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ARTICLE

Quadrivalent asymmetry in reciprocal translocation carriers predicts meiotic segregation patterns in cleavage stage embryos

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Dr Yueping Zhang graduated with a master's degree in reproductive endocrinology in 1992 and a PhD in perinatal medicine in 2000 from Fudan University. Since June 1994, she has worked in the area of genetic counselling and prenatal diagnosis. In 2011, Dr Zhang Yueping and her medical team received government approval to offer preimplantation genetic diagnosis services in Shanghai. Dr Zhang Yueping is the director of genetic division in Shanghai Ji Ai Genetics and IVF Institute, Obstetrics and Gynecology Hospital, Fudan University. Her research fields include reproductive genetics and prevention of birth defects.

Abstract The effect of quadrivalent geometry on meiotic behaviour was evaluated. Segregation patterns of 404 cleavage stage embryos from 40 reciprocal translocation carriers undergoing 75 PGD cycles were analysed according to the asymmetric degree of quadrivalent. The percentage of alternate products with severe asymmetric quadrivalents was significantly lower than patients with mild asymmetric quadrivalents (22.5% versus 38.7%, $P = 0.001$). The incidence of 3:1 products was significantly higher in patients with severe compared with mild asymmetric quadrivalents (23.1% versus 12.2%, $P = 0.004$). The incidence of adjacent 1 (25.8% versus 24.3%), 2 (11.5% versus 12.6%) and 4:0/other segregation products (17.0% versus 12.2%) were not statistically significantly different between embryos from patients with severe or mild asymmetric quadrivalents. After adjusting for the confounder of sex using a logistic regression model, the odds of alternate embryos is about one-half for carriers classified as severe (OR 0.456, 95% CI 0.291 to 0.705), and the odds of 3:1 embryos is 2.2 times higher for carriers with severe asymmetric quadrivalents (OR 2.235, 95% CI 1.318 to 3.846). Our results suggest that the meiotic segregation pattern is related to the degree of asymmetry of specific quadrivalents. Severe asymmetric quadrivalents increases the risk of abnormal embryos.

KEYWORDS: meiotic segregation pattern, preimplantition genetic diagnosis, quadrivalent asymmetry, reciprocal translocation

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Introduction

Reciprocal translocations are one of the most common structural chromosome abnormalities in humans, with an incidence of 0.14% in newborns (Nielsen and Wohlert, 1991) and 0.6% in infertile couples (Meschede et al., 1998). The prevalence is even higher in men with azoospermia or severe oligozoospermia (1.4%) (Clementini et al., 2005) and in couples with a history of recurrent spontaneous abortions (6.2%, Stern et al., 1999). Carriers are phenotypically normal, as there is no loss or gain of genetic material. They are, however, at a high risk of producing genetically unbalanced gametes that are associated with recurrent spontaneous abortion, infertility or children with birth defects, developmental or intellectual disabilities, or both. Because of these outcomes, there is great interest in understanding the meiotic segregation behaviour of translocated chromosomes found in the gametes of translocation carriers.

At meiosis I, the two pairs of chromosomes involved in a reciprocal translocation synapse to form a quadrivalent. There are three broad modes of chromosome segregation from a quadrivalent: 2:2 (two chromosomes segregate to one cell and two chromosomes to the other), 3:1 (three chromosomes to one cell and one to the other), and 4:0 (all chromosomes of the quadrivalent go to one cell and none to the other). Within the 2:2 mode of segregation, chromosome disjunction can be alternate, adjacent 1, or adjacent 2. Allowing for recombination, 32 possible products can be produced in gametes, each with different chromosomal combinations (Scriven et al., 1998). Alternate segregation is the only segregation pattern that yields gametes with balanced genetic complements: one with normal chromosomes and the other with the balanced translocated chromosomes. On the basis of theoretical modes of segregation for reciprocal translocation carriers, the chance for balanced gametes and normal offspring is low.

Studies on meiotic segregation patterns of sperm from reciprocal translocation carriers have revealed extreme patient to patient variability for segregation modes as follows: alternate segregation (18.6 to 77.2%); adjacent 1 (3.7 to 63.4%); adjacent 2 (0.7 to 40.1%); 3:1 (0 to 46.8%); and 4:0 (0 to 0.8%) (Benet et al., 2005). Moreover, data from embryos of patients undergoing PGD showed variable frequencies for segregation patterns in different studies (Ko et al., 2010; Lim et al., 2008; Munné, 2005; Ye et al., 2012). It is postulated that each reciprocal translocation behaves differently at meiosis owing to the geometry of the quadrivalent and, therefore, the frequency of each mode of segregation will be patient specific and depend on the position of chromosome breakpoints (Kékesi et al., 2007; Mackie Ogilvie and Scriven, 2002). Therefore, certain translocations will be predisposed toward specific modes of segregation (Benet et al., 2005; Lim et al., 2008). As a result, although some carriers are associated with a high risk of spontaneous abortion or abnormal live births, others seem to experience less reproductive problems and have a greater frequency of pregnancies with normal or balanced chromosomes.

In order to provide each translocation carrier couple with more appropriate genetic counselling, the unique characteristics of their translocation should be distinguished. It has been reported that reciprocal translocation carriers with terminal breakpoints produce a lower per cent of alternate products (Ye et al., 2012), whereas translocations with acrocentric chromosomes produce a higher rate of 3:1 segregants (Ye et al., 2012; Yilmaz et al., 2012). Therefore, breakpoints at terminal or centromeric positions, or translocations involving acrocentric chromosomes seem to have skewed segregation toward unbalanced products. Because quadrivalent configurations will usually be highly asymmetric when the translocated or centric segments are small in size, it is likely that resulting segregation patterns can be correlated with the asymmetry profile of a specific quadrivalent. If so, it may be possible to predict with more precision the patient-specific chance for chromosomally balanced or unbalanced gametes by the degree of asymmetry of the quadrivalent. In this study, we investigated the relationship between the degree of asymmetry of the quadrivalent and the segregation patterns of translocated chromosomes in cleavage stage embryos as well as the clinical outcome of PGD in these couples.

Materials and methods

Patients

Between January 2011 and August 2013, PGD was carried out on 40 reciprocal translocation couples. The karyotypes of each patient are described in **Table 1**. Genetic consultation was carried out, and informed consent was obtained from all couples before initiating the PGD cycle.

The protocol used was approved by our Institutional Ethics Committee on 26 December 2013. The total number of IVF-PGD cycles was 75, with 44 cycles from 22 female carriers and 31 cycles from 18 male carriers. Probe combinations were tested on peripheral blood lymphocytes before application in the clinical PGD cases to ensure that all probes were working optimally and that signals were clear and interpretable. In probe combinations from some of the manufacturers (which were used in 14 patients), the probe efficiencies were 98–100% for centromeric probes and 95–98% for telomeric or locus-specific probes. In probe combinations from different manufacturers (which were used in 26 patients), the probe efficiencies were 98–99% for centromeric probes and 95–96% for telomeric probes.

Ovarian stimulation and in vitro fertilization

Pituitary function was down-regulated using gonadotrophin-releasing hormone (GnRH) agonist (Decapeptyl; Ferring Pharmaceuticals, Switzerland) or antagonist (Cetrotide; Merck-Serono, Geneva, Switzerland). Recombinant FSH (Gonal F, Merck-Serono, Geneva, Switzerland) was used for ovarian stimulation. Follicular growth was monitored by transvaginal ultrasound and serum oestradiol concentrations. A dose of 10000 IU of HCG (Profasi; Merck-Serono, Geneva, Switzerland) was given to induce final oocyte maturation. Oocytes were retrieved transvaginally under ultrasound guidance 36 h after HCG administration. Retrieved metaphase II oocytes were fertilized by intracytoplasmic sperm injection (ICSI). Embryos