Biochemical and Biophysical Research Communications 432 (2013) 472–474

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Pericentric inversion of chromosom 12 [Inv (12) (p12q12)] associated with idiopathic azoospermia in one infertile Tunisian man

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ARTICLE INFO

Article history:
Received 22 January 2013
Available online 8 February 2013

Keywords:
Pericentric inversion
Chromosome 12
Non-obstructive azoospermia

ABSTRACT

Chromosome aberrations are found in 2–7% of couples with fertility problems and pericentric inversions are structural chromosomal abnormalities, potentially associated with infertility or multiple miscarriages. In this study, we report the first case of pericentric inversion of chromosome 12 associated with non-obstructive azoospermia. A karyogram revealed pericentric inversion of chromosome 12 with breakpoints at 12p12 and 12q12. Testicular histopathology confirmed the Sertoli cell-only syndrome.

1. Introduction

Chromosomal abnormalities are common genetic causes of male infertility. The Klinefelter syndrome is the most frequent aberration, but autosomal anomalies like robertsonian and reciprocal translocations and inversions are also involved in male infertility [1]. Inversions act as cross-over suppressors; a very large inverted segment forms loops and crossing over is reduced inside and around loop due to incomplete pairing. When crossing over occurs in the pairing loop, unbalanced gametes can then ensue, sharing duplications and deletions and leading to infertility or abortion [2]. Many autosomal and gonosomal pericentric inversion were reported in male infertility; they involved Y chromosome [3], chromosome 1 [4,5], chromosome 5 [2] chromosome 6 [6] chromosome 7 [7] chromosome 9 [8], chromosome 10 [9]. Recently, a paracentric inversion was observed in a non-obstructive azoospermia [10]. In the present study, we describe the first case of pericentric inversion of chromosome 12 found in an idiopathic azoospermic man.

2. Materials and methods

2.1. Patient

A 36-year-old man presented to our laboratory for semen analysis after 6 years of sexual intercourse without conception. His wife, 28 years, did not have any fertility problems. No history of infertility was noted in the family. The patient underwent physical examination, semen analysis, hormonal exploration, and genetic investigations. Physical examination revealed small testes with intact vas deferences, no evidence of gynaecomastia and normal secondary sexual characteristics.

Laboratory investigation revealed azoospermia in semen analysis (performed three times) associated with high levels of serum follicle stimulating hormone (FSH) and luteinic hormone (LH) concentrations (33 mUI/ml and 18.6 mUI/ml, respectively); testosterone was within the normal range (1.8 ng/ml). Serum Inhibin B concentration was low (20.37 pg/ml). The amounts of seminal fructose (24.17 μmol/ml), citrate (30.38 mmol/ml) and α-glucosidase (81.3 mUI/ml) in seminal plasma were normal. No extended or partial Y chromosome microdeletions were found.

2.2. Methods

After receiving informed consent, cytogenetic investigation was performed on lymphocyte chromosomes obtained from peripheral blood. Metaphases were studied with a standard RHG banding procedure. The karyotype revealed the presence of a pericentric inversion 46, XY, inv (12) (p12q12) (Fig. 1).

Testicular histological investigation revealed that all seminiferous tubules were empty of germ cells and the seminal epithelium was reduced to Sertoli cells (Fig. 2).

3. Discussion

Chromosome inversion is an equilibrated structural chromosome anomaly observed in 0.02% of newborns [11]. Despite being

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http://dx.doi.org/10.1016/j.bbrc.2013.01.110

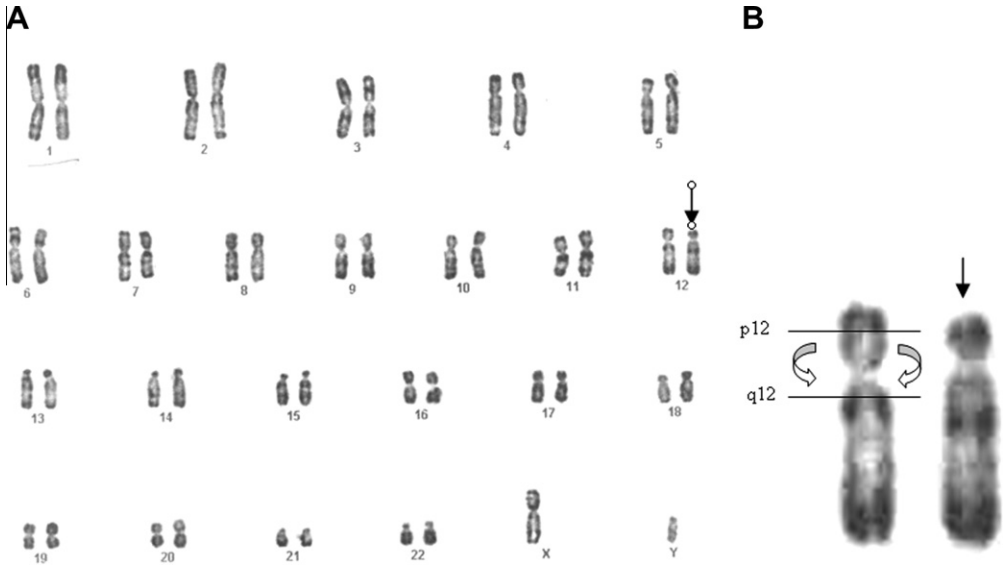

Fig. 1. In A, karyotypic finding of chromosome 12 inversion and in B, the pair of normal and inverted chromosome 12 from the patient. Arrows indicate the inverted chromsome 12.

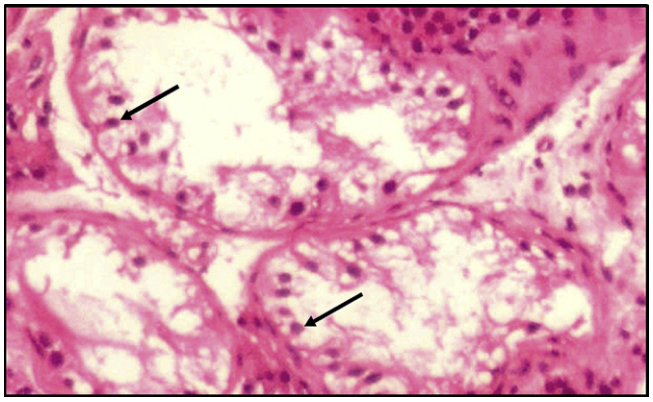

Fig. 2. Hematoxyll in and eosin stain of histological section of patient testis, schowing seminifer tubules without germ cells (Sertoli cell only syndrome). Arrows indicate the nuclei of 2 Sertoli cells.

categorized as a minor chromosomal rearrangement which does not correlate with abnormal phenotypes, percicentric inversion has been implicated as a possible cause of recurrent abortion or infertility. Indeed, Mozdarani et al. observed an inversion of chromosome 9 in 2.5% of infertility cases [12]; similar result was also found in an earlier report by Sasiadek et al. [13] in recurrent spontaneous abortion cases. Recently, Akin et al. also reported a case of patient with 46, XY, inv9 (p11; q13) karyotype [15].

In this study we report the first case of pericentric inversion of chromosome 12 associated with non obstructive azoospermia. A centric inversion of this chromosome was reported earlier in a case of primary male infertility [14]; the patient was diagnosed as having Klinefelter syndrome by conventional cytogenetic analysis, which also showed an abnormal chromosome 12. Fluorescence in situ hybridization (FISH) analysis showed a break in the alphoid repeats followed by an inversion within the short arm, resulting in a pseudodicentric chromosome.

Literature data show that pericentric inversion of chromosome 12 was also reported in patients with malignant hematologic disorders [16,17] and in patients with familial pericentric inversion [18–20].

In our case report, the pericentric inversion of chromosome 12 was associated with a very severe testicular phenotype including the absence of germinal cells in all seminifar tubules. This phenotype may be due to the inactivation by deletion of genes located within or near of the breakpoints and acting on the spermatogenesis process. In fact, within 12p12 region, there are three genes highly expressed in testis: Cytidine 5-Prime-Monophosphate N-Acetylineuraminic Acid Synthetase (CMAS), Ethanolamine Kinase1

Table 1
Genes located in 12q12 and 12p12 and expressed in testis.

Genes	Locus	Position	Protein Fonction
ARID2	12q12	Chr12:46,231,104–46,301,819	ARID2 is a subunit of the PBAF chromatin-remodeling complex, which facilitates ligand-dependent transcriptional activation by nuclear receptors [21]
ADAMTS20	12q12	Chr12:43,748,012–43,945,724	The protein encoded by this gene is a member of the ADAMTS family of zinc-dependent proteases. The encoded protein has a signal peptide that is cleaved to release the mature peptide, which is secreted and found in the extracellular matrix. This protein may be involved in tissue remodeling process.
TWF1	12q12	Chr12:44,187,526–44,200,178	This gene encodes twinfilin, an actin-binding protein involved in motile and morphological processes. Inhibits actin polymerization, likely by sequestering G-actin. By capping the barbed ends of filaments, it also regulates motility. Seems to play an important role in clathrin-mediated endocytosis and distribution of endocytic organelles.
CMAS	12p12	Chr12:22,199,159–22,218,602	Sialic acids are a family of nine-carbon sugars on cell surface glycoproteins and glycolipids that play a pivotal role in determining the structure and function of many animal tissues and play important roles in cell–cell communications and immune responses.
ETNK1	12p12	Chr12:22,778,076–22,843,608	This gene encodes an ethanolamine kinase, which functions in the first committed step of the phosphatidylethanolamine synthesis pathway. This cytosolic enzyme is specific for ethanolamine and exhibits negligible kinase activity on choline.
SLCO1C1	12p12	Chr12:20,848,399–20,906,320	The encoded protein is a transmembrane receptor that mediates the sodium-independent uptake of thyroid hormones in brain tissues

(ETNK1) and Solute Carrier Organic Anion Transporter Family, member 1C1 (SLCO1C1) (http://genome.ucsc.edu/). In the 12q12 locus there are also three genes expressed in the testis: AT-Rich Interaction Domain-Containing Protein 2 (ARID2), A Disintegrin-Like and Metalloproteinase with Thrombospondin Type 1 Motif 20 (ADAMTS20) and Twinfilin Drosophila Homolog of 1 (TWF1) (Table 1).

To explore eventual implication of one or more of these apoptosis regulator genes in spermatogenesis impairing observed in our case, further analysis by FISH using specific probes is needed; this procedure will also lead us to elucidate the possible implication of others genes in spermatogenesis process.

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