GMR Genetics and Molecular Research
Online Journal
ISSN:1676-5680

FSHR gene Thr307Ala and Asn680Ser polymorphisms in infertile men: an association study in North China and meta-analysis

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Genet. Mol. Res. 14 (2): 5592-5601 (2015)
Received July 30, 2014
Accepted January 19, 2015
Published May 25, 2015
DOI http://dx.doi.org/10.4238/2015.May.25.11

ABSTRACT. Male infertility is a complex multifactorial and polygenic disease, and genetic factors play an important role in its formation and development. Recently, the association between follicle stimulating hormone receptor (*FSHR*) gene polymorphisms and male infertility risk has attracted widespread attention due to the unique biological functions of FSH. The aim of this study was to further explore the associations between the Thr307Ala and Asn680Ser polymorphisms of the *FSHR* gene and male infertility. A case-control study of 212 infertile and 164 fertile men from North China was performed. *FSHR* polymorphism genotypes were obtained through direct DNA sequencing. A meta-analysis was also performed. In the single-site association analysis, no significant associations were identified between *FSHR* Thr307Ala and Asn680Ser polymorphisms and male infertility ($P > 0.05$). However, we found that the combined genotypic frequency of Thr/Ala + Asn/Asn was higher in infertile patients than in controls (6.6 *vs* 1.8%; odds ratio (OR) = 3.795; 95% confidence interval (CI): 1.072-13.434, $P = 0.027$). In the meta-analysis, there was also no evidence of *FSHR* polymorphism (rs 6165 and rs 6168) association with male infertility

(P > 0.05). However, we found that the combined genotypes Thr/Thr + Asn/Asn had an increased risk of male infertility (OR = 1.238; 95%CI: 1.001-1.537, P = 0.049). Our studies further confirmed reports that there were no significant associations between the *FSHR* Thr307Ala and Asn680Ser polymorphisms and male infertility risk. However, a combined FSHR genotype showed significant association with male infertility.

Key words: Male infertility; Idiopathic infertility; Meta-analysis; Follicle-stimulating hormone receptor; Single nucleotide polymorphisms

INTRODUCTION

Male infertility is a complex disease that involves both environmental and genetic factors. It has been identified that approximately 15% of infertility cases could be attributed to genetic defects, including congenital hypogonadotrophic hypogonadism, congenital absence of the vas deferens, and primitive testicular failure (Krausz, 2011). However, there are still many male patients with infertility for whom the exact etiology is unknown; this is described as idiopathic male infertility. Because idiopathic infertility accounts for approximately 50% of male infertility (Forti and Krausz, 1998), a clear understanding of the pathogenesis of male infertility is critical for management of this disorder. Nowadays, an increasing number of researchers have focused their attention to the study of the correlation between genetic polymorphism with male infertility; e.g., within the cytochrome P4501A1 (*CYP1A1*) (Luo et al., 2014), sex hormone-binding globulin (*SHBG*) (Lazaros et al., 2008), and follicle stimulating hormone receptor (*FSHR*) (Ahda et al., 2005) genes, among others.

FSH plays an important role in the maintenance of qualitatively and quantitatively normal spermatogenesis (Nieschlag et al., 1999; Plant and Marshall, 2001). Its biological effects are exerted through binding with its receptor (FSHR), a member of the G protein-coupled receptor family. The *FSHR* gene consists of 9 introns and 10 exons and a promoter region and is located on chromosome 2p21 (Simoni et al., 1997). Mutation screening has identified several single nucleotide polymorphisms (SNPs) in the *FSHR* gene (Themmen and Huhtaniemi, 2000). Among these, the linked SNPs at positions 307 and 680 in exon 10 of the *FSHR* gene (GenBank accession No. NM_000145) have attracted widespread attention. However, despite the many studies that have investigated the possible associations between the Thr307Ala and Asn680Ser polymorphisms in the *FSHR* gene and male infertility, the findings remain unclear. Shimoda et al. (2009) reported that the combination of heterozygous *FSHR* variants might be responsible for male infertility in a Japanese population. Similar results were found by Safarinejad et al. (2011) in an Iranian population, and Song et al. (2013) in a Chinese population. Therefore, *FSHR* polymorphisms are thought to play a certain role in male infertility.

To further explore the association between Thr307Ala and Asn680Ser polymorphisms in the *FSHR* gene and male infertility, a case-control study of 212 infertile and 164 fertile men from North China was carried out, as well as a meta-analysis performed by combining our results with previous reports.

MATERIAL AND METHODS

Study subjects

Both male patients with infertility (N = 212) and controls (N = 164) were recruited by the Reproductive Medicine Center, Shanxi Maternal and Child Health Care Hospital, Taiyuan, China from October 2012 to December 2013. All subjects were of Han ethnicity from the Shanxi Province in North China. No difference in age was found between patients (32.753 ± 5.52 years) and controls (30.805 ± 2.87 years) ($P > 0.05$). According to the World Health Organization guidelines (WHO Laboratory Manual for the Examination and Processing of Human Semen, 5th edn., 2010), routine analysis of semen was conducted at least twice. The study was approved by the local Medical Ethical Committee and all participants provided consent.

The patients selected consisted of infertile men with idiopathic infertility ranging from oligospermia to azoospermia. Other diseases that could cause secondary infertility, such as obstructive azoospermia, karyotype abnormalities, Y chromosome microdeletions, and cryptorchidism, were excluded.

The controls consisted of normospermic patients who were from couples suffering infertility due to the woman's issues and no genetic or reproductive tract disease.

Genomic DNA extraction and genotyping

Genomic DNA was extracted from heparinized venous blood with the E.Z.N.A. Blood DNA Kit (Omega, Bio-Tek, Norcross, GA, USA) according to the manufacturer protocol. Each 50-µL polymerase chain reaction (PCR) contained 100 ng genomic DNA, 0.3 M forward and reverse primer, 0.2 mM dNTPs, 2.5 U Taq DNA polymerase, and 2 mM $MgSO_4$. To genotype codon 680, we used forward primer: 5' - TTT GTG GTC ATC TGT GGC TGC - 3' and reverse primer: 5' - CAA AGG CAA GGA CTG AAT TAT CAT T - 3', whereas for codon 307, we used forward primer: 5' - CCT GCA CAA AGA CAG TGA TG - 3' and reverse primer: 5' - TGG CAA AGA CAG TGA AAA G - 3'. The PCR amplification was performed by an initial step at 94°C for 5 min; followed by 30 cycles consisting of denaturation at 94°C for 30 s, annealing at 55°C (for Ala307Thr) or 60°C (for Ser680Asn) for 30 s, and elongation at 72°C for 1 min; with a final extension at 72°C for 10 min. All PCR products were subjected to direct DNA sequencing (Figure 1).

Meta-analysis

We searched the potential eligible articles published in English and Chinese using PubMed, Google Scholar literature databases, the Chinese VIP database, the Chinese National Knowledge Infrastructure (CNKI) database, and the Chinese Wanfang database. The literature search was updated on February 20, 2014, using the key words "follicle stimulating hormone receptor or FSHR" and "Thr307Ala or rs6165" and "Asn680Ser or rs6168" and "variant or genotype or polymorphism or single nucleotide polymorphism or SNP" and "male infertility or idiopathic infertility". A total of nine articles involving an association study with the *FSHR* gene Thr307Ala polymorphism were identified, and a total of 12 publications with Asn680Ser; four of these involved the combined genotypes of *FSHR* polymorphisms and the associated risk of male infertility.

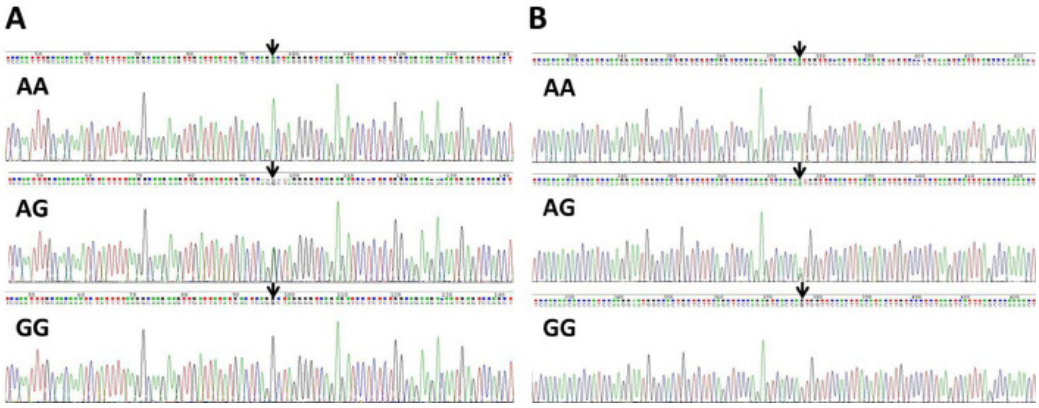

Figure 1. DNA sequencing results for the *FSHR* gene Thr307Ala and Asn680Ser polymorphisms. **A.** DNA sequencing of the Thr307Ala polymorphism (AA, AG, GG) is indicated by the arrow. **B.** DNA sequencing of the Asn680Ser polymorphism (AA, AG, GG) is indicated by the arrow. FSHR: follicle stimulating hormone receptor.

Statistical analysis

Case-control study

Genotype and allele frequencies were compared between patients and controls using a χ^2 test. The odds ratio (OR) and their respective 95% confidence intervals (95%CIs) were calculated. Hardy-Weinberg equilibrium (HWE) of each SNP in the patient and control groups was examined to check the genotypic distribution using a χ^2 test. Statistical analyses were performed using the SPSS 16.0 statistical package (SPSS, Chicago, IL, USA). All reported P values are two-tailed and were considered to be statistically significant if P was <0.05.

Meta-analysis

For each case-control study, we also first tested whether the genotype frequencies were in HWE using a χ^2 test. ORs and 95%CIs were calculated as the strength of association between Thr307Ala and Asn680Ser polymorphisms and male infertility. The pooled ORs and their corresponding 95%CIs were computed for the allele (G *vs* A), homozygous (GG *vs* AA), heterozygous (AG *vs* AA), and dominant (AG/GG *vs* AA) and recessive (GG *vs* AA/AG) models. The significances of the pooled ORs were determined by the Z test; $P < 0.05$ was considered to be statistically significant. The statistical heterogeneity among studies was assessed by Q-test and I^2 statistics (Higgins and Thompson, 2002). When $P > 0.1$ or $I^2 < 50\%$, no heterogeneity among studies was indicated, and the fixed-effects model was used; otherwise, the random-effects model was used. Subgroup analysis was performed by ethnicity. Publication bias was explored using Begg's funnel plots and Egger's regression test ($P < 0.05$ indicated statistical significance) (Egger et al., 1997; Munafo et al., 2004). Sensitivity analysis was performed after excluding each study in turn to assess the stability of the results. All statistical tests were two-sided, and $P < 0.05$ was considered to be statistically significant. All data analyses were performed using STATA version 12.0 (STATA Corporation LP, College Station, TX, USA).

RESULTS

Case-control study of *FSHR* gene polymorphisms in infertile men

In this study, patients (N = 212) and control individuals (N = 164) were recruited from the Shanxi Province of North China. The results of statistical analysis of the distribution of *FSHR* polymorphism genotype and allele frequencies between infertile men and controls are shown in Table 1. The genotypes of *FSHR* codons 680 and 307 in patients and controls were in HWE, and showed a demographic representation. However, there were no significant separate associations between the Thr307 and Asn680Ser polymorphisms and male infertility risk (all P values > 0.05). We further checked whether the haplotypes of the two SNPs were associated with male infertility (Table 2). The results showed that the combined genotypes of Thr/Ala + Asn/Asn had a higher frequency in infertile patients than in controls (6.6% *vs* 1.8%; OR = 3.795; 95%CI: 1.072-13.434, P = 0.027).

Table 1. Genotype and allele frequencies of the *FSHR* polymorphisms between infertile men and controls.

	Allele [N (%)]		P value	OR (95%CI)	Genotype [N (%)]			P value	HW test
Thr307Ala	Thr (A)	Ala (G)			Thr/Thr (AA)	Thr/Ala (AG)	Ala/Ala (GG)		
Patients	285 (67.2%)	139 (32.8%)	0.192	1.232 (0.900-1.687)	95 (44.8%)	95 (44.8%)	22 (10.4%)	0.222	0.807
Controls	235 (71.6%)	93 (28.4%)			80 (48.8%)	75 (45.7%)	9 (5.5%)		0.108
Asn680Ser	Asn (A)	Ser (G)			Asn/Asn (AA)	Asn/Ser (AG)	Ser/Ser (GG)		
Patients	292 (68.9%)	132 (31.1%)	0.359	1.160 (0.845-1.592)	100 (47.2%)	92 (43.4%)	20 (9.4%)	0.485	0.861
Controls	236 (72.0%)	92 (28.0%)			82 (50.0%)	72 (43.9%)	10 (6.1%)		0.261

FSHR = follicle stimulating hormone receptor; OR = odds ratio; CI = confidence interval; HW test = Hardy-Weinberg equilibrium test; P value from chi-squared test.

Table 2. Combined genotype frequencies of the *FSHR* polymorphisms among the patients and controls.

Variants	Patients (N = 212)	Controls (N = 164)	OR (95%CI)	P value
Thr/Thr + Ser/Ser	3 (1.4%)	1 (0.6%)	2.340 (0.241-22.702)	0.635[a]
Thr/Thr + Asn/Asn	84 (39.6%)	78 (47.6%)	0.724 (0.479-1.092)	0.123[b]
Thr/Thr + Asn/Ser	8 (3.8%)	1 (0.6%)	6.392 (0.791-51.630)	0.084[a]
Ala/Ala + Ser/Ser	16 (7.5%)	6 (3.7%)	2.150 (0.822-5.622)	0.111[b]
Ala/Ala + Asn/Asn	2 (0.9%)	1 (0.6%)	1.552 (0.140-17.270)	1.000[a]
Ala/Ala + Asn/Ser	4 (1.9%)	2 (1.2%)	1.558 (0.282-8.610)	0.700[a]
Thr/Ala + Ser/Ser	1 (0.5%)	3 (1.8%)	0.254 (0.026-2.468)	0.322[a]
Thr/Ala + Asn/Asn	14 (6.6%)	3 (1.8%)	3.795 (1.072-13.434)	**0.027**[b]
Thr/Ala + Asn/Ser	80 (37.7%)	69 (42.1%)	0.834 (0.550-1.265)	0.394[b]

FSHR = follicle stimulating hormone receptor; OR = odds ratio; CI = confidence interval; [a]Fisher's Exact Test; [b]Pearson Chi-Square test; P value and OR (95%CI) from the chi-squared test.

Meta-analysis of *FSHR* gene polymorphisms in infertile men

These studies represented in the meta-analysis had conducted single-site analyses FSHR polymorphism genotypes including 1897 patients and 2113 controls (for codon 307),

and 3021 patients and 3553 controls (for codon 680). The allele and genotype distributions of infertile men and controls are presented in Table 3. Overall, there was no significant association between Thr307Ala and Asn680Ser polymorphisms and male infertility risk (for G *vs* A, GG *vs* AA, AG *vs* AA, AG/GG *vs* AA, or GG *vs* AA/AG) (Table 4). In subgroup analysis by ethnicity (Non-Asian and Asian), we also found no positive evidence for the association between Thr307Ala and Asn680Ser polymorphisms individually and male infertility for all genetic models analyzed. In sensitivity analyses, statistically similar data were obtained after sequentially excluding each study, which indicated that our results were statistically reliable. The Begg's funnel plots were shown to be symmetrical (for AG/GG *vs* AA) (Figure 2) and the Egger's regression test did not show any evidence of publication bias (for codon 307: P = 0.402; for codon 680: P = 0.465). These data indicated that there was no significant publication bias in this meta-analysis.

Table 3. Main characteristics of all studies in the meta-analysis.

	Year	Country	Ethnicity	Patients (N)	Controls (N)	Patients (N)					Controls (N)					HW test
Thr307Ala						AA	AG	GG	A	G	AA	AG	GG	A	G	
Ahda Y	2005	Germany	Non-Asian	341	186	101	166	74	368	314	74	77	35	225	147	0.068
Pengo M	2006	Italy	Non-Asian	215	351	75	96	44	246	184	114	153	84	381	321	0.023
Shimoda	2009	Japan	Asian	343	146	118	179	46	415	271	68	61	17	197	95	0.560
Lend Ak	2010	Estonia	Non-Asian	150	208	50	72	28	172	128	67	106	35	240	176	0.526
Safarinejad MR	2011	Iran	Non-Asian	172	172	62	90	20	214	130	78	74	20	230	114	0.702
Li Y	2011	China	Asian	176	469	75	88	13	238	114	189	230	50	608	330	0.103
Ghirelli-Filho M	2012	Brazil	Non-Asian	138	217	33	72	33	138	138	74	89	54	237	197	0.011
Song D	2013	China	Asian	150	200	65	63	22	193	107	81	88	31	250	150	0.386
This study			Asian	212	164	95	95	22	285	139	80	75	9	235	93	0.108
Asn680Ser						AA	AG	GG	A	G	AA	AG	GG	A	G	
Ahda Y	2005	Germany	Non-Asian	438	304	126	216	96	468	408	101	143	60	345	263	0.466
Pengo M	2006	Italy	Non-Asian	215	351	75	96	44	246	184	114	153	84	381	321	0.023
Zalata AA	2008	Egypt	Non-Asian	52	30	18	20	14	56	48	14	10	6	38	22	0.122
Shimoda C	2009	Japan	Asian	340	146	131	164	45	426	254	72	62	12	206	86	0.791
Lend Ak	2010	Estonia	Non-Asian	150	208	50	73	27	173	127	66	107	35	239	177	0.451
Balkan M	2010	Turkey	Non-Asian	270	240	176	59	35	411	129	154	49	37	357	123	0.000
Li Y	2011	China	Asian	176	469	80	82	14	242	110	203	220	46	626	312	0.221
Safarinejad MR	2011	Iran	Non-Asian	172	172	69	80	23	218	126	85	72	15	242	102	0.964
Ghirelli-Filho M	2012	Brazil	Non-Asian	138	217	32	66	40	130	146	49	88	80	186	248	0.011
Song D	2013	China	Asian	150	200	69	58	23	196	104	86	87	27	259	141	0.506
Grigorova M	2013	Baltic	Non-Asian	708	1052	264	356	125	884	606	379	507	168	1265	843	0.943
This study			Asian	212	164	100	92	20	292	132	82	72	10	236	92	0.261

HW test = Hardy-Weinberg equilibrium test.

Among the studies included in the meta-analysis, four had also performed analysis of combined genotype frequencies of the *FSHR* polymorphisms among cases and controls (Table 5). Meta-analysis results of these studies suggested that the combined genotypes of Thr/Thr + Asn/Asn might increase the risk of male infertility (OR = 1.238, 95%CI: 1.001-1.537, P = 0.049).

Table 4. Results of meta-analysis for the association between FSHR gene Thr307Ala and Asn680Ser polymorphisms and risk of male infertility.

Variable	G *vs* A				GG *vs* AA				AG *vs* AA				AG/GG *vs* AA				GG *vs* AA/AG			
	OR (95%CI)	P_H	I^2%	P value	OR (95%CI)	P_H	I^2%	P value	OR (95%CI)	P_H	I^2%	P value	OR (95%CI)	P_H	I^2%	P value	OR (95%CI)	P_H	I^2%	P value
Thr307Ala (N = 9)																				
Non-Asian	0.903 (0.777-1.050)	0.214	31.1	0.186[R]	0.869 (0.673-1.123)	0.382	4.3	0.283[R]	0.774 (0.589-1.017)	0.107	47.5	0.066[R]	0.798 (0.615-1.037)	0.094	49.6	0.091[R]	1.005 (0.807-1.251)	0.778	0.0	0.967
Asian	0.930 (0.753-1.150)	0.098	52.3	0.504[R]	0.882 (0.541-1.439)	0.105	51.1	0.616[R]	0.895 (0.678-1.182)	0.145	44.5	0.436[R]	0.894 (0.671-1.191)	0.095	52.8	0.442[R]	0.965 (0.706-1.317)	0.199	35.5	0.821
Overall	0.915 (0.814-1.029)	0.143	34.4	0.140[R]	0.875 (0.694-1.103)	0.242	22.6	0.258[R]	0.829 (0.686-1.001)	0.084	42.5	0.051[R]	0.841 (0.700-1.011)	0.061	46.3	0.066[R]	0.991 (0.828-1.186)	0.596	0.0	0.923
Asn680Ser (N = 12)																				
Non-Asian	0.975 (0.897-1.061)	0.241	23.6	0.557	0.959 (0.811-1.135)	0.373	7.4	0.628	0.936 (0.821-1.068)	0.845	0.0	0.327	0.947 (0.838-1.070)	0.584	0.0	0.378	1.003 (0.863-1.165)	0.423	0.8	0.971
Asian	0.916 (0.791-1.061)	0.132	46.5	0.241	0.802 (0.573-1.121)	0.192	36.7	0.197	0.952 (0.776-1.167)	0.291	19.8	0.634	0.921 (0.758-1.120)	0.17	40.3	0.411	0.820 (0.595-1.130)	0.354	7.8	0.226
Overall	0.960 (0.893-1.033)	0.171	27.9	0.275	0.925 (0.796-1.075)	0.29	15.8	0.312	0.941 (0.842-1.051)	0.785	0.0	0.279	0.939 (0.847-1.042)	0.468	0.0	0.236	0.967 (0.845-1.108)	0.408	3.8	0.631

FSHR = follicle stimulating hormone receptor; OR = odds ratio; CI = confidence interval; R random-effects model was used; otherwise, fixed-effects model was used ; P_H and I^2 test for heterogeneity; P value from Z test.

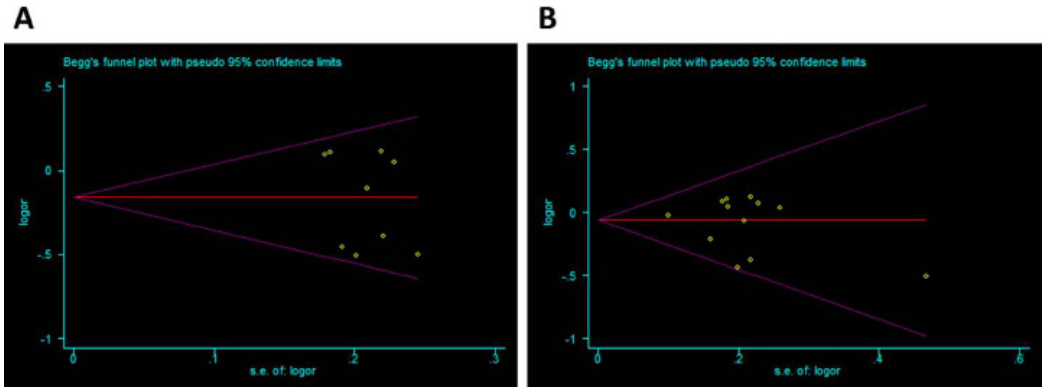

Figure 2. Begg's funnel plots for publication bias (AG/GG *vs* AA). Funnel plot for codon 307 (**A**) and for codon 680 (**B**).

Table 5. Results of meta-analysis for the combined genotypes of the *FSHR* polymorphisms among patients and controls.

Variants	OR (95%CI)	P_H	I^2	P value
Thr/Thr + Ser/Ser	0.386 (0.118-1.259)	0.442	0.0%	0.115
Thr/Thr + Asn/Asn	1.238 (1.001-1.537)	0.943	0.0%	**0.049**
Thr/Thr + Asn/Ser	0.999 (0.198-5.035)	0.001	82.3%	0.999[R]
Ala/Ala + Ser/Ser	0.583 (0.316-1.074)	0.076	56.4%	0.083[R]
Ala/Ala + Asn/Asn	0.784 (0.262-2.352)	0.827	0.0%	0.665
Ala/Ala + Asn/Ser	2.521 (0.444-14.320)	0.018	70.2%	0.297[R]
Thr/Ala + Ser/Ser	2.390 (0.957-5.969)	0.395	0.0%	0.062
Thr/Ala + Asn/Asn	0.737 (0.245-2.211)	0.001	81.8%	0.586[R]
Thr/Ala + Asn/Ser	0.789 (0.422-1.475)	0.000	88.0%	0.458[R]

FSHR = follicle stimulating hormone receptor; OR = odds ratio; CI = confidence interval; [R] random-effects model was used; otherwise, fixed-effects model was used; P_H and I^2 test for heterogeneity; P value from Z test.

DISCUSSION

Male infertility has become a major social problem that affects men's health and family happiness. In recent years, with the development of assisted reproductive technology (ART), the technologies of *in vitro* fertilization and intracytoplasmic sperm injection have been applied to help infertile couples to have children of their own, but these may also have negative effects. Although in recent years studies have found that, compared with natural pregnancy, ART does not carry increased risks of adverse health in the offspring, the finding that ART offspring have higher risks of birth defects, low birth weight, chromosomal abnormalities, and increased incidence of rare genetic disorders has motivated investigations of its safety issues in further depth (Hansen et al., 2005; Schieve et al., 2007; Davies et al., 2012). It has therefore become an important goal to illuminate the pathogenesis of infertility and explore the newly identified genes related to male infertility.

It is well known that the interaction between FSH and FSHR plays an indispensable role in normal gametes. In males, FSH regulates the function of Sertoli cells by its surface receptor (FSHR) (Laan et al., 2012). However, the influence and importance of FSHR variants on infertility risk is not completely understood. At present, the association between *FSHR* gene polymorphisms and the risk of male infertility has been reported both in China and

abroad, the conclusions from these studies have been inconsistent. Some studies have reported no significant association between the *FSHR* gene Thr307Ala and Asn680Ser polymorphisms and male infertility, and found that these polymorphisms also had no effect on serum FSH level or semen quality (Ghirelli-Filho et al., 2012). However, Shimoda et al. (2009) and Safarinejad et al. (2011) reported that the combination genotypes Thr/Ala-Ser/Asn increased the risk of male infertility. Since then, another study in the Yangtze River delta region of China also reported a similar result (Song et al. 2013). Based on the above research, it was assumed that *FSHR* polymorphisms might indeed play a certain role in male infertility.

In this study, we explored the association between the *FSHR* Thr307Ala and Asn680Ser polymorphisms and male infertility risk in Shanxi Province of North China. Results from this study failed to demonstrate significant individual associations between the *FSHR* gene Thr307Ala and Asn680Ser polymorphisms and male infertility. When the combined genotypes of both Thr307Ala and Asn680Ser polymorphisms were analyzed, we found an association between the Thr/Ala + Asn/Asn combined genotypes and male infertility. Considering the relatively smaller sample size in this analysis, we combined all available studies in a meta-analysis. We also found no association between the individual *FSHR* Thr307Ala and Asn680Ser polymorphisms and the risk of male infertility. This was consistent with a previous meta-analysis (Wu et al., 2012). The association between the combined genotypes of *FSHR* polymorphisms and the risk of male infertility were also assessed by our meta-analysis, which found that the combined genotypes of Thr/Thr + Asn/Asn increased the risk of male infertility.

It should be pointed out that there are also some limitations and insufficiencies from the meta-analysis in this study, such as inadequate sample size, inappropriate control subjects, positive publication bias, and ethnic and geographic differences. At the same time, the meta-analysis of the association between the combined genotypes of *FSHR* polymorphisms and the risk of male infertility included only four studies, which may have reduced the statistical power. Therefore, future research should focus on expanding the sample size and sample types, and access to a large sample base from different countries, races, regions, and medical centers.

In conclusion, our study and previously published related analyses indicates that there is no significant association between the *FSHR* gene Thr307Ala and Asn680Ser polymorphisms and the risk of male infertility. However, the combined genotypes of both Thr307Ala and Asn680Ser polymorphisms might have some effect on male infertility.

ACKNOWLEDGMENTS

Research supported by the International Science and Technology Cooperation Project in Shanxi Province (#2011081070) and the Overseas Returnee Research Fund in Shanxi Province (2010). Furthermore, we are very grateful to Dr. Yi Luo (University of Iowa) for editing the manuscript.

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