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Short Communication

Follicle stimulating hormone receptor G-29A, 919A>G, 2039A>G polymorphism and the risk of male infertility: A meta-analysis

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ABSTRACT

Studies of the relationship between male infertility and polymorphisms in the regions of *FSHR* G-29A (rs1394205), 919A>G (Thr^{307}Ala, rs6165) and 2039A>G (Asn^{680}Ser, rs6166) have reported inconsistent results. To assess the association between them, a meta-analysis was conducted. PubMed and CBMdisc literature search were conducted to identify all eligible studies investigating such a relationship. The pooled ORs were performed for co-dominant model, dominant model and recessive model in *FSHR* G-29A, Thr^{307}Ala and Asn^{680}Ser respectively to assess the strength of association.

A total of 1644 male infertility cases and 1748 controls were collected from seven case–control studies. In the overall analysis, no significant association between the three polymorphisms and risk of male infertility was observed. Stratified analysis showed that there were no significantly increased risks of azoospermia and oligoasthenoteratozoospermia (OAT) in any of the genetic models. This meta-analysis supports that *FSHR* G-29A, Thr^{307}Ala and Asn^{680}Ser polymorphisms may not be capable of causing male infertility susceptibility.

1. Introduction

Male infertility in humans is important cause of couple's inability to bear children in 20–25% of total cases. The etiology of nearly half of the cases remains idiopathic (De Kretser and Baker, 1999). In approximately 15% of male infertile cases, genetic factors, including chromosomal aberrations and single gene mutations, could be present, which may result in spermatogenic failure and sperm dysfunction (Pieri Pde et al., 2002; Ferlin et al., 2006).

Follicle-stimulating hormone (FSH) is fundamental for normal reproductive functions (Chappel and Howles, 1991). In the testis, FSH has been generally considered essential for Sertoli cell (SC) proliferation in fetal life and for the initiation of spermatogenesis at puberty, and thereby determines the final testicular size. In the adult, FSH together with testosterone, secreted by Leydig cells in response to LH, has a synergistic effect in the induction and maintenance of normal spermatogenesis (Krishnamurthy et al., 2000). FSH action is mediated by a specific receptor (FSHR), which belongs to a subfamily of G protein-coupled receptors and locates exclusively on the surface of SCs in the testis (Fan and Hendrickson, 2005). Given the significant role of FSH in fertility, *FSHR* polymorphism would be expected to affect normal spermatogenesis.

The human *FSHR* gene spans a region of 54 kb, consists of 10 exons and 9 introns, and is mapped to chromosome locus 2p21 (Minegishi et al., 1991). Mutation screening of the *FSHR* gene revealed various single nucleotide polymorphisms (SNPs) both in the core promoter and in the coding region (Gromoll and Simoni, 2005; Wunsch et al., 2005). Generally, a common SNP in the core promoter is at nucleotide position −29, resulting in a G/A exchange in a potential GGAAA binding domain for a c-E-twenty-six specific (c-ETS) transcription factor (Simoni et al., 2002). In the coding region, two common polymorphisms

Abbreviations: c-ETS, c-E-twenty-six specific; CI, confidence interval; FSH, follicle-stimulating hormone; OAT, oligoasthenoteratozoospermia; OR, odds ratio; SC, Sertoli cell; SNPs, single nucleotide polymorphisms.

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are found in exon 10 at nucleotide positions 919 (codon 307) and 2039 (codon 680). Both are tightly linked A to G non-synonymous substitutions leading to Thr to Ala and Asn to Ser amino acid changes, respectively. The polymorphisms in exon 10 contribute to two major, almost equally common allelic variants in the Caucasian population: Thr307–Asn680 and Ala307–Ser680 (Simoni et al., 1999). These SNPs influence the sensitivity of the FSHR to FSH in women, for the reason that it is associated with serum FSH levels, menstrual cycle lengths, follicular growth dynamics and response to ovarian stimulation (Gromoll and Simoni, 2005). However, in men, the impact of the polymorphisms of *FSHR* is unclear and spermatogenesis is only affected in men homozygous for inactivating *FSHR* mutations to some extent (Tapanainen et al., 1997). To date, several epidemiological studies have been done to evaluate the association between *FSHR* G-29A (rs1394205), 919A>G ($Thr^{307}Ala$, rs6165), 2039A>G ($Asn^{680}Ser$, rs6166) polymorphisms and male infertility. However, the results remain inconsistent (Table 1) (Ahda et al., 2005; Pengo et al., 2006; Zalata et al., 2008; Lend et al., 2010; Shimoda et al., 2009; Balkan et al., 2010; Li et al., 2010), partially due to the relative small sample size of individual studies. In order to overcome the limitation and to get a more precise estimation of the association, we performed a meta-analysis based on seven eligible studies including 1644 cases and 1748 controls and explored the between-study heterogeneity.

2. Materials and methods

2.1. Study selection

Eligible articles were identified by searching PubMed for relevant reports (last search update: July 2011), using the search terms '(Follicle Stimulating Hormone Receptor or *FSHR*) and (polymorphism or polymorphisms) and male infertility'. CBMdisc, the Chinese Biomedical Literature Database, which is the main Chinese medical literature retrieval system, was also used to search pertinent literature in the Chinese language. The retrieved literatures were then read in their entirety to assess their appropriateness for the inclusion in this meta-analysis by two authors independently. Review articles and bibliographies of other relevant studies identified were hand-searched to find additional eligible studies. Included studies had to satisfy the following criteria: (i) evaluation of the G-29A, $Thr^{307}Ala$, $Asn^{680}Ser$ polymorphism and male infertility risk (ii) studied on human beings; (iii) in a case–control study design; (iv) had detailed genotype frequency of cases and controls or could be derived from the article text.

2.2. Data extraction

Two investigators (Wei Wu and Hongquan Cai) extracted the data independently. Discrepancies about inclusion of studies and interpretation of data were resolved by discussion, consensus and arbitration by an expert. For each study, the following data were extracted from each study if available: the first author's name, year of publication, country of origin, ethnicity, number of cases and controls, genotype frequency for cases and controls, minor allele frequency in the controls and Hardy–Weinberg proportion. Different ethnicity was categorized as Asian and Caucasian.

2.3. Statistical analysis

The risk of male infertility associated with the three polymorphisms of the *FSHR* gene was estimated for each study by odds ratio (OR), together with its 95% confidence interval (CI), respectively. Heterogeneity assumption was checked by the χ^2-based Q-test and was regarded to indicate significance for $P<0.05$ (Lau et al., 1997). A fixed-effect model using the Mantel–Haenszel method and a random-effects model using the DerSimonian and Laird method were used to combine values from studies. These two models provide similar results when heterogeneity between studies is absent; otherwise, the random-effects model is more appropriate (Mantel and Haenszel, 1959; DerSimonian and Laird, 1986). For the G-29A polymorphism, we first estimated the risks of the heterozygote and variant homozygote compared with the wild-type homozygote and then evaluated the risks of the combined variant homozygote and heterozygote vs. the wild-type

Table 1
Main characteristics of all studies included in the meta-analysis.

First author	Year	Country	Ethnicity	Case	Control[a]	Case									Control				HWE[c]
						Azoospermia			OAT[b]			Total							
−29(G>A)						GG	GA	AA	GG	GA	AA	GG	GA	AA	GG	GA	AA	A allele (%)	
Ahda Y	2005	Germany	Caucasian	438	304	165	153	27	0	0	0	165	153	27	102	74	10	94 (25.3)	Yes
Pengo M	2006	Italy	Caucasian	215	351	27	11	0	99	62	16	126	73	16	203	121	27	175 (24.9)	Yes
Lend AK	2010	Estonia	Caucasian	150	208	14	20	2	64	41	9	78	61	11	110	85	13	111 (26.7)	Yes
Balkan M	2010	Turkey	Caucasian	270	240	116	26	8	87	27	6	203	53	14	178	49	13	75 (15.6)	No
Li Y	2010	China	Asian	176	469	24	51	22	18	45	16	42	96	38	118	250	101	452 (48.2)	Yes
$Thr^{307}Ala$ (A>G)						AA	AG	GG	AA	AG	GG	AA	AG	GG	AA	AG	GG	G allele (%)	
Ahda Y	2005	Germany	Caucasian	438	304	101	166	74	0	0	0	101	166	74	74	77	35	147 (39.5)	Yes
Pengo M	2006	Italy	Caucasian	215	351	14	16	8	61	80	36	75	96	44	114	153	84	321 (45.7)	No
Shimoda C	2009	Japan	Asian	343	146	…[d]	…[d]	…[d]	…[d]	…[d]	…[d]	118	179	46	68	61	17	95 (32.5)	Yes
Lend AK	2010	Estonia	Caucasian	150	208	10	22	4	40	50	24	50	72	28	67	106	35	176 (42.3)	Yes
Li Y	2010	China	Asian	176	469	44	46	7	31	42	6	75	88	13	189	230	50	330 (35.2)	Yes
$Asn^{680}Ser$ (A>G)						AA	AG	GG	AA	AG	GG	AA	AG	GG	AA	AG	GG	G allele (%)	
Ahda Y	2005	Germany	Caucasian	438	304	126	216	96	0	0	0	126	216	96	101	143	60	263 (43.2)	Yes
Pengo M	2006	Italy	Caucasian	215	351	14	16	8	61	80	36	75	96	44	114	153	84	321 (45.7)	No
Zalata AA	2008	Egypt	Caucasian	52	30	0	0	0	18	20	14	18	20	14	14	10	6	22 (36.7)	Yes
Shimoda C	2009	Japan	Asian	343	146	…[d]	…[d]	…[d]	…[d]	…[d]	…[d]	131	164	45	72	62	12	86 (29.5)	Yes
Lend AK	2010	Estonian	Caucasian	150	208	10	22	4	40	51	23	50	73	27	66	107	35	177 (42.5)	Yes
Balkan M	2010	Turkey	Caucasian	270	240	94	46	10	82	13	25	176	59	35	154	49	37	123 (25.6)	No
Li Y	2010	China	Asian	176	469	48	42	7	32	40	7	80	82	14	203	220	46	312 (33.3)	Yes

[a] Normozoospermia or fertile controls.
[b] Oligoasthenoteratozoospermia; Including OAT, severe OAT, oligozoospermia and teratozoospermia.
[c] Hardy–Weinberg equilibrium; *Yes* the genotype distribution is in the HWE in control group; *No* the genotype distribution is not in the HWE in control group.
[d] …: An absence of data for that study.

homozygote, and the variant homozygote vs. the combined heterozygote and wild-type homozygote, assuming dominant and recessive effects of the variant allele respectively. For the Thr^{307}Ala and Asn^{680}Ser polymorphisms, we evaluated the same effects.

Meta regression was used to illustrate potential reasons of between-study heterogeneity. An estimate of potential publication bias was evaluated by the funnel plot in which the standard error of log (OR) of each study was plotted against its log (OR). An asymmetric plot suggested a possible publication bias. The funnel plot asymmetry was assessed with Egger's test (Egger et al., 1997). Publication bias was assessed with Egger's test; $P<0.05$ was considered statistically significant. HWE in the control group was tested using the Pearson chi-square test for goodness of fit; $P<0.05$ was considered significant.

All statistical tests for this meta-analysis were performed with Stata version 9.2 software (Stata, College Station, TX, USA). All statistical evaluations were made assuming a two-sided test with a significance level of 0.05, unless stated otherwise.

3. Results

3.1. Study characteristics

The characteristics of the selected studies are summarized in Table 1. Publication dates ranged from 2005 to 2011. There were two studies of Asian population and five studies of Caucasian population in total. The genotype distributions among the controls of all studies followed HWE except for one study performed by Pengo et al. (2006) and one study performed by Balkan et al. (2010).

3.2. Meta-analysis results

The results of the association between the G-29A, Thr^{307}Ala, Asn^{680}Ser polymorphisms and male infertility risk, along with the heterogeneity test are shown in Table 2, Table 3 and Table 4. Overall, there was significant between study heterogeneity in the magnitude of the observed association between the presence of the Thr^{307}Ala polymorphism and male infertility in the AG/GG vs. AA ($P=0.036$) comparison. Thus, random-effects estimates would be more appropriate for data synthesis, and fixed-effects estimates are not shown.

In the overall analysis, no significant association between *FSHR* G-29A, Thr^{307}Ala, Asn^{680}Ser polymorphisms and the risk of male infertility was found (for G-29A polymorphism, GA vs. GG: OR, 1.06; 95% CI, 0.88–1.27; $P=0.829$ for the heterogeneity test; AA vs. GG: OR, 1.11; 95% CI, 0.82–1.51; $P=0.823$ for the heterogeneity test; dominant model, GA/AA vs. GG: OR, 1.07; 95% CI, 0.90–1.27; $P=0.724$ for the heterogeneity test; recessive model, AA vs. GG/GA: OR, 1.07; 95% CI, 0.81–1.41; $P=0.895$ for the heterogeneity test; A vs. G: OR, 1.05; 95% CI, 0.93–1.20; $P=0.680$ for the heterogeneity test; for Thr^{307}Ala polymorphism, GA vs. AA: OR, 1.17; 95% CI, 0.98–1.40; $P=0.079$ for the heterogeneity test; GG vs. AA: OR, 1.07; 95% CI, 0.83–1.36; $P=0.132$ for the heterogeneity test; dominant model, AG/GG vs. AA: OR, 1.14; 95% CI, 0.96–1.35; $P=0.036$ for the heterogeneity test; recessive model, GG vs. AA/AG: OR, 0.98; 95% CI, 0.78–1.22; $P=0.475$ for the heterogeneity test; G vs. A: OR, 1.06; 95% CI, 0.94–1.19; $P=0.053$ for the heterogeneity test; for Asn^{680}Ser polymorphism, GA vs. AA: OR, 1.09; 95% CI, 0.93–1.28; $P=0.620$ for the heterogeneity test; GG vs. AA: OR, 1.05; 95% CI, 0.85–1.30; $P=0.214$ for the heterogeneity test; dominant model, AG/GG vs. AA: OR, 1.07; 95% CI, 0.93–1.24; $P=0.274$ for the heterogeneity test; recessive model, GG vs. AA/AG: OR, 1.01; 95% CI, 0.84–1.23; $P=0.471$ for the heterogeneity test; G vs. A: OR, 1.04; 95% CI, 0.94–1.15; $P=0.130$ for the heterogeneity test) (Table 2, Table 3 and Table 4). As shown in Figures S1–S5, we can also conclude that Asn^{680}Ser polymorphism may not be capable of causing male infertility susceptibility in all genetic models. Additionally, we stratified sperm concentration of the case group, and the stratified analysis showed that no significantly increased risk of azoospermia or oligoasthenoteratozoospermia (OAT) was found in any of the genetic models (Table 2, Table 3 and Table 4).

3.3. Publication bias

Begg's funnel plot and Egger's test were conducted to assess the publication bias of the literature. The shape of funnel plots did not reveal any evidence of funnel plot asymmetry. The statistical results still did not show publication bias (for G-29A polymorphism: $P=0.806$ for AG vs. GG and AA vs. GG , $P=0.221$ for dominant model and recessive model, and $P=1.000$ for G vs. A; for Thr^{307}Ala polymorphism: $P=0.806$ for GG vs. AA and recessive model, $P=0.221$ for GA vs. AA, $P=0.462$ for dominant model and G vs. A; for Asn^{680}Ser polymorphism: $P=1.000$ for GA vs. AA and dominant model, $P=0.368$ for GG vs. AA and recessive model, and $P=0.230$ for G vs. A) (Figure S6).

4. Discussion

The literature on the relationship between FSHR polymorphisms and male infertility risk is replete with small studies that report controversial findings. No clear consensus has been reached. There have been two meta-analyses (Lend et al., 2010; Tuttelmann et al., 2007) concerning *FSHR* polymorphisms and the risk of male infertility. However, both studies had relative small study population. One meta-analysis conducted by Tuttelmann et al. (2007) in 2007 of over 700 patients and 600 controls concludes that there is not any association between male infertility and *FSHR* Asn^{680}Ser polymorphism. The other meta-analysis conducted by Lend et al. (2010) in 2010 of only three studies indicates that the G-29-A919-A2039 haplotype may be a protective factor against male sterility. To resolve the conflicting results, we carried out a meta-analysis of seven studies involving 1644 cases and 1748 controls to derive a more precise estimation of the association. In the overall analysis, no significant association between the three polymorphisms and risk of male infertility was observed. Besides, stratified analysis showed that no significantly increased risks of azoospermia and OAT in any of the genetic models.

Table 2
Main results for the *FSHR* −29 (G>A) polymorphism in the meta-analysis.

	Studies	GA vs. GG		AA vs. GG		GA/AA vs. GG (Dominant model)		AA vs. GG/GA (Recessive model)		A vs. G	
		OR (95% CI)	P_h[a]	OR (95% CI)	P_h[a]	OR (95% CI)	P_h[a]	OR (95% CI)	P_h[a]	OR (95% CI)	P_h[a]
Total	5	1.06 (0.88–1.27)	0.829	1.11 (0.82–1.51)	0.823	1.07 (0.90–1.27)	0.724	1.07 (0.81–1.41)	0.895	1.05 (0.93–1.20)	0.680
Sperm concentration of case group											
Azoospermia	5	1.08 (0.86–1.37)	0.234	1.07 (0.72–1.60)	0.486	1.08 (0.86–1.34)	0.125	1.05 (0.73–1.50)	0.604	1.05 (0.89–1.24)	0.093
OAT[b]	4	1.03 (0.81–1.30)	0.973	1.11 (0.75–1.65)	0.973	1.04 (0.83–1.30)	0.872	1.01 (0.84–1.22)	0.952	1.04 (0.87–1.23)	0.962

[a] Test for heterogeneity in groups.
[b] Oligoasthenoteratozoospermia; including OAT, severe OAT, oligozoospermia and teratozoospermia. Only studies that provided specific data on subgroups of cases are included.
CI, confidence interval; OR, odds ratio.

Table 3
Main results for the *FSHR* Thr[307]Ala (A > G) polymorphism in the meta-analysis.

	Studies	GA vs. AA		GG vs. AA		AG/GG vs. AA (Dominant model)		GG vs. AA/AG (Recessive model)		G vs. A	
		OR (95% CI)	P_h[a]	OR (95% CI)	P_h[a]	OR (95% CI)	P_h[a]	OR (95% CI)	P_h[a]	OR (95% CI)	P_h[a]
Total	5	1.17 (0.98–1.40)	0.079	1.07 (0.83–1.36)	0.132	1.14 (0.96–1.35)[b]	0.036	0.98 (0.78–1.22)	0.475	1.06 (0.94–1.19)	0.053
Sperm concentration of case group											
Azoospermia	4	1.18 (0.90–1.53)	0.192	1.07 (0.74–1.53)	0.204	1.14 (0.89–1.46)	0.114	0.95 (0.68–1.31)	0.479	1.05 (0.88–1.25)	0.137
OAT[c]	3	0.96 (0.73–1.26)	0.642	0.88 (0.61–1.27)	0.627	0.94 (0.73–1.21)	0.872	0.92 (0.67v1.27)	0.331	0.95 (0.79–1.13)	0.801

[a] Test for heterogeneity in group.
[b] Random-effects model was used when the *P*-value for heterogeneity test was ≤ 0.05, otherwise the fixed-effect model was used.
[c] Oligoasthenoteratozoospermia; including OAT, severe OAT, oligozoospermia and teratozoospermia. Only studies that provided specific data on subgroups of cases are included.
CI, confidence interval; OR, odds ratio.

Theoretically, FSH is considered essential in humans for the initiation of spermatogenesis at puberty and the maintenance of quantitatively normal sperm production in adults. Therefore, genetic abnormalities of the *FSHR*, as well as *FSH*, would be expected to affect sperm production in males. However, in this meta-analysis, we did not find that the *FSHR* gene variant associates with spermatogenetic impairment, which might suggest that different important aspects should be considered when analyzing the association. First, the significance of this association needs to be verified by large sample size studies in other populations, possibly of different ethnic origin. Because several studies have suggested associations between gene polymorphisms and male infertility with possible ethnic differences, such as the *DAZL* gene (Teng et al., 2002; Becherini et al., 2004; Tschanter et al., 2004) and the *POLG* gene (Rovio et al., 2001; Jensen et al., 2004; Krausz et al., 2004). Besides, a possible role of ethnic differences in genetic backgrounds and the environment they live in may affect this result. Therefore, it is likely that polymorphisms only in association with a specific genetic background and/or with environmental factors can lead to spermatogenetic impairment or testicular dysfunction. *FSHR* gene polymorphisms seem not to have a direct influence on spermatogenesis, but a possible contribution to male infertility, alone or in combination with other genetic and environmental factors, cannot be excluded. Moreover, all studies excluded patients with genetic causes of infertility (karyotype mutations, Y-chromosome microdeletions and Klinefelter syndrome) from the analysis; however, not all known genetic causes of male infertility, for example, another kind of chromosomal aberrations, Robertsonian translocations, were reported to be excluded in all studies. It is possible that the distribution of this polymorphism among different male infertility subcategories is quite different, thus affecting the result.

Last but not the least, an individual with a clinical disorder is not the product of the single gene that is disrupted, but that the genetic disruption is embedded within the context of that individual's entire genome and environment exposure (Dipple et al., 2001). Hence, it is possible that we did not find a significant difference because we only examined three *FSHR* polymorphisms. In fact, some other genes related to follicular growth could also play an important role in spermatogenesis. Recently, a study (Safarinejad et al., 2010) revealed that significant differences in the frequency distribution of PvuII and XbaI in the *ER-α* gene and RsaI and AluI in the *ER-β* gene between infertile males and controls. The presence of the *ER-α* PvuII TC, *ER-α* XbaI AG, and *ER-β* AluI GG genotypes suggests a protective effect for infertility, while the *ER-β* RsaI AG and *ER-β* AluI AG genotypes are associated with increased infertility risk.

Some limitations of this meta-analysis should be addressed. First, some studies with small sample size may not have enough statistical power to explore the real association. Second, lack of the original data limited our further evaluation of potential interactions because the interactions among gene–gene, gene–environment, and even different polymorphic loci of the same gene might modulate male infertility risk. Third, the overall outcomes were based on unadjusted estimates, whereas a more precise evaluation should be adjusted by other covariants such as age, body mass index, gender, ethnicity, and alcohol habit. Forth, the numbers of published studies were not sufficiently large for a comprehensive analysis.

In conclusion, our meta-analysis suggests that *FSHR* G-29A, Thr[307]Ala and Asn[680]Ser polymorphisms were not associated with spermatogenetic impairment. Susceptibility to male infertility may be confined to a certain population. It would be more productive to look for other interesting genetic factors or discuss the interaction of the *FSHR* gene variant with other polymorphisms or the environment. Large, well-designed studies are warranted to validate the association in specific ethnic populations.

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Table 4
Main results for the *FSHR* Asn[680]Ser (A > G) polymorphism in the meta-analysis.

	Studies	GA vs. AA		GG vs. AA		AG/GG vs. AA (Dominant model)		GG vs. AA/AG (Recessive model)		G vs. A	
		OR (95% CI)	P_h[a]	OR (95% CI)	P_h[a]	OR (95% CI)	P_h[a]	OR (95% CI)	P_h[a]	OR (95% CI)	P_h[a]
Total	7	1.09 (0.93–1.28)	0.620	1.05 (0.85–1.30)	0.214	1.07 (0.93–1.24)	0.274	1.01 (0.84–1.23)	0.471	1.04 (0.94–1.15)	0.130
Sperm concentration of case group											
Azoospermia	5	1.14 (0.92–1.41)	0.333	0.88 (0.66–1.19)	0.132	1.04 (0.85–1.28)	0.500	0.85 (0.65–1.11)	0.118	0.97 (0.84–1.12)	0.331
OAT[b]	5	0.90 (0.71–1.15)	0.244	1.04 (0.77–1.39)	0.662	0.95 (0.77–1.18)	0.668	1.06 (0.81–1.39)	0.495	1.00 (0.85–1.16)	0.697

[a] Test for heterogeneity in groups.
[b] Oligoasthenoteratozoospermia; including OAT, severe OAT, oligozoospermia and teratozoospermia. Only studies that provided specific data on subgroups of cases are included.
CI, confidence interval; OR, odds ratio.

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References

Ahda, Y., et al., 2005. Follicle-stimulating hormone receptor gene haplotype distribution in normozoospermic and azoospermic men. J. Androl. 26, 494–499.

Balkan, M., et al., 2010. FSHR single nucleotide polymorphism frequencies in proven fathers and infertile men in Southeast Turkey. J. Biomed. Biotechnol. 201, 640318.

Becherini, L., Guarducci, E., Degl'Innocenti, S., Rotondi, M., Forti, G., Krausz, C., 2004. DAZL polymorphisms and susceptibility to spermatogenic failure: an example of remarkable ethnic differences. Int. J. Androl. 27, 375–381.

Chappel, S.C., Howles, C., 1991. Reevaluation of the roles of luteinizing hormone and follicle-stimulating hormone in the ovulatory process. Hum. Reprod. 6, 1206–1212.

De Kretser, D.M., Baker, H.W., 1999. Infertility in men: recent advances and continuing controversies. J. Clin. Endocrinol. Metab. 84, 3443–3450.

DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Control. Clin. Trials 7, 177–188.

Dipple, K.M., Phelan, J.K., McCabe, E.R., 2001. Consequences of complexity within biological networks: robustness and health, or vulnerability and disease. Mol. Genet. Metab. 74, 45–50.

Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629–634.

Fan, Q.R., Hendrickson, W.A., 2005. Structure of human follicle-stimulating hormone in complex with its receptor. Nature 433, 269–277.

Ferlin, A., Arredi, B., Foresta, C., 2006. Genetic causes of male infertility. Reprod. Toxicol. 22, 133–141.

Gromoll, J., Simoni, M., 2005. Genetic complexity of FSH receptor function. Trends Endocrinol. Metab. 16, 368–373.

Jensen, M., et al., 2004. Frequent polymorphism of the mitochondrial DNA polymerase gamma gene (POLG) in patients with normal spermiograms and unexplained subfertility. Hum. Reprod. 19, 65–70.

Krausz, C., et al., 2004. The clinical significance of the POLG gene polymorphism in male infertility. J. Clin. Endocrinol. Metab. 89, 4292–4297.

Krishnamurthy, H., Danilovich, N., Morales, C.R., Sairam, M.R., 2000. Qualitative and quantitative decline in spermatogenesis of the follicle-stimulating hormone receptor knockout (FORKO) mouse. Biol. Reprod. 62, 1146–1159.

Lau, J., Ioannidis, J.P., Schmid, C.H., 1997. Quantitative synthesis in systematic reviews. Ann. Intern. Med. 127, 820–826.

Lend, A.K., et al., 2010. Follicle-stimulating hormone receptor gene haplotypes and male infertility in Estonian population and meta-analysis. Syst. Biol. Reprod. Med. 56, 84–90.

Li, Y., et al., 2010. FSH receptor gene polymorphisms in fertile and infertile Han-Chinese males. Clin. Chim. Acta 412, 1048–1052.

Mantel, N., Haenszel, W., 1959. Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. 22, 719–748.

Minegishi, T., Nakamura, K., Takakura, Y., Ibuki, Y., Igarashi, M., Minegish, T., 1991. Cloning and sequencing of human FSH receptor cDNA. Biochem. Biophys. Res. Commun. 175, 1125–1130.

Pengo, M., et al., 2006. FSH receptor gene polymorphisms in fertile and infertile Italian men. Reprod. Biomed. Online 13, 795–800.

Pieri Pde, C., Pereira, D.H., Glina, S., Hallak, J., McElreavey, K., Moreira-Filho, C.A., 2002. A cost-effective screening test for detecting AZF microdeletions on the human Y chromosome. Genet. Test. 6, 185–194.

Rovio, A.T., et al., 2001. Mutations at the mitochondrial DNA polymerase (POLG) locus associated with male infertility. Nat. Genet. 29, 261–262.

Safarinejad, M.R., Shafiei, N., Safarinejad, S., 2010. Association of polymorphisms in the estrogen receptors alpha, and beta (ESR1, ESR2) with the occurrence of male infertility and semen parameters. J. Steroid Biochem. Mol. Biol. 122, 193–203.

Shimoda, C., et al., 2009. Single nucleotide polymorphism analysis of the follicle-stimulating hormone (FSH) receptor in Japanese with male infertility: identification of codon combination with heterozygous variations of the two discrete FSH receptor gene. Endocr. J. 56, 859–865.

Simoni, M., et al., 1999. Mutational analysis of the follicle-stimulating hormone (FSH) receptor in normal and infertile men: identification and characterization of two discrete FSH receptor isoforms. J. Clin. Endocrinol. Metab. 84, 751–755.

Simoni, M., Nieschlag, E., Gromoll, J., 2002. Isoforms and single nucleotide polymorphisms of the FSH receptor gene: implications for human reproduction. Hum. Reprod. Update 8, 413–421.

Tapanainen, J.S., Aittomaki, K., Min, J., Vaskivuo, T., Huhtaniemi, I.T., 1997. Men homozygous for an inactivating mutation of the follicle-stimulating hormone (FSH) receptor gene present variable suppression of spermatogenesis and fertility. Nat. Genet. 15, 205–206.

Teng, Y.N., et al., 2002. Association of a single-nucleotide polymorphism of the deleted-in-azoospermia-like gene with susceptibility to spermatogenic failure. J. Clin. Endocrinol. Metab. 87, 5258–5264.

Tschanter, P., Kostova, E., Luetjens, C.M., Cooper, T.G., Nieschlag, E., Gromoll, J., 2004. No association of the A260G and A386G DAZL single nucleotide polymorphisms with male infertility in a Caucasian population. Hum. Reprod. 19, 2771–2776.

Tuttelmann, F., Rajpert-De Meyts, E., Nieschlag, E., Simoni, M., 2007. Gene polymorphisms and male infertility—a meta-analysis and literature review. Reprod. Biomed. Online 15, 643–658.

Wunsch, A., et al., 2005. Single-nucleotide polymorphisms in the promoter region influence the expression of the human follicle-stimulating hormone receptor. Fertil. Steril. 84, 446–453.

Zalata, A.A., Hassan, A.H., Nada, H.A., Bragais, F.M., Agarwal, A., Mostafa, T., 2008. Follicle-stimulating hormone receptor polymorphism and seminal anti-Mullerian hormone in fertile and infertile men. Andrologia 40, 392–397.