryo	153/71.5	18/69.2			148/72.9	18/64.3		

Note: "*" representing correction for continuity of chi-square test was used.

TABLE 5 Comparison of de novo abnormal embryo ratio of difference gender carrier in translocation carrier couples

	Robertsonian translocation (*n*/%)		Reciprocal translocation (*n*/%)		Translocation (*n*/%)	
Gender	**De novo**	**Non de novo**	**De novo**	**Non de novo**	**De novo**	**Non de novo**
Maternal	20/22.0	71/78.0	65/28.1	166/71.9	85/26.4	237/73.6
Paternal	18/29.5	43/70.5	69/28.7	171/71.3	87/28.9	214/71.1
χ^2	1.104		0.022		0.489	
p	.293		.883		.484	

TABLE 6 Comparison of testing embryos constitutes of the different carrier gender in reciprocal translocation and Robertsonian translocation

Group	**Normal/translocation (*n*/%)**	**Relevant (*n*/%)**	**Relevant and de novo (*n*/%)**	**Completely de novo (*n*/%)**	χ^2	***p***
Robertsonian translocation						
Maternal	40/44.0	31/34.1	5/5.5	15/16.5	0.001	.975
Paternal	33/54.1	10/16.4	6/9.8	12/19.7		
Reciprocal translocation						
Maternal	90/37.55	81/33.8	37/15.4	32/13.3	2.029	.566
Paternal	96/41.6	70/30.3	29/12.6	36/15.6		
Total	256	192	77	95		

with translocation in the PGT-SR; however, no significant difference was found in the number of de novo abnormal chromosomes among the three groups. Additional pairwise comparisons were made among the three groups that indicated that the ICE was obvious among the reciprocal translocation and the Robertsonian translocation carriers. This result was consistent with existing studies on reciprocal and Robertsonian translocations (Tulay et al., 2015). In the chromosome segregation of reciprocal translocation patients, the exchanged chromosome fragments interfered with the pairing and segregation of other chromosomes. In Robertsonian translocation patients, this may be due to the short arm of the acrocentric chromosome comprising ribosomal RNA tandem copies, which are located in the nucleolus during the interphase of cell division. When the Robertsonian translocation chromosome forms, the short arm will disappear, resulting in the failure to integrate with the nucleolus during the interphase and a change in the nucleolar structure that may affect other chromosomes. Research conducted by Alfarawati et al. (Alfaravati et al., 2012) implied that the ICE was only clearly observed during the cleavage stage and not in the polar bodies (oocytes) or blastocyst specimens, indicating that the ICE may have originated from mitosis rather than meiosis; the study also considered the ICE to have been limited to a narrow window of development, that is, the immediate process of cell division after fertilisation. A possible reason for this was because of the loss or fossilisation of cellular regulatory mechanisms such as cell cycle checkpoints, of which the function is to maintain chromosome segregation and

genomic integrity during the period from fertilisation to the 4–8 cell stage, which, in turn, will lead to instability of the embryonic genome that provides the necessary environment for the ICE. In this study, the ICE was observed in the blastocysts of the reciprocal translocation and the Robertsonian translocation carriers. Compared with existing studies, we included more cases and employed comprehensive monitoring of chromosomes by NGS.

An existing study found that the meiotic segregation pattern of the reciprocal translocation carriers was affected by carrier age (Zhang et al., 2018). The age-related tendency of chromosome non-segregation and the ICE led to obvious errors in other chromosomes, which aggravated the frequency of embryonic chromosome aneuploidy during meiosis in the reciprocal translocation carriers (Xie et al., 2018). However, some scholars posited the opposite opinion, that is, that age did not affect the meiotic segregation behaviour of translocation carriers (Ko et al., 2010). In the Robertsonian translocation group, there was no significant difference in the ratios of de novo chromosome abnormalities and age between the paternal groups aged <35 and ≥35 years, whether grouped by maternal or paternal age ($p > .05$). In the reciprocal translocation carriers, there was also no significant difference in the ratios of de novo chromosome abnormalities and age between the <35- and ≥35-year-old groups, whether grouped according to maternal or paternal age ($p > .05$). Our results again confirmed that the occurrence of de novo chromosome abnormalities was unrelated to maternal age. In general, advanced maternal age has always been considered a risk factor for embryonic chromosome abnormalities. The incidence of chromosome abnormalities increases significantly with a higher maternal age (Grande et al., 2012), particularly concerning the chromosome aneuploidy rate. In this study, the abnormal embryo ratio increased with age. More than 90% of chromosomal imbalances in embryos were maternal, which may have been due to the premature separation of sister chromatids during egg meiosis (Cimadomo et al., 2018). In the reciprocal and the Robertsonian translocation carriers, the influence of maternal age on the de novo abnormal embryos may have been masked by the chromosome translocation status. Therefore, we inferred that the influence of couple chromosome status on de novo abnormal embryo occurrence was greater than maternal and paternal age in the translocation carriers.

In the separation pattern of the reciprocal translocation carriers tetravalent and the Robertsonian translocation carriers trivalent, only alternating separation can produce usable equilibrium gametes. Some studies validated that carrier gender affected the pattern of gamete meiotic separation (Scriven et al., 2013). The proportion of gamete meiotic segregation patterns in Robertsonian translocation carriers varies significantly, based on the carrier's gender, although alternating segregation was the most common meiotic segregation in Robertsonian translocation carriers (Xie et al., 2018). The alternating segregation proportion among the paternal Robertsonian translocation carriers was significantly higher than that of the maternal carriers, while the proportion of adjacent segregation among the maternal carriers was higher. As such, the maternal carriers were more likely to produce unbalanced translocation gametes than the paternal carriers were. In this study, the normal/translocation embryo rate of the paternal carriers was higher than that of the maternal carriers in the reciprocal translocation and the Robertsonian translocation groups. The mechanism here may be related to the different germline checkpoints of mammals. The spermatocyte meiosis checkpoint appears to produce haploid gametes much more easily with the correct DNA content than the oocyte meiosis checkpoint; in this situation, the proportion of unbalanced sperm produced is typically lower than that of unbalanced oocytes. In addition, with maternal ageing, the probability of the non-separation of homologous chromosomes and sister chromatids, or premature separation during gamete meiosis, increases, resulting in a higher probability of de novo abnormal embryos (Cimadomo et al., 2018). Accordingly, it is believed that maternal meiosis is more prone to errors that are likely to lead to abnormal embryos compared with paternal meiosis. Although gender may give rise to different meiotic patterns in translocation carriers, scholars have found that these differences did not affect the proportion of balanced embryos in reciprocal translocation carriers (Lledó et al., 2010). In the cases of translocation without acrocentric chromosomes, the proportion of available embryos in the paternal carriers was similar to that in the maternal carriers, and gender did not affect the abnormal embryo rate of the Robertsonian translocation carriers (Huang et al., 2010). This study further confirmed that gender had no effect on the incidence of de novo abnormal embryos in the reciprocal and the Robertsonian translocation carriers, and different gender carriers did not affect the incidence of embryonic chromosomal types in the translocation carriers.

5 | LIMITATIONS

This study included several limitations. First, it was a single-centre trial; multiple centre trials are needed in the future to support the findings presented herein. Second, the sample size of this study was limited; hence, conducting a larger trial with more participants is necessary.

6 | CONCLUSION

This study showed that the chromosome translocation of carriers had an effect on the de novo abnormal embryo rate in the blastocyst stage. An ICE was present for translocation carriers. The de novo abnormal embryo ratio increased with age in both the Robertsonian and the reciprocal translocation carriers. Chromosome translocation status had a larger influence than age. Different gender carriers did not affect the de novo abnormal embryo ratio. Therefore, when genetic consultation is conducted, the chromosomal status of spouses and their ages should be taken into consideration and accompanied by reasonable suggestions.

AUTHOR CONTRIBUTIONS

Fan JM designed and interpreted the data and wrote the first draft of the article. Zhang XL designed and critically reviewed and edited drafts. Wu XQ and Yan MQ critically reviewed and edited the drafts. Chen YH analysed, interpreted data. Zhang JK, Zhang L, Bi XY, Wang JB and Huang X collected materials and interpreted data. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

All the authors have no personal, financial, commercial, or academic conflicts of interest to declare.

ETHICAL STATEMENT

This study is a retrospective analysis and has been approved by the Medical Ethics Committee of Children's Hospital of Shanxi and Women Health Center of Shanxi (IRB-KYYN-2020-001). Written informed consent has been obtained from all participants.

CONSENT FOR PUBLICATION

The manuscript is not submitted for publication or consideration elsewhere.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article.

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REFERENCES

Alfarawati, S., Fragouli, E., Colls, P., & Wells, D. (2011). First births after preimplantation genetic diagnosis of structural chromosome abnormalities using comparative genomic hybridization and microarray analysis. *Human Reproduction*, *26*, 1560–1574. https://doi.org/10.1093/humrep/der068

Alfarawati, S., Fragouli, E., Colls, P., & Wells, D. (2012). Embryos of robertsonian translocation carriers exhibit a mitotic interchromosomal effect that enhances genetic instability during early development. *PLoS Genetics*, *8*, e1003025. https://doi.org/10.1371/journal.pgen.1003025

Anton, E., Vidal, F., & Blanco, J. (2008). Reciprocal translocations: Tracing their meiotic behavior. *Genetics in Medicine*, *10*, 730–738. https://doi.org/10.1097/GIM.0b013e318187760f

Cimadomo, D., Fabozzi, G., Vaiarelli, A., Ubaldi, N., Ubaldi, F. M., & Rienzi, L. (2018). Impact of maternal age on oocyte and embryo competence. *Frontiers in Endocrinology*, *9*, 327. https://doi.org/10.3389/fendo.2018.00327

Farra, C., Choucair, F., & Awwad, J. (2018). Non-invasive preimplantation genetic testing of human embryos: An emerging concept. *Human Reproduction*, *33*, 2162–2167. https://doi.org/10.1093/humrep/dey314

Grande, M., Borrell, A., Garcia-Posada, R., Borobio, V., Munoz, M., Creus, M., Soler, A., Sanchez, A., & Balasch, J. (2012). The effect of maternal age on chromosomal anomaly rate and spectrum in recurrent miscarriage. *Human Reproduction*, *27*, 3109–3117. https://doi.org/10.1093/humrep/des251

Huang, J., Liu, P., Qiao, J., Lian, Y., & Chen, Y. J. (2010). Translocation chromosome karyotypes of the Robertsonian translocation carriers' embryos. *Fertility and Sterility*, *93*, 1061–1065. https://doi.org/10.1016/j.fertnstert.2008.11.020

Ko, D. S., Cho, J. W., Park, S. Y., Kim, J. Y., Koong, M. K., Song, I. O., Kang, I. S., & Lim, C. K. (2010). Clinical outcomes of preimplantation genetic diagnosis (PGD) and analysis of meiotic segregation modes in reciprocal translocation carriers. *American Journal of Medical Genetics. Part A*, *152a*, 1428–1433. https://doi.org/10.1002/ajmg.a.33368

Kokkali, G., Traeger-Synodinos, J., Vrettou, C., Stavrou, D., Jones, G. M., Cram, D. S., Makrakis, E., Trounson, A. O., Kanavakis, E., & Pantos, K. (2007). Blastocyst biopsy versus cleavage stage biopsy and blastocyst transfer for preimplantation genetic diagnosis of beta-thalassaemia: A pilot study. *Human Reproduction*, *22*, 1443–1449. https://doi.org/10.1093/humrep/del506

Lejeune, J. (1963). Autosomal disorders. *Pediatrics*, *32*, 326–337.

Lledó, B., Ortiz, J. A., Morales, R., Ten, J., de la Fuente, P. E., García-Ochoa, C., & Bernabeu, R. (2010). The paternal effect of chromosome translocation carriers observed from meiotic segregation in embryos. *Human Reproduction*, *25*(7), 1843–1848. https://doi.org/10.1093/humrep/deq111

Mateu-Brull, E., Rodrigo, L., Peinado, V., Mercader, A., Campos-Galindo, I., Bronet, F., García-Herrero, S., Florensa, M., Milán,

M., & Rubio, C. (2019). Interchromosomal effect in carriers of translocations and inversions assessed by preimplantation genetic testing for structural rearrangements (PGT-SR). *Journal of Assisted Reproduction and Genetics*, *36*, 2547–2555. https://doi.org/10.1007/s10815-019-01593-9

Miller, D. E. (2020). The Interchromosomal effect: Different meanings for different organisms. *Genetics*, *216*, 621–631. https://doi.org/10.1534/genetics.120.303656

Morin, S. J., Eccles, J., Iturriaga, A., & Zimmerman, R. S. (2017). Translocations, inversions and other chromosome rearrangements. *Fertility and Sterility*, *107*, 19–26. https://doi.org/10.1016/j.fertnstert.2016.10.013

Piomboni, P., Stendardi, A., & Gambera, L. (2014). Chromosomal aberrations and aneuploidies of spermatozoa. *Advances in Experimental Medicine and Biology*, *791*, 27–52. https://doi.org/10.1007/978-1-4614-7783-9_3

Scriven, P. N., Flinter, F. A., Khalaf, Y., Lashwood, A., & Ogilvie, C. M. (2013). Benefits and drawbacks of preimplantation genetic diagnosis (PGD) for reciprocal translocations: Lessons from a prospective cohort study. *European Journal of Human Genetics*, *21*, 1035–1041. https://doi.org/10.1038/ejhg.2013.9

Tulay, P., Gultomruk, M., Findikli, N., Yagmur, E., & Bahceci, M. (2015). Is the interchromosomal effect present in embryos derived from Robertsonian and reciprocal translocation carriers particularly focusing on chromosome 10 rearrangements? *Zygote*, *23*, 908–915. https://doi.org/10.1017/S0967199414000628

Xie, Y., Xu, Y., Wang, J., Miao, B., Zeng, Y., Ding, C., Gao, J., & Zhou, C. (2018). Preliminary analysis of numerical chromosome abnormalities in reciprocal and Robertsonian translocation preimplantation genetic diagnosis cases with 24-chromosomal analysis with an aCGH/SNP microarray. *Journal of Assisted Reproduction and Genetics*, *35*, 177–186. https://doi.org/10.1007/s10815-017-1045-9

Zhang, L., Jiang, W., Zhu, Y., Chen, H., Yan, J., & Chen, Z. J. (2019). Effects of a carrier's sex and age on the segregation patterns of the trivalent of Robertsonian translocations. *Journal of Assisted Reproduction and Genetics*, *36*, 1963–1969. https://doi.org/10.1007/s10815-019-01534-6

Zhang, S., Lei, C., Wu, J., Sun, H., Zhou, J., Zhu, S., Wu, J., Fu, J., Sun, Y., Lu, D., Sun, X., & Zhang, Y. (2018). Analysis of segregation patterns of quadrivalent structures and the effect on genome stability during meiosis in reciprocal translocation carriers. *Human Reproduction*, *33*, 757–767. https://doi.org/10.1093/humrep/dey036

Zhang, W., Liu, Y., Wang, L., Wang, H., Ma, M., Xu, M., Xu, X., Gao, Z. Y., Duan, J., Cram, D. S., & Yao, Y. (2016). Clinical application of next-generation sequencing in preimplantation genetic diagnosis cycles for Robertsonian and reciprocal translocations. *Journal of Assisted Reproduction and Genetics*, *33*, 899–906. https://doi.org/10.1007/s10815-016-0724-2

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