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LETTER TO THE EDITOR

Male Infertility

A rare complex chromosomal rearrangement in an oligospermic male: a case report and review of the Chinese literature

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Dear Editor,

Complex chromosome rearrangements (CCRs) are structural aberrations involving at least three chromosomes with three or more chromosomal breakpoints. CCRs are very rare events in the human population. As reviewed by Pellestor *et al.*,[1] less than 255 cases of CCRs involving three or more chromosomes have been reported. In China, approximately 136 cases of CCRs, including 40 males with reproductive problems, have been reported up to the time this review was compiled.

CCRs have been classified into three major categories, according to their structure: three-way exchange, double two-way exchange, and exceptional CCRs. The double two-way exchange is the simplest CCR, in which there is a coincidence of two separate simple reciprocal translocations or a reciprocal translocation with a Robertsonian translocation or an inversion. CCRs can be familial or *de novo* and may be balanced or unbalanced. Because balanced CCRs can lead to an unbalanced condition of the gametes or a meiotic disturbance, CCR carriers are at high risk of having a child with an unbalanced karyotype, spontaneous abortions, and infertility. In phenotypically normal individuals, female carriers of CCRs are frequently identified after giving birth to malformed babies or suffering from repeated miscarriages;[2] whereas, most of the male carriers of CCRs are detected due to infertility problems arising from oligozoospermia or azoospermia.

Here, we report the case of a 32-year-old man who was referred for chromosome karyotyping and Y chromosome microdeletion analysis due to his 6 years of male factor infertility. His family history contained no relevant information. No abnormal symptoms were detected, and a physical examination showed that the patient was phenotypically normal. His testes were soft and normal in size. The ductus deferens was palpable and normal in shape bilaterally, and there were no signs of varicocele on either side. The serum follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone (T) values were within the normal ranges.

Semen analysis revealed severe oligospermia, with a volume of 3 ml, a sperm concentration of $0.67 \times 10^6\,ml^{-1}$, forward motility of 16.6%, vitality of 33.3% at 1 h and 20% normal forms. The total ejaculate contained a mean volume of only 3 ml. Cytogenetic analysis showed a male karyotype with a double two-way CCR: 46, XY, t (3;4) (p21;q21), t (12;14) (q14;q31) (**Figure 1**). Y chromosome microdeletion analysis was also carried out using polymerase chain reaction (PCR) and electrophoresis. It was found that the patient did not have any genomic deletions in the AZFa, AZFb and AZFc regions on the long arm of the Y chromosome.

This was a case of a phenotypically normal male carrier of a *de novo* CCR involving four chromosomes. The four breakpoints were located at 3p21, 4q21, and 12q14, and 14q31. As a result, four derivative chromosomes were formed. To the best of our knowledge, this is a new type of CCR that has never been reported before. The CCR presented here may be a cause of oligospermia.

CCRs are very rare. According to Farra *et al.*,[3] only 37 males with reproductive problems associated with CCR have been published in the literature. However, no examples from the Chinese literature were included in this number. Therefore, we reviewed the Chinese literature on CCR carriers who were identified through their reproductive problems and found that approximately 40 male cases of 37 types have been reported in China (Supplementary Table 1).

It is generally believed that three-way exchanges are the most common type of CCR, while exceptional CCRs are the least common. Among the 40 male CCR cases, there were 14 three-way exchange cases (35%), 15 double two-way exchange cases (37.5%) and 11 exceptional cases (27.5% ; Supplementary Table 2). Previous reports have shown that males with CCRs of all types mainly manifest with infertility (56.8%) by genital hypoplasia, spermatogenic failure or pre- or postimplantation losses.[3] However, in Chinese males with CCRs, 60% (24/40) of cases were accompanied by recurrent pregnancy loss or a malformed child. The incidence of spontaneous abortions was 88.7% (63/71), a figure higher than the one reported by Madan *et al.*[4] The other eight pregnancies resulted in two dead fetuses *in utero*, three infant deaths, one malformed fetus and two balanced CCR carriers.

It has been thought that the number of chromosomes involved or the location of the breakpoints may also play a role in the reproductive condition of CCR carriers. Giardino *et al.*[5] have noted that chromosomes 2, 3, 4, 7, and 11 are more frequently implicated in CCRs. All of the chromosomes, except for chromosomes 19, X and Y, were involved in the 40 CCRs; the most frequently involved were

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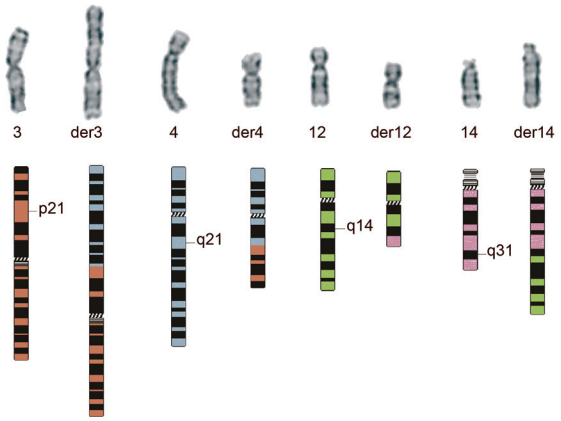

Figure 1: Karyotype showing the normal and derivative chromosomes from the t (3;4), t (12;14) Complex chromosome rearrangement (CCR). Below are the corresponding ideograms, colored to display the chromosome of origin, with chromosome 3 in orange, chromosome 4 in blue, 12 chromosome in green and chromosome 14 in pink.

chromosomes 1, 2, 5, 7 and 4. Moreover, breakpoints on chromosomes 6, 7, 8, 11 and 16 have frequently been reported in men with recurrent miscarriages; whereas, breakpoints on chromosomes 10 and 14 have mostly been associated with spermatogenetic failure.

The breakpoints were randomly distributed. However, some 'hot spot' chromosome bands for breakage can be identified. Gorski *et al.*[6] observed a nonrandom distribution of specific breakpoints at the following sites: 1q25, 4q13, 6q27, 7p14, 9q12, 11p11, 11p15, 12q21, 13q31 and 18q21. We also found that 1p22, 1q25, 2q31, 5p13, 5q35, 6q23, 8q13 and 20p13 underwent breakage more than three times. The breakpoints at 2q31, 5q35 and 8q13 were particularly associated with recurrent miscarriages, while 1p22 breakage was only related to spermatogenetic failure. In addition, breakpoint 3p21, which was one of the four breakpoints described in the present case, has been previously reported to be related to spermatogenetic failure.[7] This relationship may not be just a coincidence; rather, genes included in these 'hot' breakpoints may play important roles in embryogenesis and spermatogenesis.

The occurrence of CCRs is rare, and its mechanism remains mysterious. It is difficult but important to provide adequate genetic counseling for these patients. The risks of spontaneous abortion and unbalanced live born children for phenotypically normal male carriers of CCRs are higher than the figures determined by Gorski *et al.*,[6] and Madan *et al.*[4] Although intracytoplasmic sperm injection (ICSI) is widely used to treat sperm-related infertility problems, male CCR carriers with spermatogenic failure seem to have a much lower chance of benefiting from ICSI.

AUTHOR CONTRIBUTIONS

YJC performed the literature search and drafted the manuscript. WWZ and XMS carried out the molecular genetic studies. CJH revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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