Original Article

Cytogenetic Results of Patients with Infertility in Middle Anatolia, Turkey: Do Heterochromatin Polymorphisms Affect Fertility?

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Abstract

Introduction: Infertility is a significant multifactorial disorder that can be caused by chromosomal abnormalities. In this study, we aimed to cytogenetically investigate male and female patients admitted to the Genetic Diagnostic Laboratory of Kayseri Educational Hospital in Kayseri, Turkey with varied clinical prediagnoses of infertility.

Materials and Methods: Chromosomes from cultured peripheral blood lymphocytes of 274 patients and 427 individuals as the controls were analyzed using Giemsa-Trypsin-Giemsa (GTG) banding. The individuals with sex chromosome aneuploidy or mosaicism were classified as carriers and with chromosomal polymorphism, respectively. The results of the two groups were compared statistically.

Results: Pure sex chromosome aneuploidy was found in 29 (10.5%) patients and mosaic sex chromosome aneuploidy in 15 (5.5%) cases and the total rate of abnormalities was 16%. Karyotypes were composed of an overall polymorphism rate of 8% in the patient and 4% in the control groups with no statistically significant difference ($p = 0.2$ and $p > 0.05$, respectively).

Conclusion: The present study shows that chromosomal polymorphisms are common among infertile patients. Chromosomal abnormalities and even heteromorphisms are significant etiologic factors leading to fertility problems.

The overall high prevalence of chromosomal polymorphisms in infertile couples, compared to the normal population, needs to be confirmed with further investigations and larger study populations to delineate the role of "harmless" chromosomal aberrations in the etiology of infertility.

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Received: Apr. 14, 2010
Accepted: Jul. 14, 2010

Keywords: Chromosomal aberration, Cytogenetics, Infertility, Karyotype, Polymorphism, Sex chromosome aneuploidy

To cite this article: Caglayan AO, Ozyazgan I, Demiryilmaz F, Dundar M. Cytogenetic Results of Patients with Infertility in Middle Anatolia, Turkey: Do Heterochromatin Polymorphisms Affect Fertility?. J Reprod Infertil. 2010;11(3):179-81.

Introduction

Infertility is a significant marital problem, affecting up to 15% of couples of reproductive age (1). Infertility can be caused by defects in the development of the urogenital system or its function by genetic defects of the endocrine system, including the hypothalamic-pituitary-gonadal axis, or by defects in gametogenesis, sexual function, fertilization or early embryonic development.

Secondary or acquired infertility, such as after-tubal diseases, vasectomy or exposure to gonadotoxins, may occur (2). Cytogenetic abnormalities (both somatic and meiotic) are a major cause of male infertility (3). Cytogenetic studies have been reported to determine the contribution of chromosomal abnormalities in parents with reproductive failure from various countries (4 - 6). The aim of the present study was to evaluate the prevalence

and nature of chromosomal aberrations in Turkish couples with infertility in middle Anatolia, Turkey, as there seemed to be an inadequate number of studies done in this region.

Materials and Methods

Patients: In a period between January 1998 to January 2009, 151 female and 123 male patients (n = 274) were referred to the Department of Medical Genetics for chromosome analysis as part of their infertility work up. In addition, 427 individuals who were undergoing different work ups other than infertility and had one or more children were simultaneously analyzed for polymorphisms. All the patients were evaluated by a skilled medical specialist and tested for anti-phospholipid antibodies and relevant hormones. Ultrasouography was done to rule out other causes of infertility.

Cytogenetic Analysis: Chromosome preparations were obtained from routine peripheral blood lymphocyte cultures. A minimum of twenty GTG banded metaphases (minimally, 500-band level) were analyzed for each person. Karyotypes were recorded according to the recommendations of the International Standing Committee on Human Cytogenetic Nomenclature 1995 (7).

The purpose of the study was explained to the patients, and informed consent forms were signed by them. The institutional ethics committee approval was obtained before beginning the study.

Statistical Analyses: The results of the two groups were compared by two-tailed Fisher's exact test, and calculated online at GraphPad Software website (8).

Results

We classified the individuals with sex chromosome aneuploidy or mosaicism as carriers and individuals with chromosomal polymorphism (Table 1). Pure sex chromosome aneuploidy was found in 29 (10.5%) and mosaic sex chromosome aneuploidy in 14 (6.5%) patients, putting the total rate of abnormalities at 16.1%. The karyotypes were composed of an overall polymorphisms rate of 8% in the patient and 4% in the control groups which were not statistically different, (respectively, $p = 0.2$ and $p > 0.05$, confidence level: 87.4%).

Table 1. The patients' karyotypes and their relevant frequencies

Karyotype	Frequency	Percentage (%)
46,XX	145	53
46,XY	73	26,7
Sex Chromosome Aneuploidies		
mos 45,X / 46,XY	4	1,5
mos 45,X / 47,XXX / 46,XX	1	0,4
mos 45,X / 47,XXX / 46,XX	1	0,4
mos 47 XXY / 48 XXXY / 46 XX / 46 XY	1	0,4
47,XXY	29	10,5
mos 47,XXY/46,XY	8	2,9
Polymorphisms		
46,XX 16 qh+	4	1,5
46,XY Yqh+	5	1,82
46,XYqh-	2	0,9
46,XY inv (9) (p11q12) yqh+	1	0,5
46,XY 1qh+	1	0,5

Discussion

Reproductive disorders are closely associated with cytogenetic abnormalities. Studies have demonstrated that 2 - 14% of infertile men have constitutional chromosomal abnormalities. The prevalence of chromosomal aberrations is dependent on the definition of 'infertility', and is approximately 2% in males with combined indications of infertility (9), 5% in men with oligozoospermia and 14% with azoospermia (10).

The most common types of karyotypic abnormality include sex chromosomal abnormalities and Robertsonian translocations. The frequency of somatic chromosomal abnormalities in infertile men varies from 3% - 19%: that is 3% in the cases of mild infertility and 19% in men with non-obstructive azoospermia (NOA).

In the present study, we did not find any structural mutations in the patients, perhaps due to our strictly selected study population, but a high frequency of Klinefelter's karyotype was detected. Earlier studies had not investigated polymorphism and chromosomal aberrations as a determining factor in infertility in Kayseri, Turkey, therefore, this study could be of importance in this regard (11, 12).

Morphological variations of constitutive heterochromatin are frequently detected during routine cytogenetic analysis. Most often, chromosomes vary in size and position of heterochromatin in

1qh, 9qh, and 16qh regions. Although inherited variants have been reported not to be associated with any risk for phenotypic abnormalities, chromosomal heteromorphisms have been found to have a higher frequency relative to the normal population and have been regarded as abnormalities in some studies (5, 8, 13, 14). Recent studies suggest that classical euchromatic variants of 9q12/qh+ and heteromorphism on chromosome 6q may be responsible for recurrent abortions (15, 16). However, no statistical association was found between heteromorphism and infertility.

In recent years, reproductive problems have been associated not only with somatic chromosomal abnormalities but also with cytogenetic ones in the germ cells of infertile individuals with a normal constitutional karyotype (3). Research in this area has become more clinically relevant in the past few years with the advent of intracytoplasmic sperm injection (ICSI). Sperm chromosome complements in infertile men with normal 46,XY karyotype have been studied to determine whether meiosis in these men is prone to errors of nondisjunction, leading to aneuploidy. Unfortunately, the laboratory was not provided with semen samples for cytogenetic examination. Thus, we were not able to directly confirm seminal abnormalities or the direct influence of these chromosomes on spermatogenesis.

Conclusion

The way chromosomal abnormalities affect gametogenesis or embryogenesis is not explicitly evident and reaching a common conclusion demands further investigation in this field.

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