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# Mosaic Ring Chromosome 13 Presented with Isolated Male Infertility: Case Report

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## Abstract

Ring chromosomes are the result of breakage and re-union of distal ends of chromosomal arms. They have a general frequency of 1 in 50,000 and 1 in 58,000 for chromosome 13. Ring chromosome 13 is usually presented as a syndromic situation stigmatized by particular features, including developmental delay, mental retardation and CNS, skeletal or organ anomalies. As an experimental study, here we report a 31 years old male with no major phenotypic manifestation who was evaluated for azoospermia, while his karyotype revealed presence of a mosaic ring chromosome 13. He had a history of bilateral varicocelectomy and no other major finding in his routine infertility work up was determined. Genetic counseling did not provide any clue for mental disability or dysmorphic features. Pathology examination of the testicular tissue revealed very scarce number of spermatid/spermatozoa within the tubules in conjunction with degrees of maturation arrest mostly in spermatocyte stage. In our knowledge, this is the first report of a ring chromosome 13, manifested by an isolated male infertility.

***Keywords:*** Azoospermia, Case Report, Male Infertility, Ring Chromosome

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## Introduction

Ring chromosomes are the result of breakage and re-union of distal ends of chromosomal arms. They have a general frequency of 1 in 50,000 (1) and 1 in 58,000 for chromosome 13 (2). For ring chromosome 13, the clinical syndrome is broad and dependent on the amount of deleted segment in chromosome 13 as well as the stability of the ring structure (3). Inherent instability within the ring structure may lead to creation of various clones with secondary aberrations. That is why ring structure are similarly called "dynamic mosaicism" (4). The full spectrum of clinical manifestation in ring chromosome 13 syndrome may include delay in growth and developmental steps, mental retardation, microcephaly, facial dysmorphic features, gastrointestinal atresia, genital anomaly, eye abnormalities (retinoblastoma) and skeletal dysmorphologies (5). Isolated infertility, as a consequence of ring chromosome 13, was previously reported only in a Chinese female with premature ovarian failure (6). To our knowledge, this is the first report of a case of ring chromosome 13 presented with isolated male infertility. The aim of this study is to evaluate association of mosaic ring chromosome 13 and male infertility.

### Editorial policies and ethical considerations

The study was approved by the Ethical Review Board of the Royan Reproductive and Biomedicine Research Centre (Tehran, Iran, IR.ACECR.ROYAN.REC.1401.013). A written informed consent was provided by the patient. The study was performed in accordance with the ethical standards, as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

### Case report

A 31 years old man was married to a 42 years old woman and referred to infertility clinic, while their unconsanguineous marriage could not lead to a successful pregnancy after more than six months of unprotected sexual intercourse. This was his second marriage, while the first was terminated after less than 10 months. He had a primary level education (grade 5) and was employed as a scaffolding worker. He had a history of bilateral varicocelectomy and his two latest consecutive spermograms revealed severe oligospermia and azoospermia respectively (Table 1).

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**Table 1:** Spermogram details

| Spermogram | Volume (CC) | Color | pH | Liquefaction Time | Count |
|---|---|---|---|---|---|
| First | 5.7 | Opaque grey | 8-9 | 30-60 | Only 5 immotile and 2 motile sperms in total |
| Second | 6.2 | Opaque grey | 7-8 | 15-30 | 0 |

There was no history of infertility in his first degree relatives. No positive finding was detected in his physical examination, except for the incisional scars due to varicocelectomy, while external genitalia seemed to be normal. Genetic counseling did not provide any clues for mental disability or dysmorphic features. Hormonal assessments showed no impairment as total testosterone=5.19 ng/mL, luteinizing hormone (LH)=4.63 mIU/mL and follicle-stimulating hormone (FSH)=6.79 mIU/mL were all in normal ranges. In ultrasound scan of scrotom, size of the right and left testes were respectively 35×17 mm and 27×16 mm, while some varicose veins were also observed in the left side. The patient also went under diagnostic biopsy of the testis. Microscopic evaluation revealed unsatisfactory for the quality as well as the quantity of sperm content. Pathology examination of the testicular tissue revealed very scarce number of spermatid/spermatozoa within the tubules in conjunction with degrees of maturation arrest mostly in spermatocyte stage. There were a few spermatid/spermatozoa with abnormal morphology within only three tubules. The patient was also nominated for testicular sperm extraction (TESE) procedure which resulted in 0-1 sperm in each high power field (HPF). Testicular extracts were then cryopreserved for future assisted reproductive treatments (ARTs). For blood karyotyping, GTG banding of peripheral blood lymphocytes was carried out. Findings revealed mosaic ring chromosome 13 as the following; 46, XY, r(13) (p11.2q34) [24]/45, XY, -13[4]/46, XY, dicr (13;13) (p11.2q34;p11.2q34) [2].

Three different lines were observed with dominancy of a simple ring chromosome 13 with breakpoints at p11.2 and q34, a line with deletion of chromosome 13 and finally a minor line with double ring chromosome 13 at the same break points (Fig.1). The patient was briefed with the possible assisted reproductive technology (ART) outcomes, necessity of undergoing preimplanation genetic testing for aneuploidy (PGT-A) of their own biologic child and the other reproductive options, including embryo donation as well as adoption.

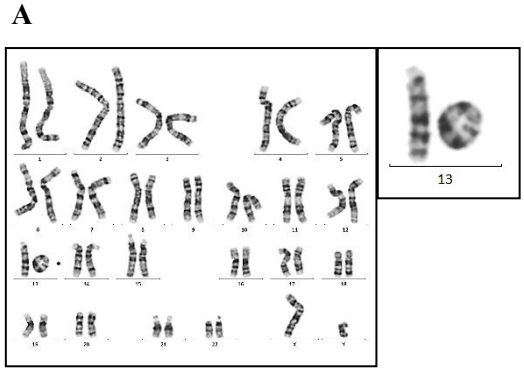


**Fig.1:** The karyograms prepared from peripheral blood of the patient with ring chromosome 13 including three different lines. **A.** 46,XY,r(13)(p11.2q34): the line with a ring chromosome 13 with breakpoints at p11.2 and q34. **B.** 45,XY,-13: a line with a missing chromosome 13. **C.** 46,XY,dicr(13;13)(p11.2q34;p11.2q34): the line with a double ring of chromosome 13 at the same breakpoints.

## Discussion

Ring chromosome 13 is a rare genetic syndrome, whilst it is still considered as the most frequent ring chromosome abnormality (7). The spectrum of clinical features is wide and basically dependent on the deleted material from chromosome 13 (especially the long arm) and therefore it is related to the breakpoints in the chromosomal arms (8). In addition, stability of the ring structure is an important indicator for the clinical consequences (9). The smaller deleted region of the 13q causes milder clinical abnormalities. In addition, more proximal deletions, particularly those with intact 13q32 usually show mild to moderate phenotypes, while extension of deleted materials to 13q32 present severe mental retardation, growth delay and major abnormalities, such as microcephaly, gastrointestinal defects, dysmorphic extremities. Finally, very distal deletions affecting q33-34 have severe mental retardation, but usually do not show growth impairments or major organ abnormalities (10). With regards to the reproductive system, there are reports of ring chromosome 13 accompanied by genitourinary tract malformations or ambiguous genitalia (11, 12), while isolated infertility was only previously reported

in a woman evaluated for premature ovarian failure (6). To the best of our knowledge, the current case is the first report of a ring chromosome 13 presented with isolated male infertility. He was 31 years old with normal mental function, and no other detectable abnormal or dysmorphic feature. He was referred to infertility clinic for evaluation of azoospermia. The only positive finding was a history of bilateral varicocelectomy. Testis tissue assessment also revealed maturation arrest in spermatocytic stage.

## Conclusion

With regards to the inheritance of ring chromosome 13, most of the cases are sporadic and they are usually the result of breakage and re-union of the chromosomal ends within the egg or sperm which usually happens during meiosis. Whilst there have been rare reports of transmission of ring chromosome from a parent to the offspring. Therefore, parental karyotyping in our case may help determine the origin of abnormal structure, while for reproductive management, they were recommended to use egg donation.

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### Authors' Contributions

M.T.; Performed the cytogenetic experiments. H.S.; Performed the clinical consultation for the patient to enter the study and he was also the scientific consultant. P.B.B.; Collected the data and revised the manuscript. N.A.; Did the genetic consultation and draw pedigree. M.R.Z.; Designed the case study, collected and interpreted the data, drafted the manuscript, and revised and edited the paper. All authors approved revisions and the final paper.

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