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Chromosome heteromorphisms are more frequent in couples with recurrent abortions

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ABSTRACT. Chromosomal heteromorphism is considered a variant of a normal karyotype, but it is more frequent in couples with repeated miscarriages. We investigated chromosomal heteromorphism in couples with repeated miscarriages in comparison with a control group. A total of 455 couples who applied to our genetic diagnosis laboratory in Diyarbakir, Turkey, were evaluated for chromosome heteromorphisms; 221 of these couples (the study group) had recurrent abortions and 234 of them (the control group) had no history of abortions and had at least one living child. The patient group of couples with recurrent abortions were found to have a significantly higher rate of chromosome heteromorphism (8.4%) in comparison with the control group (4.9%). When the patients were evaluated according to gender, males had a significantly higher rate of chromosome heteromorphism (11.3%) than females (5.4%). We conclude that since couples with recurrent abortion and males have higher

rate of chromosome heteromorphism, cases of heteromorphism should not be disregarded in the etiological investigation of recurrent abortions. Further research should be done to investigate the phenotypic effects of chromosome heteromorphism.

Key words: Cytogenetic; Chromosome heteromorphism; Recurrent pregnancy loss

INTRODUCTION

Common cytogenetic polymorphisms detected by G-banding are considered heteromorphisms. They have heterochromatic regions of chromosomes 1, 9, 16, and Y, with prominent acrocentric short arms, satellites and stalks. Such heteromorphic chromosomes have been observed since the early studies of cytogenetics and are believed to have no impact on the phenotype (Brothman et al., 2006). In recent studies, however, patient groups with recurrent pregnancy loss have been found to have higher rates of chromosome heteromorphism compared to the rest of society and to control groups, which may not be merely an incidental finding (Nakamura et al., 2001; Düzcan et al., 2003; Yakin et al., 2005; Sahin et al., 2008). Furthermore, studies by cell biologists suggest that heterochromatin may have important cellular roles in different clinical conditions, including fertility (Madon et al., 2005).

The aim of this study was to work with couples who applied to Diyarbakır Dicle University Faculty of Medicine for chromosomal analysis and to compare the rates of chromosome heteromorphism between couples with recurrent abortion and a control group, thereby contributing to the literature in this field. This study is the first report on chromosome heteromorphism in the southeast region of Turkey.

MATERIAL AND METHODS

Couples with an indication of recurrent pregnancy loss who applied to the laboratory of Diyarbakır Dicle University Faculty of Medicine, Department of Medical Biology and Genetics, for chromosome analysis between the years 2005 and 2010 were taken into the scope of this study. A total of 442 individuals were investigated in the study group (group A), which made 221 couples with a history of two or more miscarriages. The control group (group B) consisted of 234 couples, that is, 468 individuals who had at least one child and whose karyotypes were examined with an indication other than recurrent abortion.

Karyotyping was performed on routine peripheral blood lymphocyte cultures using G-banding after Trypsin and Giemsa staining (GTG) (Verma and Babu, 1989). At least 20 GTG-banded metaphases were analyzed for each case. After the detection of a chromosome heteromorphism, other banding techniques (C-banding, NOR-banding) were used if necessary. The findings were considered heteromorphic if the chromosome region of interest was greater than the same region on its homolog. As for the Y chromosome, if it was larger than the G-group chromosomes, it was reported as Yqh+ (Wyandt and Tonk, 2004). The common pericentric inversion of chromosome 9 was also considered a heteromorphism. The position and partial karyotypes of heteromorphic chromosomes (1, 9, 16, 22, and Y) are presented in Figure 1.

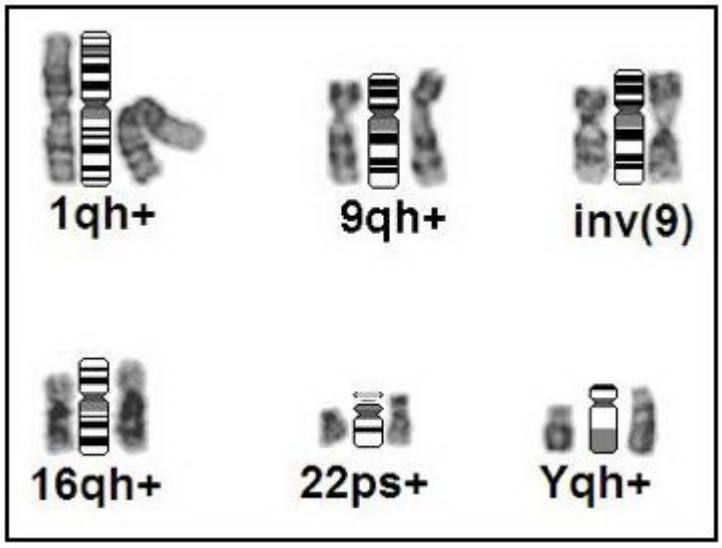

Figure 1. Partial karyotypes showing samples of chromosome heteromorphisms. Ideograms are shown in the middle; heteromorphic chromosomes are on the right, and normal chromosomes are on the left.

Statistical analyses

The results of the two groups were compared using the two-tailed Fisher exact test, calculated online at http://www.graphpad.com/quickcalcs/contingency2.cfm.

RESULTS

The distribution of chromosome heteromorphism among different chromosomes in the study groups is presented in Table 1. The most frequent heteromorphism was found to be "9qh+" both in the group of patients with recurrent abortion and the control group, while the least frequent heteromorphism was found to be "1qh+" in both groups.

Table 1. Distribution of chromosome heteromorphisms among different chromosomes in the study population.

Chromosome heteromorphisms	1qh+	9qh+	İnv(9)	16qh+	D/G group	Yqh+	Total (%)
Group A (recurrent abortions)	1	14	6	2	10	4	37 (8.4)
Group B (control)	0	9	5	1	6	2	23 (4.9)

Table 2 shows the distribution of chromosome heteromorphism in individuals with recurrent abortion and the control group, where 8.37% (37/442) of the A group couples with recurrent abortion were found to have chromosome heteromorphism compared to 4.91% (23/468) in the control group. The rate of heteromorphism was significantly higher in the patient group compared to the control group ($P < 0.05$).

Table 2. Prevalence of chromosome heteromorphism in the study population.

	Gender	N	Chromosome heteromorphism	%
Group A (recurrent abortions)	Female	221	12	5.4
	Male	221	25	11.3
	Total	442	37	8.4 ($P < 0.05$)
Group B (control)	Female	234	9	3.8
	Male	234	14	6.0
	Total	468	23	4.9
Total		910	60	($P < 0.05$)

Evaluating the frequency of chromosome heteromorphism in the A group in terms of gender, the heteromorphism rate was significantly higher in men (11.31%) than in women (5.43%) ($P < 0.05$). In the control group, however, there was no significant difference in rates according to gender ($P > 0.05$).

DISCUSSION

Cytogenetic research conducted on patient groups with recurrent pregnancy loss reports between 4 and 18.9% chromosome heteromorphism, which is higher than the normal population, and it has been suggested that these cases of heteromorphism may be associated with fetal loss (Makino et al., 1990; Düzcan et al., 2003; Sahin et al., 2008; De la Fuente-Cortés et al., 2009; Caglayan et al., 2010). However, comparative studies with control groups have yielded contradictory results. In this respect, there are many studies suggesting that there is no relationship between control groups and couples with fetal loss (Blumberg et al., 1982; de Braekleer and Dao, 1990). In recent studies, however, Caglayan et al. (2010) have reported a statistically higher rate of chromosome heteromorphism in the patient group (8%) compared to the control group (4%), suggesting that if the patients experiencing recurrent abortion have such heteromorphisms, their chances for further abortions may be higher than other populations without such heteromorphisms in future pregnancies. Sahin et al. (2008) found a statistically higher rate of chromosome heteromorphism in infertile couples (6.52%) compared to the control group (1.77%). In our study, couples with recurrent abortion were found to have a higher rate of chromosome heteromorphism (8.4%) compared to the control group with proven fertility (4.9%) ($P < 0.05$).

Previous cytogenetic research revealed that infertile men had a higher rate of chromosome heteromorphism (Eiben et al., 1987). The largest survey from a Japanese study reported that the incidence of heterochromatin polymorphism in infertile men was higher than in normal men in the control group (Nakamura et al., 2001). Yakin et al. (2005) reported a higher rate of chromosome heteromorphism in infertile men compared to men with proven fertility. On the other hand, Mau et al. (1997), Penna-Videau et al. (2001), and Düzcan et al. (2003) reported, respectively, 34.5, 8.7 and 5% chromosome heteromorphism in the studies they conducted on infertile men. When our patient group was studied in terms of gender, men were found to have a higher rate of chromosome heteromorphism compared to women ($P < 0.05$). There was no significant difference according to gender in the control group. These findings support the view that heterochromatin polymorphisms may modify the genetic control of spermatogenesis as suggested by Yakin et al. (2005).

According to a widely held opinion, the chromatin that causes chromosome hetero-

morphism is formed out of the repetitive DNA regions that do not code for genes. Considering the studies of cell biologists, however, heterochromatin plays an essential role in spindle attachment and chromosome movement, meiotic paring, and sister chromatid cohesion (Karpen and Kndow, 1998). Polymorphic heterochromatic regions were found to alter the synapsis of homologous chromosomes during meiosis. These regions are the last to enter synapsis, changing the timing of the whole division and leading first to probable meiotic defects, and eventually to infertility (Codina-Pascual et al., 2006). In light of the developments in cell biology and studies in infertility, we think that chromosome heteromorphisms may not be merely unharmful changes as previously thought and that they need to be taken into consideration.

As a result, chromosome variants should not be ignored by cytogeneticists and clinicians working on couples with recurrent abortion, for they may be contributory factors that have not been fully discovered. Further research is necessary for shedding light on the subject.

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