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Y chromosome polymorphism in Turkish patients with reproductive problems: a genetic centre experience

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ABSTRACT

Objectives: Male infertility is a large and unexplored global health problem in terms of prevalence. Chromosomal polymorphisms may be associated with infertility and recurrent spontaneous abortions. Non-protein coding and frequently repetitive satellite DNA sequences are found in these regions.

Methods: This study aims to present a genetic laboratory experience in the evaluation of frequency, type and significance of Y chromosome polymorphism of Turkish patients with reproductive system problems. The study included 435 patients aged 18-60 years with a documented clinical diagnosis of infertility.

Results: In our study, 435 individuals were analyzed cytogenetically and 75 of them (17.24%) were found to carry chromosomally polymorphic variants in Y chromosome. We detected increased heterochromatin structure in the long arm of chromosome Y (Yqh+) as a common variant in our patient group. The frequency of chromosomal polymorphism Yqh- is % 11.26. The rate of chromosomal polymorphism we detected is close to those reported in the literature (10-15%) and statistically significant ($p < 0.001$), twice that found in the normal population (2-5%).

Conclusions: Findings support that Y chromosome polymorphisms may be associated with infertility risk and may play an important role in the development of infertility. More research combining genome studies and other fields is needed to clarify the relationship of Y chromosome polymorphisms with and to infertility.

Keywords: Male infertility, chromosomal polymorphisms, Y chromosome

By definition, infertility is the clinical absence of pregnancy despite regular and unprotected sexual intercourse for 1 year. It is a disease characterized by the deterioration of the reproductive capacity of the person or his partner [1]. Male infertility is a health problem that has not been studied or studied to fully understand its magnitude and prevalence. Globally, accurate information on male infertility rates is lacking and not properly reported [2]. Nowadays, assisted reproduction centers allow couples, with a previous diagnosis of male infertility linked to chromosomal aberrations, to procreate using the assisted reproductive technique: Intracytoplasmic sperm injection [3, 4]. Therefore, it is important to perform genomic screening in male patients for the detection of genetic etiologies linked to male infertility.

There are chromosomal polymorphisms, inherited variation that spans heterochromatic regions within the genome. They are most frequently seen in the pericentric heterochromatin region of the long arms of chromosomes 1, 9 and 16, heterochromatin on the long arm of the Y chromosome, and heterochromatin in the

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satellites or bodies of chromosomes 13, 14, 15, 21, 22. Chromosomal polymorphisms may be associated with infertility and recurrent pregnancies resulting in miscarriage (RSA). These regions are composed of frequently repetitive satellite DNA sequences that do not code for proteins. When located on the same chromosome, repeat sequences may predispose to homologous unequal recombination leading to chromosomal micro rearrangements, deletions, duplications and inversions that can affect a clinical condition such as infertility and recurrent miscarriage. This study aims to present an experience from a different geography in frequency and type evaluation and significance of Y chromosome polymorphism of Turkish patients with reproductive system problems. First, we screened the frequencies of heteromorphisms in our patient cohort retrospectively. In continuation, we examined whether there are significant manifestations of heteromorphisms, as the complex nature of heterochromatin structure may indicate common occurrences that may have clinical implications.

METHODS

The study was conducted in the Laboratory of Medical genetics, University hospital Trakya, Edirne, Turkey, within 4 year period (2017-2021). The design was the retrospective type of observation.

Inclusion criteria are the following: (1) Men with no previously known history of infertility, (2) Men of legal age, and (3) Men who signed informed consent and agreed to participate in the study. Exclusion criteria: 1. Men older than 65 years, 2. Men with previous surgical treatments in the reproductive area, 3. Foreign patients.

The study included 435 patients aged 18-60 years with a documented clinical diagnosis of infertility. Karyotyping was performed using peripheral blood lymphocytes cultured for 72 hours in RPMI-1640 medium supplemented with fetal bovine serum and phytohemagglutinin. The chromosomes were stained by GTG banding technique. At least twenty GTG banded metaphases (450-500 band levels) were analyzed for each patient. Karyotyping of metaphases was performed and defined according to the International System for Human Cytogenetic Nomenclature 2016 guideline. Karyotypes were independently examined under the light microscope by three laboratory technicians at different time intervals for consistency of analysisPolymorphisms of Y chromosome were determined as Yqh + or Yqh-. Additionally, Y pericentric inversion is a structural anomaly of the human Y chromosome, with a prevalence of 1 in 1000 for males with this structural abnormality. The inverted Y chromosome has often been associated with specific phenotypic abnormalities. Its association with fertility problems has not been reported. It is considered to be one of the heteromorphisms.

The karyotype analyzes of all patients included in the study were normal. Patients with numerical and structural chromosomal abnormalities, including mosaicism, and AZF deletion by Y microdeletion analysis were not included in the study.

Ethical Approval

The study was carried out with the approval of the Trakya University Hospital Ethics Committee (TÜTF-BAEK 2021/210).

Statistical Analysis

SPSS 25.0 (IBM Corporation, Armonk, New York, United States) was used for statistics. Monte Carlo stimulation technique, Pearson Chi-square and Fisher Exact tests were used for categorical variable analysis. Column ratios were compared among themselves. Expressed as p value with Benjamini-Hochberg correction. Categorical variables were expressed as n (%). A $p < 0.05$ were considered statistically significant.

RESULTS

Four hundred and thirty-five individuals were evaluated cytogenetically within the project. It was determined that 75 individuals (17.24%) of the patient group carried polymorphic variations in the Y chromosome. The most common polymorphism detected in this population under analysis was an increased heterochromatin domain on the long arm of chromosome Y (Yqh+) (Fig. 1). The frequency of chromosomal polymorphism Yqh- is % 11.26 (Fig. 2). The rate of chromosomal polymorphisms is in line with those re-

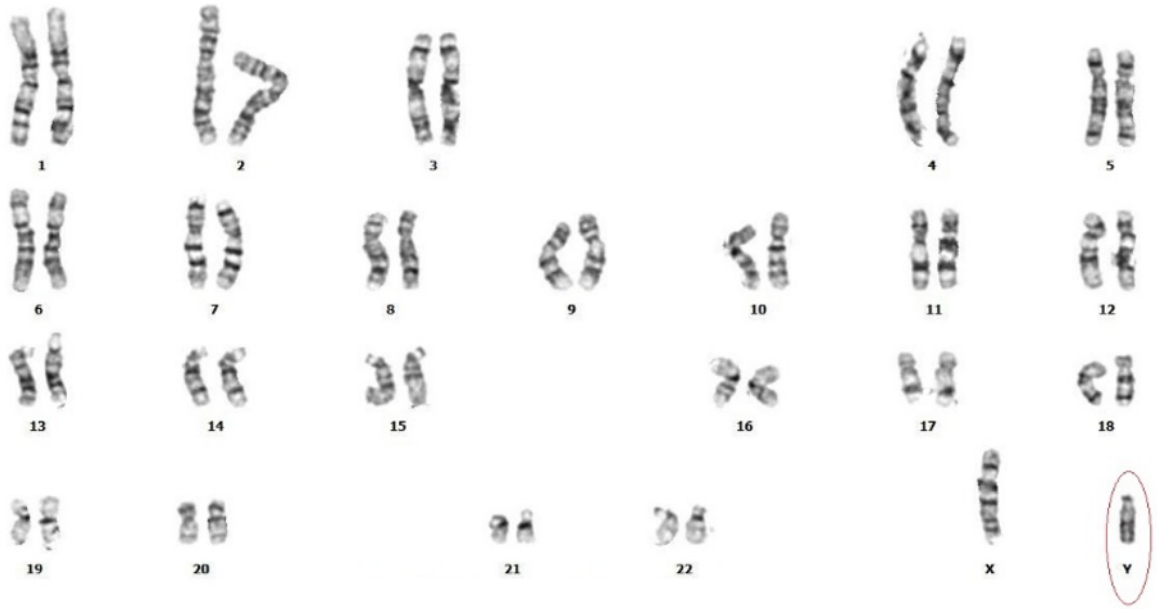

Fig. 1. Methaphase image of a 34-year-old male patient. An example of the Yqh+ polymorphism.

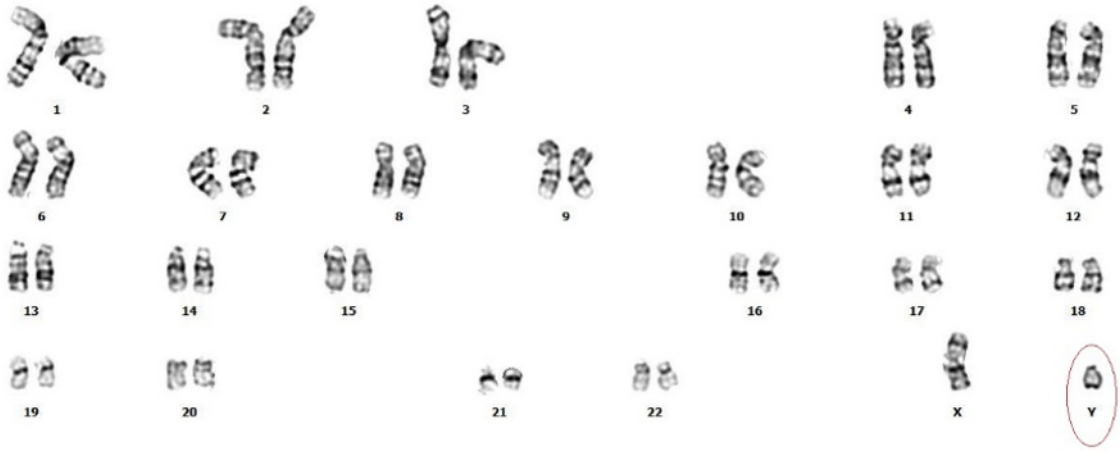

Fig. 2. Methaphase image of a 30-year-old male patient. An example of the Yqh-polymorphism.

ported in the literature (10-15%) and statistically significant ($p < 0.001$), twice that found in the normal population (2-5%) [5, 6]. It varies greatly between individuals and different populations.

DISCUSSION

The result obtained is a unidirectional trend with data from Turan, which is explained by variants of the Y chromosome, which are thought to have an adverse effect on spermatogenesis and may have an adverse effect on the outcome of ART (Assisted reproductive technology) procedures. The Y chromosome shows variations not only among individuals, but also between different population groups. Information on the importance of Y chromosome polymorphisms in infertility is still conflicting [7]. Whether or not Y chromosome heteromorphisms are of clinical importance, there are reports suggesting that epigenetic modifica-

tions in the heterochromatic region of the Y chromosome may play a factor in male factor infertility. Madon *et al*. [8], Minocherhomji *et al*. [9], Şahin *et al*. [10], Mierla and Stoian [11] and Yakin *et al*. [12] are some of the researchers who found significant associations between heteromorphisms and infertility.

Y chromosome polymorphism in 29.2% of infertile men [13]; 30.7% [14]; It was determined as 65.1% [15]. These data are consistent with our study results. The increased heterochromatin region for Yqh+ was thought to play an important role in the reproductive process. It has been reported to be associated with suppression of gene expression, especially for genes related to fertility in spermatogenesis. On the other hand, altered heterochromatin and euchromatin regions by induction of epigenetic changes in the male-specific region may be the reason for heterochromatin polymorphisms of the Y chromosome and its association with infertility. There is increasing evidence that heterochromatin regions contain significant amounts of repetitive DNA in heterogeneous content and that Chromosomal polymorphisms are an expression of morphological variability associated with increases or decreases in heterochromatin area. Chromosomal variations are thought to regulate gene expression with an opposite shift between heterochromatin formation, heterochromatin (non-coding DNA sequences) and euchromatin. (expressed DNA sequences) [16].

The number of studies examining the association of heteromorphisms with IVF failure apart from infertility is relatively less. Liang *et al*. [17] and Xiao Z *et al*. [18] observed that the effect of male polymorphisms on fertilization rates was negative. According to the Yqh- variation, the results of IVF treatment were found to be significantly more unsuccessful in couples carrying Yqh+ [17, 18].

Recent studies have reported that Y chromosome polymorphisms can affect homologous chromosome pairing and chromosome segregation. In addition, polymorphisms of the Y chromosome can cause errors in homologous chromosome pairing during cell division, resulting in disorders in cell division, developmental disorders in the embryo, teratogenicity disorders, stillbirth, and abortion.

A study in the field of cytogenetics shows that an increase (Yqh+) or decrease (Yqh-) in heterochromatin in the long arm of the Y chromosome can cause mitotic errors and thus cause stillbirth or miscarriage [19].

During meiosis, the pairing and synapse of the X and Y chromosomes are altered due to DNA repeats in certain regions of the Y chromosome, which can reduce reproductive capacity [20-21]. Similarly, we believe that molecular studies will help identify more precise roles for heterochromatin and chromosomal polymorphic variations, which have yet to be realized. Variations in the Y chromosome may occur due to inhibition of gene transcription, possibly due to the silencing effect on genes/gene promoters.

In the study of Ghahfarrokhi *et al*. [22] Y chromosome polymorphisms were also observed in people with Azoospermia and severe oligospermia. In their study, 6% of men with azoospermia and 4% of all men had qh+ chromosome. Also, infertile people have long and short Y chromosomes. Y chromosome variants are frequently seen as Yqh + or Yqh- with a frequency of 3.4% and 27.3%, respectively [22].

CONCLUSION

Y is fighting a losing battle: Loss of genes on Y may make fewer loci develop or suppress driving, while accumulation of repeats and heterochromatinization may make Y an easier target for drivers on X. This means that the silencing effect of heterochromatin increased on the chromosome can inhibit expression on Y within the genome. As a summary, our data show that Y chromosome polymorphisms may be associated with infertility risk and may play an important role in infertility. In conclusion, it is clear that more research, including molecular genetics, genomics, and other fields, is urgently needed to elucidate the mechanisms by which Y chromosome polymorphisms are particularly associated with and lead to infertility.

Authors' Contribution

Study Conception: EİA, HG; Study Design: EA; Supervision: ÇM, SD; Funding: N/A; Materials: HG, SY; Data Collection and/or Processing: EA; Statistical Analysis and/or Data Interpretation: EİA; Literature Review: EİA; Manuscript Preparation: EİA and Critical Review: HG, SD.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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