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GENETICS

The effect of chromosomal polymorphisms on the outcomes of fresh IVF/ICSI–ET cycles in a Chinese population

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Abstract
Purpose Chromosomal polymorphisms (CPs) have been reported to be associated with infertility; however, their effects on the outcomes of in vitro fertilization/intracytoplasmic sperm injection–embryo transfer (IVF/ICSI–ET) are still controversial. In this retrospective study, we aimed to evaluate the effect of CPs on IVF/ICSI–ET outcomes.
Methods To investigate whether CPs affected the outcomes of fresh IVF/ICSI–ET cycles in a Chinese population, we evaluated infertile couples with male carriers of CPs ($n = 348$), infertile couples with female carriers ($n = 99$), and unaffected couples ($n = 400$) who had received their first treatment cycles in our hospital between January 2013 and March 2015.
Results CPs in either male or female carriers seemed to have adverse effects on IVF/ICSI–ET outcomes. CPs in male carriers affected outcomes mainly by decreasing the rates of fertilization, embryo cleavage, good quality embryos, clinical pregnancies, ongoing pregnancies, and deliveries as well as increasing the biochemical pregnancy rate ($P < 0.05$); CPs in female carriers affected outcomes only by lowering the embryo cleavage rate ($P < 0.05$). The mean fertilization rate of couples with male CP carriers undergoing IVF was significantly lower than that in those undergoing ICSI (61.1 versus 66.5 %, respectively; $P = 0.0004$).
Conclusions Our data provide evidence for the involvement of CPs in the poor outcomes of fresh IVF/ICSI–ET cycles in a Chinese population. The use of ICSI might improve outcomes by increasing the fertilization rate for men with CPs.

Keywords Chromosomal polymorphisms · Clinical outcomes · IVF/ICSI cycles · Fertilization rate · Cleavage rate

Capsule Our data provide evidence for the involvement of CPs in the poor outcomes of fresh IVF/ICSI–ET cycles in a Chinese population.

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Introduction

Chromosomal polymorphisms (CPs) are heritable variants of segments located in heterochromatic chromosomal regions [1, 2]. Human CPs on non-acrocentric chromosomes usually occur in the heterochromatic regions of the long arms of chromosomes 1, 9, and 16 and on the distal heterochromatic region of the Y chromosome (qh+) [3]. For acrocentric chromosomes, including chromosomes 13, 14, 15, 21, and 22, CPs mostly occur on satellites and satellite stalks on the short arms (pss+ or pstk+). Pericentric inversions on chromosomes 1, 2, and 9 are also regarded as polymorphisms including inv(1)(p13q21), inv(2)(p11.2q13), and inv(9)(p12q13) [2, 4].

Because heterochromatic regions are enriched with tandemly organized highly repetitive satellite DNA sequences and do not encode proteins [5, 6], CPs are usually considered as harmless variants with no functional or phenotypic impact on the carriers. The incidence of CPs in the general population is approximately 2–5 % [7]. However, CPs seem to have a higher incidence (approximately 10–15 %) in infertile populations: approximately three to five times higher than in the

general population [8–11]. This suggests that CPs are associated with infertility and should not be ignored [6, 12]. In addition, increased rates of recurrent spontaneous abortions and embryonic losses and other adverse obstetric histories were also found to be correlated with CPs [10, 13]. Nevertheless, the etiological mechanisms for these phenomena remain largely elusive.

Differences in the incidences of CPs have been discovered between infertile men and women [6, 10]. The high incidence of CPs in men is associated with the presence of Y chromosome variants. Therefore, the higher incidence of CPs in infertile men than in infertile women suggests that CPs (especially Y chromosome variations) might have deleterious effects and play important roles in reducing male infertility by influencing a variety of physiological processes, including spermatogenesis and sperm quality [14, 15]. However, few studies have provided any details on the mechanisms involved.

In vitro fertilization/intracytoplasmic sperm injection–embryo transfer (IVF/ICSI–ET) procedures have been widely used for treating severe infertility and have significantly improved the treatment outcomes. CPs were originally considered *benign*, and for a long time, carriers were assumed to have reproductive outcomes similar to those of non-carrier couples. Nevertheless, in recent clinical observations, CP carriers had more frequent reproductive failure compared with non-carriers. The effect of CPs on IVF/ICSI–ET outcomes is still controversial [4, 8, 14–16]. Therefore, an in-depth understanding of the genetic basis of pregnancy failure is essential to appropriately manage the treatment options for infertile couples.

To further elucidate the association of CPs between different male and female carriers and IVF/ICSI–ET outcomes, we comprehensively compared CPs and the outcomes of fresh treatment cycles for infertile couples who were treated in our hospital over the last 3 years. We found that CPs in either male or female partners seemed to have adverse effects on treatment outcomes.

Materials and methods

Subjects

This retrospective study was carried out on 447 infertile couples with CP undergoing IVF/ICSI treatments in the Reproductive Medicine Hospital of the First Hospital of Lanzhou University, Lanzhou, Gansu, China, from January 2013 to March 2015. Couples were excluded for the following conditions: (1) both were diagnosed as carriers with CP; (2) the female with an anatomical defect of the reproductive system, age >40 years old, and basal serum FSH level >10 IU/L; and (3) chromosomal abnormalities and azoospermia factor (AZF) microdeletions. All procedures performed in studies involving human participants were in accordance with the ethical standards of the ethics committee of the Reproductive Medicine Hospital of the First Hospital of Lanzhou University and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent of the ethics committee was not required. Informed consent was obtained from all individual participants included in the study.

Karyotype analysis

Karyotype analysis was carried out using G-band staining (for all subjects), C-band staining (for the subjects with qh+), and N-band staining (for the subjects with the ps+) of peripheral blood lymphocytes. Culturing peripheral blood lymphocyte and chromosomal preparation were performed according to the routine experimental protocol [4]. CPs were reported according to the International System for Chromosomal Nomenclature 2013 (ISCN2013) [2]. In this study, qh+ (1, 9, 16, and Y chromosomes), qh− (Y chromosome), ps+ in D/G genomes, and pericentric inversions (1, 9, and Y chromosomes) were found in the infertile couples (Online Resource 2).

Subdivisions of study groups

For IVF/ICSI patients, all couples were subjected to chromosomal analysis as a part of routine examination prior to the IVF/ICSI–ET treatment. Among the 3956 couples identified, 469 couples were found to have CP (11.9 %; couples with chromosomal abnormalities and AZF microdeletions were excluded). Male partners were diagnosed as carriers in 348 couples (8.8 %), and female partners were diagnosed as carriers in 99 couples (2.5 %). Twenty-two couples (0.6 %) with both were diagnosed as CP carriers and excluded for small sample size. Couples with male carriers only were set as group 1 ($n = 348$); couples with female carriers only were set as group 2 ($n = 99$). Four hundred couples with normal karyotypes under G-banding test were randomly selected from the remaining 3487 couples and set as controls (group 3, $n = 400$). In group 1, 232 couples were treated with IVF and 116 couples were treated with ICSI. In group 2, 62 couples were treated with IVF and 37 couples were treated with ICSI. In group 3, 276 couples were treated with IVF and 124 couples were treated with ICSI.

Controlled ovarian stimulation

Long luteal downregulation protocol was used for all experimental subjects and controls. Gonadotropin-releasing hormone (GnRH) agonist (0.1 mg/ampoule, Tryptorelin, Ferring, Germany) administration was given in the mid luteal phase of the previous cycle until the day of HCG administration. When satisfactory pituitary desensitization was achieved (serum E2 level was lower than 50 pg/mL), human

menopausal gonadotropin (75 U/ampoule, Lebaode, Lizhu Ltd., China) was given by intramuscular injection from day 3 of the menstrual phase. Subsequently, 5 to 7 days after human menopausal gonadotropin was given, ovarian follicles were monitored and evaluated by transvaginal ultrasound examination and serum E2 concentration. HCG (10,000 IU, HCG, Lizhu Ltd., China) was administered when at least two follicles reached 18 mm or more in diameter. Oocyte retrieval took place 36–40 h after HCG administration using transvaginal ultrasound-guided follicular aspiration. Following fertilization by routine IVF/ICSI and in vitro embryo culture according to the standard protocols of our laboratory, two embryos per couple were transferred 3 days after oocyte retrieval. The luteal phase was supported with progesterone (20 mg/ampoule; Xianju Ltd., Zhejiang, China). IVF treatment was routinely performed. However, couples with the following conditions would be performed ICSI treatment, for instance severe oligoasthenoteratozoospermia, <25 % fertilization rate and failed pregnancy in the first IVF cycle, two failed pregnancies in the first two IVF cycles, and so on.

Outcome survey

To determine the IVF/ICSI–ET outcomes affected by CPs, fertilization rate, cleavage rate, good quality embryo rate, positive pregnancy rate, biochemical pregnancy rate, clinical pregnancy rate, early spontaneous abortion rate, ongoing pregnancy rate, delivery rate, and the ratio of boys to girls were compared between the three groups.

Fertilization rate referred to the percentage of fertilized oocytes (oocytes with two pronuclei after insemination) in the inseminated oocytes. A positive pregnancy rate referred to the percentage of positive pregnancies in the total fresh embryo transfer cycles, which was defined by >5 IU/L of plasma beta-HCG 14 days after embryo transfer. Biochemical pregnancy rate referred to the percentage of biochemical pregnancies in the positive pregnancies which indicated that a very early spontaneous abortion after a positive pregnancy was determined and the plasma beta-HCG level decreased before the ultrasound detected gestational sac(s). Clinical pregnancy rate referred to the percentage of clinical pregnancies in total fresh ET cycles which were defined as the observation of the gestational sac(s) on ultrasound 4 weeks after ET. Early miscarriage rate referred to the percentage of early miscarriages in the clinical pregnancies which indicated pregnancy termination before 12 gestational weeks. Ongoing pregnancy rate referred to the percentage of ongoing pregnancies in the fresh embryo transfer cycles which indicated pregnancies continuing over 12 gestational weeks. Delivery rate referred to the percentage of live births to fresh embryo transfer cycles. The ratio of boys to girls referred to the value of the number of the boys born divided by the number of the girls born.

Statistical analysis

In this study, all statistical analyses were performed using SPSS 17.0 for Windows. Independent sample *t* test was used to analyze numerical data. Pearson chi-square test or Fisher's exact test was used to analyze categorical data. All descriptive statistics were expressed as means ± SD or ratio. All statistical tests were two-sided. *P* values lower than 0.05 were considered to be significant.

Results

A total of 847 couples who underwent IVF/ICSI cycles from January 2013 to March 2015 were enrolled in this study, including 447 CP carrier couples (experimental group) and 400 non-carrier couples (control group). Of the experimental groups, 348 couples had only male carriers (77.9 %) and 99 (22.1 %) had only female carriers. The basal characteristics of these three groups are shown in the supplementary table (Online Resource 1). No statistically significant differences were found in the clinical characteristics of the experimental and control groups.

The distributions of CPs for the male and female carriers are shown in the supplementary table (Online Resource 2). Yqh+ was the most frequent type (60 %) of CP in male carriers, whereas 1qh+ had the highest frequency (46.3 %) in females.

To understand the specific effect of CP on IVF/ICSI–ET outcomes, the major outcomes of fresh IVF/ICSI–ET cycles were compared among the three groups (Table 1). The results for group 1 were significantly poorer than those for group 3 in terms of the rates of fertilization, embryo cleavage, formation of good quality embryos, biochemical pregnancies, clinical pregnancies, ongoing pregnancies, deliveries, and a decreased ratio of boys to girls ($P < 0.05$). A significantly poorer result of the embryo cleavage rate ($P < 0.05$) was found in group 2 compared to group 3. Worse results of the rates of formation of good quality embryos, biochemical pregnancies, clinical pregnancies, and deliveries ($P < 0.05$) were also found in group 1 compared to group 2.

To further investigate the effect of CPs on the fertilization rate of group 1, we compared the fertilization rates of IVF/ICSI cycles between groups 1 and 3 and the fertilization rate between IVF and ICSI cycles in group 1 (Tables 2 and 3). As shown in Table 2, the fertilization rate of patients undergoing IVF in group 1 was significantly lower than that in group 3 (61.1 versus 64 %, respectively; $P = 0.015$). In contrast, no significant difference in the fertilization rate of ICSI cycles was found between groups 1 and 3. As shown in Table 3, the fertilization rate of couples in group 1 undergoing IVF was significantly lower than that in those undergoing ICSI (61.1 versus 66.5 %; $P = 0.0004$). The odds ratio (OR) for

Table 1 Comparison of the outcomes of fresh IVF/ICSI–ET cycles among the three groups

Outcomes	Group 1	Group 2	Group 3	*P* value		
	n (%)			$P_{1\text{ vs. }3}$[a]	$P_{2\text{ vs. }3}$[b]	$P_{1\text{ vs. }2}$[c]
Fertilization rate (fertilized oocytes/inseminated oocytes)	2875/4580 (62.77)	848/1295 (65.48)	4178/6327 (66.03)	0.0004	0.703	0.074
Cleavage rate (cleaved zygotes/fertilized oocytes)	2785/2875 (96.88)	825/848 (97.28)	4126/4178 (98.75)	<0.001	0.001	0.54
Good quality embryo rate (good quality embryos/ cleaved zygotes)	1206/2875 (41.94)	393/825 (47.63)	2098/4426 (47.40)	<0.001	0.901	0.004
Cycle cancellation rate (embryo untransfer cycles/ oocyte retrieval cycles)	47/348 (13.51)	16/99 (16.16)	53/400 (13.25)	0.918	0.452	0.503
Positive pregnancy rate (positive beta-HCG/fresh embryo transfer cycles)	262/301 (87.04)	73/83 (87.95)	299/347 (86.16)	0.744	0.669	0.826
Biochemical pregnancy rate (biochemical pregnancies/ positive pregnancies)	119/262 (45.42)	20/73 (27.39)	84/299 (28.09)	<0.001	0.905	0.006
Clinical pregnancy rate (clinical pregnancies/fresh embryo transfer cycles)	143/301 (47.51)	53/83 (63.85)	215/347 (61.96)	0.0002	0.749	0.008
Early miscarriage rate (early miscarriages/clinical pregnancies)	22/143 (15.38)	9/53 (16.98)	31/215 (14.42)	0.801	0.6	0.745
Ongoing pregnancy rate (ongoing pregnancies/fresh embryo transfer cycles)	121/301 (40.20)	43/83 (51.81)	184/347 (53.03)	0.001	0.842	0.058
Live birth rate (live births/fresh embryo transfer cycles)	103/301 (34.22)	39/83 (46.98)	159/347 (45.82)	0.003	0.848	0.033
The ratio of boys to girls (live births of boy baby/live births of girl baby)	44/76 (1:1.73)	25/22 (1:0.88)	81/78 (1:0.96)	0.018	0.789	0.056

[a] *P* value for group 1 versus group 3

[b] *P* value for group 2 versus group 3

[c] *P* value for group 1 versus group 2

the ICSI cycles versus the IVF cycles was 1.266 (95 % CI = 1.110–1.443; $P = 0.0004$). Thus, ICSI produced significantly higher fertilization rates for male CP carriers.

Because the most common CP observed in the infertile men was Yqh+, we analyzed the major outcomes of Yqh+ carriers in group 1 and controls in group 3 (Table 4). For these men, the results for Yqh+ carriers were significantly poorer than those for controls and showed significant differences in terms of the rates of fertilization, formation of good quality embryos, biochemical pregnancies, clinical pregnancies, ongoing pregnancies, deliveries, and the ratio of boys to girls ($P < 0.05$).

Discussion

A number of mechanisms might be associated with the negative impact of CPs on IVF/ICSI–ET treatment outcomes. Some studies have suggested that the heterochromatin in CP regions might suppress or silence gene expression by the reversible transformation between heterochromatin and euchromatin [17, 18]. In addition, other reports have indicated that the heterochromatin located at centromeres plays an essential role in cell division. When chromatin variation occurs in these regions, it causes abnormal meiotic cell division, such as defects in centromere function and kinetochore assembly, difficulty in homologous chromosome pairing, and disruption of cell division, which could impair the formation of functional spermatozoa [19]. With the precise molecular techniques now available, certain genes associated with fertility are now thought to reside in heterochromatin. Transcriptional activation of these genes in constitutive heterochromatic domains of the human genome in response to environmental stress was also reported recently [6]; hence, CPs are considered to be *malignant*. However, the impact of CPs on IVF/ICSI–ET outcomes remains largely unknown.

Table 2 Comparison of fertilization rates of fresh IVF and ICSI–ET cycles between group 1 and group 3

Fertilization rates	Group 1 *n* (%)	Group 3	*P* value
Fertilization rate in ICSI cycles	942/1416 (66.53)	1656/2386 (69.40)	0.065
Fertilization rate in IVF cycles	1933/3164 (61.09)	2522/3941 (63.99)	0.012

Table 3 Comparison of fertilization rates of fresh IVF and ICSI–ET cycles in group 1

	Fertilized oocytes	Unfertilized oocytes	Total
ICSI cycles, *n* (%)	942 (66.53)	474 (33.47)	1416
IVF cycles, *n* (%)	1933 (61.09)	1231 (38.91)	3164
Total	2875	1705	4580
χ^2	12.351		
P value	0.0004		
OR	1.266		
95 % CI	1.110–1.443		

We found here that CPs in either male or female carriers seemed to have adverse effects on treatment outcomes, consistent with a previous study [4]. Here, CPs in male carriers affected the IVF/ICSI outcomes negatively, mainly by lowering the rates of fertilization, embryo cleavage, formation of good quality embryos, clinical pregnancies, ongoing pregnancies, and deliveries and by raising the biochemical pregnancy rate. For these male CP carriers, the raised biochemical pregnancy rate led directly to lower rates of clinical pregnancies, ongoing pregnancies, and deliveries. However, CP in females negatively affected IVF/ICSI–ET outcomes only by lowering the embryo cleavage rate. Few studies have investigated the relationship between female CP carriers and cleavage rate in IVF/ICSI cycles.

As indicated in Tables 2 and 3, male CP carriers had lower fertilization rates following IVF but not after ICSI cycles. Therefore, our data imply that ICSI could improve the fertilization rate for male CP carriers. As reported in Supplemental file 1, there were no differences in the sperm concentration, the progressive sperm motility rate, and the rate of normal sperm morphology between groups 1 and 3, consistent with earlier studies [20]. Therefore, CPs in men might lower the fertilization rate in IVF by altering sperm fertilizing parameters that are not obvious from conventional semen analysis.

The potential impact of Yqh+ on the outcomes of IVF–ET treatment should not be ignored. The major CPs in the men in this study were Y chromosome variants. The male-specific region of the Y chromosome (MSY) differentiates the sexes; it encodes at least 27 distinct proteins or protein families, 11 of which are expressed exclusively or predominantly in the testes and directly or indirectly influence fertility [21]. Interestingly, in the present study, the ratio of boys to girls produced by Yqh+ carriers was significantly lower than that in group 3, as shown in Table 1. Carrying a Yqh+ CP lowered the successful delivery rate, leading to a lower rate of birth of boys for these men, who could transmit this Y chromosome variant only to their sons. The results of our study were consistent with previous studies indicating that the risk of spontaneous abortions increased when the male partner had a large Y chromosome [22, 23]. However, no previous studies have investigated the relationship between the ratio of boys to girls and the Yqh+ CP in IVF/ICSI cycles.

Conclusions

The reproductive outcomes of infertile couples with CPs were significantly poorer than those of non-carrier couples. Couples where the male partner is a CP carrier with poor reproductive outcomes from IVF treatment should be advised to undergo ICSI, which could offer a better chance of fertilization than simply repeating IVF cycles. Further investigations on the heterochromatin in CPs in terms of RNA sequences and functional consequences are needed to elucidate the specific mechanisms affecting the reproductive signaling activity and the pathogenesis of male infertility.

Table 4 Comparison of the outcomes of fresh IVF/ICSI–embryo transfer cycles between the Yqh+ carriers and the controls

Outcomes	Group 1 *n* (%)	Group 3	*P* value
Fertilization rate (fertilized oocytes/inseminated oocytes)	1742/2790 (62.44)	4178/6327 (66.03)	0.001
Cleavage rate (cleaved zygotes/fertilized oocytes)	1712/1742 (98.27)	4126/4178 (98.75)	0.152
Good quality embryo rate (good quality embryos/cleaved zygotes)	758/1712 (38.31)	2098/4426 (47.40)	0.028
cancellation rate (embryo untransfer cycles/oocyte retrieval cycles)	24/211 (11.37)	53/400 (13.25)	0.507
Pregnancy rate (positive beta-HCG/fresh embryo transfer cycles)	167/187 (89.30)	299/347 (86.16)	0.299
Biochemical pregnancy rate (biochemical pregnancies/positive pregnancies)	76/167 (45.51)	84/299 (28.09)	0.00015
Clinical pregnancy rate (clinical pregnancies/fresh embryo transfer cycles)	91/187 (48.66)	215/347 (61.96)	0.003
Early miscarriage rate (early miscarriages/clinical pregnancies)	12/91 (13.19)	31/215 (14.42)	0.958
Ongoing pregnancy rate (ongoing pregnancies/fresh embryo transfer cycles)	76/187 (40.64)	184/347 (53.03)	0.008
Live birth rate (live births/fresh embryo transfer cycles)	69/187 (36.89)	159/347 (45.82)	0.047
The ratio of boys to girls (live births of boy baby/live births of girl baby)	26/56 (1:2.15)	81/78 (1:0.96)	0.004

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Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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