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The relationship between qh+ and recurrent spontaneous abortion

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Summary

Objective: To study the relationship between qh+ and recurrent spontaneous abortion (RSA). *Design:* Experimental study using human samples. *Setting:* University-affiliated hospital. *Materials and Methods:* Eight hundred sixty couples (1,720 cases) with RSA were taken as the RSA group and 871 sterile couples (1,742 cases) with a normal gestation history who came for consultation regarding oviduct factors were taken as the normal group. *Intervention(s):* The chromosome was collected from peripheral blood of patients. By analyzing the karyotypes of 860 couples (1,720 cases) with RSA and 871 sterile couples (1,742 cases) with a normal gestation history who underwent a consultation purely for oviduct factors. *Results:* One hundred ninety-three cases of chromosome polymorphisms were diagnosed in the RSA group, with a detection rate of 11.22%, among which 81 cases of qh+ were detected, with a detection rate of 4.71% (81/1720). These cases accounted for 41.97% of the cases of chromosome polymorphisms. The detection rate of chromosome polymorphisms in the normal group was 2.41% (42/1742). Comparison of the two indicates the statistical significance ($p < 0.01$) of these disparities in the detection rates of both chromosome polymorphisms and qh+. *Conclusions:* Chromosome polymorphism qh+ is related to RSA, which could provide theoretical foundations for genetic counseling and sound child rearing.

Key words: Chromosomal polymorphism; Karyotype analysis; Recurrent spontaneous abortion.

Introduction

Recurrent spontaneous abortion (RSA) refers to spontaneous abortion that has occurred two or more times; the incidence rate of RSA is approximately 1-5% [1]. The causes of RSA are complex, including chromosomal abnormalities, endocrine abnormalities, immunological factors, infection, and abnormal anatomy, and so on. Among these factors, chromosome abnormalities are among the common causes of early phase RSA. A chromosomal polymorphism refers to a subtle variation in the structure or banding strength of a chromosome and is usually associated with the genetically less active heterochromatin region, which contains a highly repetitive DNA structure. Traditional views suggest that these sorts of chromosomal polymorphisms generally occur without hereditary information transmission and will not cause phenotype abnormalities; thus, they have not been considered to have clinicopathological significance. However, clinical practices indicate that chromosomal polymorphisms are related to a series of clinical symptoms, including RSA, stillbirth, congenital malformation, semen quality decline, sterility, dysgnosia and genital dysplasia (male/female), and so on. This paper discusses the relationship between chromosome polymorphism qh+ and RSA, with the detection rate of chromosome polymorphism qh+ as the principle factor after examining the chromosomes of couples with RSA who came to the reproduction center of this hospital for consultation.

Materials and Methods

A total of 860 couples (1,720 cases) with RSA who came to the present reproductive center from June 2010 to October 2014 were taken as the RSA group, the age range of which was 22-36 years; 871 sterile couples (1,742 cases) with a normal gestation history who came for consultation regarding oviduct factors were taken as the normal group, the ages of which ranged from 22 to 38 years. The age difference of the two groups was of no statistical significance. Written informed consent was obtained from all human subjects. This study was approved by the institutional ethnic committee of affiliated hospital of Weifang Medical University.

Both of the two groups consented to examinations of their anatomy, as well as their infection, endocrine, chromosome, and immunity histories. The chromosome examination involved 2 ml of peripheral blood with anticoagulant heparin, and lymphocyte collection occurred after 68-72 hours of cultivation with a common sectioning method. G-banding and C-banding technology, if necessary, were adopted. A total of 30 well-scattered chromosomes were counted in each case during full metaphase, and the authors analyzed 5-10 karyotypes. If there were any abnormalities, the numbers of counted and analyzed chromosomes were

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Table 1. — *The detection rates of chromosome polymorphisms and the distributions of karyotypes.*

Group	n	Cases of chromosome polymorphism (incidence rate %)	Cases of different factions of chromosome polymorphism (incidence rate %)					
			1qh+	9qh+	16qh+	Yqh+	Total	Incidence rate
RSA	1720	193 (11.22%)	20 (1.16%)	16 (0.93%)	13 (0.76%)	32 (1.86%)	81	4.71%
Normal	1742	42 (2.41%)	5 (0.29%)	3 (0.17%)	3 (0.17%) 1	0 (0.57%)	21	1.21%
p	<0.01	<0.01	<0.01	<0.05	<0.05	<0.01	<0.01	

Table 2. — *Sex-related detection rates and constituent ratios of chromosome polymorphisms.*

Sex	RSA group			Normal group		
	n	Detecting rate (%)	Constituent ratio (%)	n	Detecting rate (%)	Constituent ratio (%)
Male	860 (46)	5.35	56.79	871 (12)	1.38	57.14
Female	860 (35)	4.07	43.21	871 (9)	1.03	42.86
Total	1720 (81)	4.71	100	1742 (21)	1.21	100
p		>0.05			>0.05	

doubled. This methodology is in line with ISCN 2013. The results of chromosomal abnormalities were analyzed, confirmed, and rechecked by at least two genetic experts.

With the help of the SPSS 13.0 statistical software, the measurement data were expressed in "±s" and were evaluated with group *t*-tests. The enumeration data were expressed in ratios and were treated with Chi-squared tests. A threshold of $p < 0.05$ indicated differences that were statistically significant.

Results

After excluding spontaneous causes of anatomical, infection, endocrine or immunological-related abnormalities, among the 860 couples (1,720 cases) with RSA, 193 cases of pure chromosomal polymorphism variations were detected, with a detection rate of 11.22% (193/1720). Among these, 81 cases of qh+ were detected, with a detection rate of 4.71% (81/1720), accounting for 41.97% (81/193) of the observed abnormalities. The detection rate of chromosome polymorphisms in the normal group was 2.41% (42/1742), close to the incidence rate of normal people (2.6%) [2]; the detection rate of qh+ was 1.21% (12/1742). Both the differences in chromosome polymorphisms, in general, and in qh+, in particular, were of statistical significance ($p < 0.01$).

A total of 81 cases of chromosome polymorphism qh+ were detected in the RSA group, and the detection rate in the 46 male cases was 5.35% (46/860), accounting for 56.79% (46/81) of the observed differences (Table 1). The detection rate in the 35 female cases was 4.07% (35/860), accounting for 43.21% (35/81) of the observed cases. A total of 21 cases of chromosome polymorphisms were detected in the normal group, among which the detection rate in the 12 male cases was 1.38% (12/871), accounting for 57.14% (12/21), and the detection rate in the nine female cases was 1.03% (9/871), accounting for 43.21% (9/21) of the observed variance, respectively (Table 1). Comparisons of the sex-rated detection rates in both the groups indicated $p > 0.05$; thus, the differences were of no statistical significance (Table 2).

Discussion

Chromosomal polymorphisms refer to a series of subtle variations in the chromosomes of normal people. For this sort of variation, the incidence rate among normal people is approximately 2.6% [2], in line with Mendelian heritability. These polymorphisms are mainly expressed in variations of heterochromatin, especially heterochromatin with highly repetitive DNA structures that are located in the heterochromatin regions of chromosomes 1, 9, 16 and Y, as well as in the centromere regions of the chromosome. It has been widely debated whether these chromosome polymorphisms have clinical effects. Heterochromatin contains highly repetitive uncoded DNA structures, which have been considered to be of no transcriptional activity. With the fast development of molecular cytogenetics technologies in recent years, research has increased and has studied the relationships between chromosome polymorphisms and clinical phenotypes. As the knowledge of the human genome advances day to day, it has been demonstrated that heterochromatin, which is full of repetitive DNA sequences, is not absolutely inert or unrelated to clinical phenotypes [3, 4]. Some researchers [5] have suggested that heterochromatin works as a centromere, contributing to the union of correct sister chromatids, the pairing of homologous chromosomes, and chromosome segregation. Heterochromatin also influences the regulation of gene expression during evaluation and cell differentiation. During the process of cell division, the polymorphic part of the chromosome may cause difficulties in homologous chromosome pairing, thus affecting cell division and leading to dysontogenesis and spontaneous abortion, stillbirth or chromosomal abnormalities in later generations [6]. Carp *et al.* [7] believed that chromosomal polymorphisms were obviously related to abnormal pregnancies. The incidence rate of chromosome polymorphisms in the RSA group in this study was 11.22%, while the detection rate of chromosome polymorphisms in the normal group was 2.41%, close to the incidence rate in normal people (2.6%). The difference in the chromosomal polymorphism rates between the two groups was statisti-

cally significant ($p < 0.01$), indicating that chromosomal polymorphisms were obviously related to RSA.

Secondary constrictions exist in the long-arm heterochromatin regions of 1q, 9q, and 16q. Secondary constrictions increase or decrease with highly repetitive DNA sequences [8]. There are scholars who believe that these increases or decreases in secondary constrictions do not cause phenotype effects and are unrelated to abnormal pregnancies. Other scholars have argued that these increases or decreases in highly repetitive DNA sequences could affect cell division, causing difficulties in homologous chromosome paring; thus, the resulting unbalanced gametes would die or be unable to be fertilized, leading to male sterility, spontaneous abortion or stillbirth due to the formation of aneuploid embryos [9]. Among the 1,720 cases of the RSA group, 81 cases of qh+ were detected, in which the detection rate in the 49 cases of 1qh+, 9qh+, and 16qh+ was 2.85% (49/1720). Among the 1,742 cases in the normal group, 21 cases of qh+ were detected, in which the detection rate in the 12 cases of 1qh+, 9qh+, and 16qh+ was 0.069% (12/1742). The comparative difference was obvious ($p < 0.01$). Therefore, qh+ in any of the 1q, 9q or 16q chromosomes is related to abnormal pregnancies.

The major polymorphisms of the Y chromosome include invqh, Yqh+, and Yqh- [10]. The existence rate of Yqh+, namely, the long Y chromosome, was 0.52% [11] in male infants in a large-scale research study in 11,148 cases of new born infants. Debates exist as to whether Yqh+ has clinical effects. Nie *et al.* [12] reported that the risk of fetal malformation and spontaneous abortion did not increase in the offspring of qh+ patients. Nielsen and Friedrich indicated that the spontaneous abortion rate (22%) of the mothers of the male infants with a long Y chromosome was obviously increased compared to the normal group [13]. According to Wang *et al.* [14], 78.5% of reported Yqh+ patients were sterile, and their spouses had a history of spontaneous abortion or stillbirth. Other researchers have indicated that Yqh+ is related to an increase in the spontaneous abortion rate [15]. Cytogenetics research has found that over-repetition of the DNA sequences in the long-arm heterochromatin region of the Y chromosome could increase the instability of the chromosome, causing dosage effects or subtle variations. This repeated DNA might cause errors in mitosis, leading to the chromosomal non-disjunction of gametes or zygotes in the process of meiotic mitosis, giving birth to unbalanced gametes or zygotes, which have been attributed to sterility and spontaneous abortion [16]. Among the 81 cases of qh+ of the RSA group (1,720 cases), the detection rate of the 32 cases of Yqh+ was 1.86% (32/1,720). Among the 21 cases of qh+ in the normal group, the detection rate of the ten cases of Yqh+ was 0.57% (10/1,742). The comparative difference of the two was of statistical significance ($p < 0.05$), indicating a probable relationship between chromosome polymorphisms Yqh+ and RSA.

In conclusion, chromosome polymorphism qh+ was obviously related to RSA in the present sample. To further confirm its relationship with abnormal pregnancies, follow-up surveys should be performed in individuals to comprehensively analyze their somatic cells, germ cells, aborted fetuses, abnormal daughter cell chromosomes, and to detect other molecular genetic formation mechanisms to investigate their influence on cell divisions at the level of functional genomics. These studies could provide theoretical foundations for genetic counseling and sound child rearing.

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