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ARTICLE

Azoospermia and paternal autosomal ring chromosomes: case report and literature review

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Abstract Two men of the same family presented with ring chromosome 22 and azoospermia. The literature on all autosomal ring chromosomes and semen abnormalities was reviewed. Autosomal ring chromosomes were often associated with a low sperm count. This is probably as a result of gamete instability at meiosis due to the ring chromosome which leads to an increased breakdown. In addition, ring chromosomes transmitted from the parents may manifest quite differently in the progeny. Prior to treating these patients with assisted reproduction, appropriate counselling should be offered, in view of the varying phenotypic manifestations of ring chromosomes in the resulting progeny, and prenatal diagnosis or preimplantation diagnosis must be considered.

KEYWORDS: azoospermia, cryptozoospermia, genetic counselling, male infertility, oligozoospermia, ring chromosomes

Case report

A 28-year-old man was referred for evaluation of subfertility. Azoospermia was detected. Clinical examination and gonadotrophin concentrations were normal. Karyotyping revealed a ring chromosome 22—46,XY,r(22) (p12q13.3).ishr22 (bcr+, qter+) — in all the cells. G banding showed that the ring had all the bands present in a normal chromosome 22. There were no Y chromosome microdeletions.

Coincidentally the man's brother (aged 30 years), was also referred for azoospermia and had the same abnormality at karyotyping (no mosaicism) with no Y deletion. He had undergone testicular sperm extraction 2 years previously (from both testes) and the histology showed an incomplete maturation arrest. Rare tubules contained spermatids and even rarer mature spermatozoa. The brother's serum gonadotrophin and inhibin B concentrations were normal.

A family history was taken. They were a family of four brothers and two sisters. Both the sisters were fertile. Both the proband and his brother had no identifiable dysmorphic features and were working as a security guard and a salesman, respectively. The other two brothers had not yet tried

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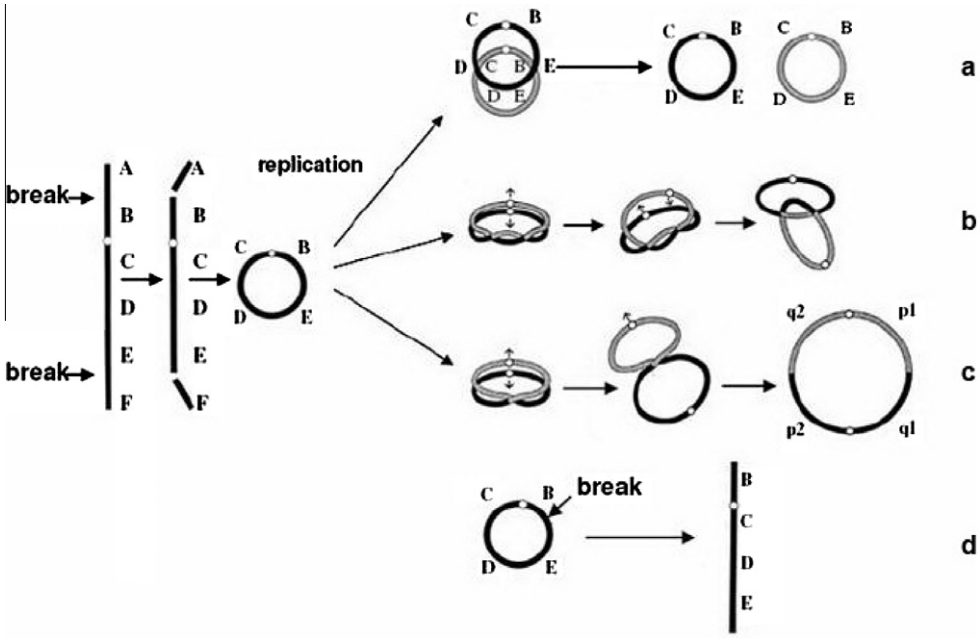

Figure 1 Scheme of ring formation and instability after replication, arising from chromatid exchanges or breaks, and originating: (a) two monocentric rings; (b) interlocked rings; (c) a double-sized dicentric ring; and (d) a broken or open ring. Reproduced with permission from Sodre et al. (2010).

to start a family. There was no family history of subfertility or recurrent miscarriages. The other family members looked apparently normal. The suggestion of karyotyping for the rest of the family was not possible due to cultural issues. The proband was referred for genetic counselling.

Approximately 2% of infertile males have somatic chromosomal abnormalities and this incidence increases as the count decreases (Chandley, 1998). Structural karyotypic abnormalities associated with azoospermia include Klinefelter syndrome 47,XXY, Y microdeletions and chromosomal translocations. In the context of these two brothers presenting with ring chromosomes and azoospermia, the literature on ring chromosomes and azoospermia was reviewed.

Review

Ring chromosomes have been identified for all human chromosomes. They commonly result from terminal breaks in both chromosome arms, followed by fusion of the broken ends. This may either result in no loss of genetic material and the formation of a complete ring chromosome, or the loss of genetic material which may result in subtelomeric microdeletion syndrome. A ring chromosome may also result from telomere-to-telomere fusion of an inherently unstable chromosome prone to circularization (Pezzolo et al., 1993). Transmission of these unstable chromosomes may lead to de-novo ring formation in the second generation, in addition to the presence of a normal cell line, accounting for a mosaic karyotype in both the parent and the offspring (Kosztolanyi et al., 1991).

During mitosis, the ring chromosome may duplicate and assort regularly to the daughter cells resulting in transmission of the ring. Alternatively sister chromatid exchange between rings may result in a double-sized ring or two interlocking rings (**Figure 1**). Such interlocking or double-sized rings may: (i) be lost from both cells resulting in a monosomic cell with possible serious effects on cell survival if the ring was autosomal, but with much less effect if of sex chromosomal origin; (ii) result in non-disjunction with production of two cell lines, one without the ring (monosomic) and the other with a double ring (trisomic); or (iii) result in symmetrical or asymmetrical breakage of the resulting ring leading to deletions and duplications in the resulting cells. The broken ends of the chromosomes may rejoin as rings of variable size or the sister chromatids of the two ends may join across, with the cycle restarting at the next cell division (Paul, 1964). Hence, an individual with a ring chromosome may have a varying chromosomal constitution in his somatic cells. This is termed dynamic tissue mosaicism.

Sodre et al. (2010) had evaluated the stability of different ring chromosomes during mitosis in lymphocyte cultures. A ring chromosome is considered 'stable' when secondary aberrations are found in 0—5% of the mitoses and 'unstable' when the aberrations are more than 5% in number. They found that cells showing ring chromosome instability carried between them different ring chromosomes (ring 4, 14, 15 and 18). In addition, two of their patients with the same ring karyotype (ring 14) showed a different frequency of metaphase cells with the ring at culture, thereby suggesting that mosaicism varies in different individuals with the same ring chromosome. They found no correlation between ring size and stability, and no difference between complete rings and rings with genetic material deletion. As karyotyping normally involves haematopoietic tissue, tissue mosaics may not be quantified. Phenotypes will vary depending on the extent of euchromatin deletion, presence of secondary aneuploid cells due to ring instability, ring stability and the degree of tissue mosaicism (Kosztolányi, 1987).