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Association between polymorphisms in the XRCC1 gene and male infertility risk

A meta-analysis

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Abstract

Background: X-ray repair cross-complementing group 1 (XRCC1) single nucleotide polymorphisms (SNPs) might correlate with male infertility susceptibility. This association has been described; however, the findings remain inconsistent. Consequently, this meta-analysis was conducted to characterize the relationship between XRCC1 SNPs and male infertility susceptibility.

Methods/main results: Studies were systematically searched in databases to evaluate the association between SNPs of XRCC1 and infertility in males. The effect measures chosen were the 95% confidence intervals (95% CIs) and odds ratios (ORs). A total of 7 studies, including 6 case-controlled studies on XRCC1 Arg399Gln and 3 case-controlled studies on XRCC1 Arg194Trp, were included. Ultimately, the results of this analysis revealed that XRCC1 Arg399Gln SNPs were significantly associated with infertility in males in homozygote comparisons (GG vs GA+AA: OR = 0.614, 95% CI: 0.40–0.937, $P = .024$). This meta-analysis did not demonstrate a relationship between XRCC1 Arg194Trp and male infertility risk.

Conclusions: Our study indicated that XRCC1 Arg399Gln polymorphism was associated with a significantly decreased male infertility risk, but not XRCC1 Arg194Trp.

Abbreviations: 95% CIs = 95% confidence intervals, APE1 = apyrimidinic endonuclease 1, BER = base excision repair, HWE = Hardy–Weinberg equilibrium, ORs = odds ratios, SNPs = single nucleotide polymorphisms, XRCC1 = X-ray repair cross-complementing group 1.

Keywords: male infertility, meta-analysis, polymorphism, XRCC1

1. Introduction

Infertility is a global health issue that affects ~15% to 20% of couples.[1,2] Male factors account for ~50% of infertile couples who are unable to conceive, due to marital and psychosocial stress.[3] Many factors have an adverse impact on male reproductive health, including lifestyle,[4,5] intratesticular varicocele,[6] varicocele,[7–9] ancestry,[10] SNPs,[11,12] etc. Unfortunately, the pathogenesis of this disease remains unknown. Gene–environment interactions may play a crucial role in male infertility.[13]

Many studies focusing on male infertility risk have been performed to date. The *XRCC1* gene, on chromosome 19q13.2–13.3,[14] encodes a protein that is implicated in the base excision repair (BER) pathway to repair single-strand breaks.[15] BER plays a crucial role in repairing spontaneous DNA damage[16] and maintaining mitochondrial DNA stability.[17] Another study showed that XRCC1 protein could repair base excision through protein–protein interactions[18] and repair DNA single strand breaks through coordinating with other genes.[19]

Multiple studies have demonstrated conflicting results between XRCC1 polymorphisms and male infertility.[13,20–22] The most extensively analyzed XRCC1 SNPs are Arg194Trp rs1799782 (NM_006297.2:c.580C>T, NP_006288.2:p.Arg194Trp) and Arg399Gln rs25487 (NM_006297.2:c.1196A>G, NP_006288.2:p.Gln399Arg).[21,23,24] This meta-analysis was conducted to screen all relevant literature to clarify the association between XRCC1 SNPs and male infertility risk.

2. Materials and methods

2.1. Search strategy

Published articles were identified in electronic databases, including PubMed, EMBASE, and Google Scholar, prior to May 16, 2018. The following search terms were used: "XRCC1 or X-ray cross-complementing gene" and "infertility or oligozoospermia or oligoasthenoteratozoospermia or azoospermia" and "polymorphism or polymorphisms or variants." Without any language restrictions, the electronic searches for literature and data were collected. Using hand searches, references of related studies were also examined for additional studies. All

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analyses were based on previous published studies, thus no ethical approval and patient consent are required.

2.2. Inclusion and exclusion criteria

Studies that met the following inclusion criteria were included in this meta-analysis:

1. studies using case-controlled analysis;
2. focusing on human beings;
3. assessment of the association between XRCC1 (Arg399Gln or Arg194Trp) SNPs and male infertility risk; and
4. containing available genotype frequency to account for the odds ratios (ORs) and 95% confidence intervals (95% CIs).

Exclusion criteria included the following:

1. duplication of previous studies;
2. reviews, meta-analyses, conference abstracts, letters and editorials; and
3. studies lacking detailed information about genotype.

2.3. Data extraction

We carefully screened and extracted the usable data that satisfied the inclusion criteria by two investigators independently. When confronted with controversy, disagreement was solved by discussion. The final data were checked by a third investigator to reach agreement.

Information in the studies was collected, including the first author name, the year of publication, country, ethnicity (Caucasian, Asian), the total numbers of cases and controls, the method of genotyping, each genotype number in cases and controls, and Hardy–Weinberg equilibrium (HWE). When HWE in the control genotype did not appear in the extracted studies, the online program (http://ihg.gsf.de/cgi-bin/hw/hwa1.p) was applied.

2.4. Methodological quality assessment

Using the Newcastle-Ottawa Scale, the quality of the included studies was evaluated, and the major factors were "gender and age." The final quality scores ranged from 0 to 9, with higher scores indicating better quality. Disagreements were settled through discussion.

2.5. Statistical analysis

This meta-analysis was performed based on the checklists and guidelines of PRISMA.[25] To obtain HWE, the Chi-square test was used in control groups of the included studies, and a P value $< .05$ was taken to indicate significant deviation from HWE. Similarly, the ORs and 95% CIs were acquired to evaluate the strength of the association between the two polymorphisms in XRCC1 (Arg399Gln, Arg194Trp) and the risk of male infertility. We calculated the pooled ORs for five genetic models: allelic comparisons model (Arg399Gln: G vs A; Arg194Trp: T vs C); homozygous comparisons (Arg399Gln: GG vs AA; Arg194Trp: TT vs CC); heterozygous comparisons (Arg399Gln: GA vs AA; Arg194Trp: CT vs CC); recessive comparisons (Arg399Gln: GG vs GA+AA; Arg194Trp: TT vs CT+CC); and dominant comparisons (Arg399Gln: GA+GG vs AA; Arg194Trp: CT +TT vs CC). According to the Z-test with $P < .05$, the statistical significance level is reported.

Using Cochran's Q statistic and the I^2 index,[26] the heterogeneity in each study was estimated. When the test value of heterogeneity $P < .10$ and/or I^2 index $> 50\%$, the random-effects model (DerSimonian and Laird method) was advocated. Otherwise, if the $P > .10$ and/or I^2 index $< 50\%$, the fixed-effects model was used (Mantel and Haenszel method).[27] Sensitivity analysis was performed to evaluate the stability of the results in total and subgroup studies. Subgroup analyses were performed by ethnicity, including Caucasian and Asian). Possible publication bias was assessed by means of Begg's[28] funnel plot and Egger's[29] tests. All of our statistical analyses were performed using Stata software 12.0 (StataCorp, College Station, TX). Differences were considered significant with a two-tailed $P < .05$, except for noted special conditions.

3. Results

3.1. Characteristics of the eligible case-controlled studies

By careful searching of the noted databases, we initially identified a total of 26 articles, from PubMed (6 articles), Embase (15 articles), and Google Scholar (5 articles). Upon scanning of the title and abstract, and based strictly on inclusion and exclusion strategy, 18 studies were excluded. Finally, with data extraction and high quality evaluation, eight case-controlled studies were included in our meta-analysis.[21–24,30–33] The detailed searching process is presented in Figure 1. The major characteristics and basic genotype frequency information are summarized and shown in Table 1. Due to the inclusion of two Gu et al studies[24,25] were obviously duplicated and one of them was removed, then two studies[22,24] presented separate genotype frequencies of Arg399Gln and Arg194Trp; therefore, each of those two studies was regarded as a separate study. Additionally, four studies for XRCC1 Arg399Gln[21,30,31,33] and one study for XRCC1 Arg194Trp[32] were included. Therefore, six included studies with 1317 cases and 1115 controls for XRCC1 Arg399Gln and three studies with 953 cases and 686 controls for XRCC1 Arg194Trp were finally included in our pooling meta-analysis. Four of the included studies of XRCC1 Arg399Gln were in Asian populations,[21–24,30] and the other two studies were in Caucasian populations.[31,33] Of the 3 studies examining XRCC1 Arg194Trp, 2 studies were conducted in Asian populations[22–24] and one study was conducted in a Caucasian population.[32] The studies utilized PCR–RFLP and PCR genotyping methods. The genotype distribution was in accord with HWE in all included studies except for one study of XRCC1 Arg399Gln.[31]

3.2. Main meta-analysis results

Summary results of the relationship between the XRCC1 Arg399Gln polymorphism and infertility in males are listed in Table 2. A significant association was observed in one recessive model (GG vs GA+AA: OR = 0.614, 95% CI: 0.40–0.937, $P = .024$ Fig. 2) (using the random-effects model) in the overall population. Therefore, the GG was confirmed to be associated with a decreased risk of male infertility. Nevertheless, the results of this meta-analysis failed to find any statistical association between XRCC1 Arg399Gln polymorphism and male infertility in four other models, including in a homozygote comparison model (GG vs AA: OR = 0.760, 95% CI: 0.415–1.392; $P = .375$), allele model (G vs A: OR = 0.803, 95% CI = 0.627, 1.027, $P = .081$), heterozygous genetic model (GA vs AA: OR = 1.276,

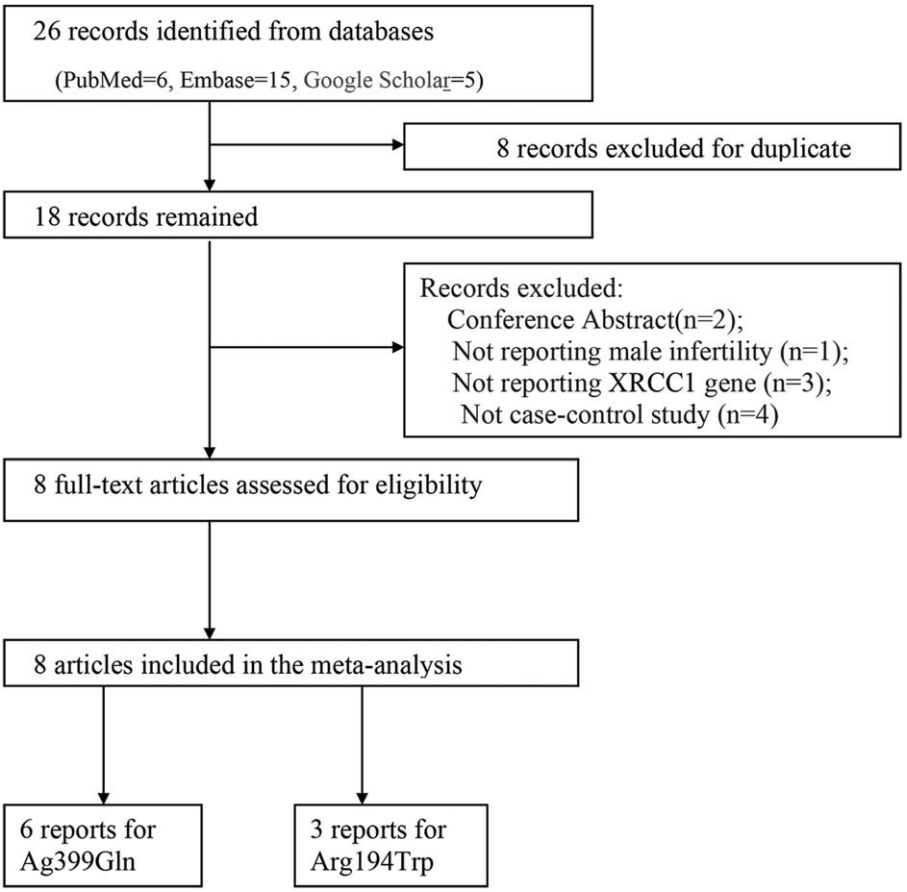

Figure 1. . Flow diagram of study selection.

95% CI: 0.929, 1.753, $P=.133$) and dominant model (GA+GG vs AA: OR=1.048, 95% CI:0.774, 1.420; $P=.760$). However, there was no significant association between XRCC1 Arg399Gln polymorphism and male infertility in all population.

For the XRCC1 Arg194Trp, however, no positive association was observed in any genetic model (T vs C: OR=1.048, 95% CI=0.884–1.243 Fig. 3; TT vs CC: OR=1.292, 95% CI=0.850–1.965; CT vs CC: OR=0.942, 95% CI=0.750–1.183; CT+TT vs CC: OR=0.991, 95% CI=0.796–1.234; TT vs CT +CC: OR=1.329, 95% CI=0.888–1.989). Because only one study[32] was performed in a Caucasian population, subgroup analysis was only assessed in the Asian population, and no significant association was seen in any genetic model (detailed in Table 3).

Table 1

Characteristics of the studies included in the meta-analysis.

						Case				Control					
Study ID	**Year**	**Country**	**Ethnicity**	**Case/control**	**Genotyping Method**	**Alleles G[a]**	**GG**	**GA**	**AA**	**Alleles G[a]**	**GG**	**GA**	**AA**	**HWE**	**Quality**
XRCC1 Arg399Trp															
Ghasemi et al	2017	Iran	Caucasian	191/191	PCR	0.689	78	106	7	0.720	92	91	8	0.012	8
Zhang et al	2016	China	Asian	79/82	PCR-RFLP	0.570	21	48	10	0.677	37	37	8	0.776	6
Marzband et al	2015	Iran	Caucasian	144/166	PCR-RFLP	0.510	21	105	18	0.654	68	81	17	0.317	6
Zheng et al	2012	China	Asian	112/156	PCR-RFLP	0.593	33	67	12	0.683	72	69	15	0.793	7
Ji et al	2010	China	Asian	620/273	PCR-RFLP	0.720	327	239	54	0.738	153	97	23	0.181	6
Gu et al	2007	China	Asian	171/247	PCR	0.783	102	64	5	0.731	135	91	21	0.317	6
XRCC1 Arg194Trp															
Marzband et al	2016	Iran	Caucasian	144/166	PCR-RFLP	0.948	129	15	0	0.937	145	21	0	0.384	7
Ji et al	2010	China	Asian	620/273	PCR-RFLP	0.694	301	258	61	0.723	140	115	18	0.383	6
Gu et al	2007	China	Asian	171/247	PCR	0.667	77	74	20	0.650	101	119	27	0.357	6

=Quality was evaluated according to NOS, and the most important factor was "age and gender", Alleles G[a]=Alleles frequencies G, HWE=Hardy-Weinberg equilibrium, and $P<0.05$ was considered as a significant departure from HWE.

Table 2

Meta-analysis of the association between XRCC1 Arg399Gln polymorphism and male infertility.

Genetic model XRCC1 Arg399Trp	Population	No. of studies	Test of association		Test of heterogeneity		
			OR (95%CI)	*P*	P_h	I^2 (%)	Model
G versus A	Total	6	0.803 (0.627,1.027)	.081	.004	71.5	R
	Caucasian	2	0.687 (0.451, 1.047)	.081	.060	71.7	R
	Asian	4	0.870 (0.640,1.182)	.373	.016	71.0	R
GA versus AA	Total	6	1.276 (0.929,1.753)	.133	.660	0.0	F
	Caucasian	2	1.258 (0.693,2.283)	.451	.898	0.0	F
	Asian	4	1.283 (0.882,1.868)	.193	.355	7.6	F
GG versus AA	Total	6	0.760 (0.415,1.392)	.375	.079	67.6	R
	Caucasian	2	0.507 (0.157,1.639)	.256	.079	67.6	R
	Asian	4	0.924 (0.453,1.885)	.827	.034	65.4	R
GA+GG versus AA	Total	6	1.048 (0.774,1.420)	.760	.321	14.5	F
	Caucasian	2	0.897 (0.501,1.603)	.713	.569	0.0	F
	Asian	4	1.112 (0.779,1.586)	.559	.153	43.1	F
GG versus GA+AA	Total	6	**0.614 (0.403,0.937)**	**.024**	.000	81.8	R
	Caucasian	2	0.435 (0.147,1.285)	.132	.002	89.9	R
	Asian	4	0.733 (0.477,1.127)	.157	.009	73.9	R

Bold value represents statistically significant results.

F = the fixed-effects model, R = the random-effects model.

P = test for overall effect, P_h = *P* value of *Q*-test for heterogeneity test, I^2 = test for heterogeneity in groups.

3.3. Heterogeneity

As shown in Table 2, a significant association between XRCC1 Arg399Gln polymorphism and infertility in males was observed. Significant heterogeneity was observed in the allele model (G vs A: $P_h = .004$; $I^2 = 71.5\%$), homozygous model (GG vs AA: $P_h = .079$; $I^2 = 67.6\%$) and recessive model (GG vs GA+AA: $P_h = .000$; $I^2 = 81.8\%$); thus, we used the random-effects model. However, when using subgroup analysis, the significant

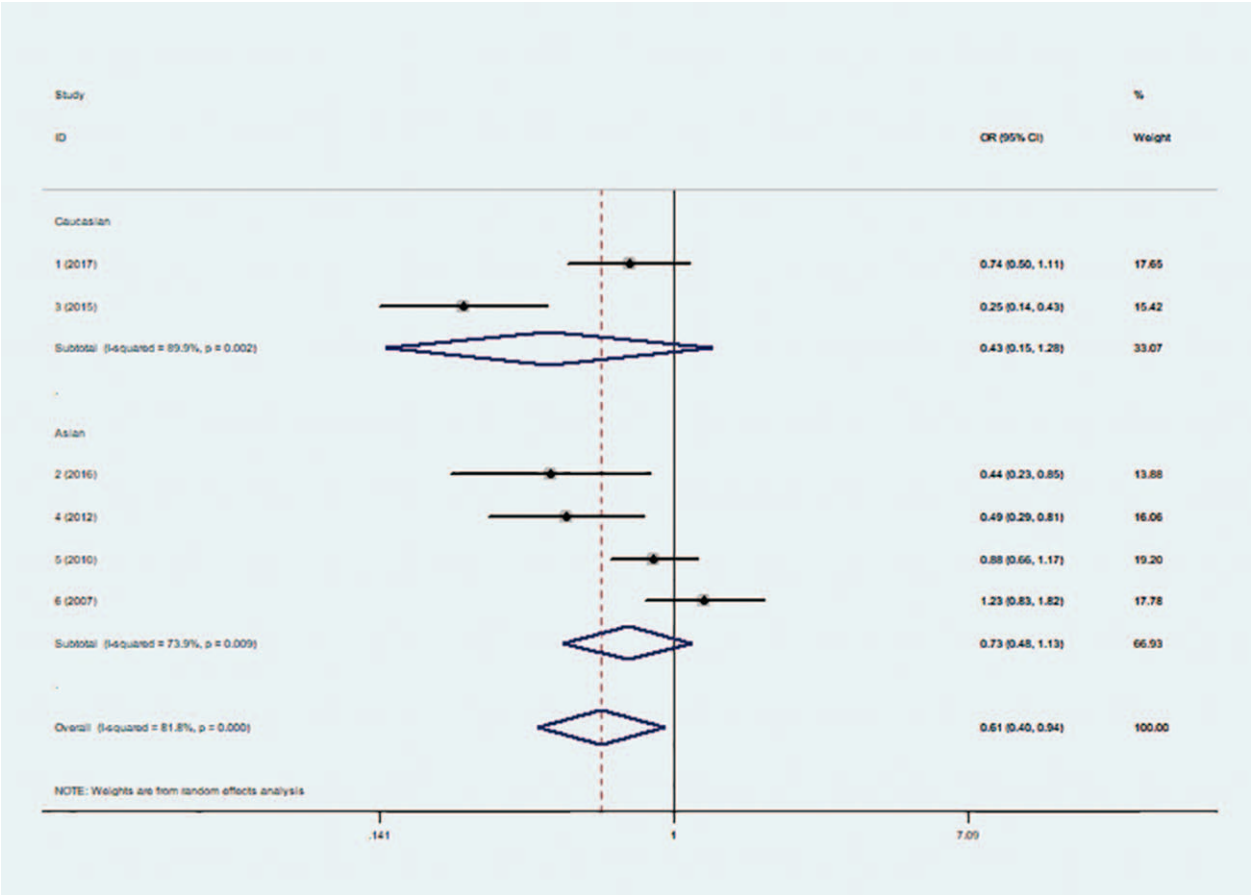

Figure 2. . Forest plot of homozygote comparison (GG versus GA+AA) of XRCC1 Arg399Gln for overall comparison, using a fixed-effects model.

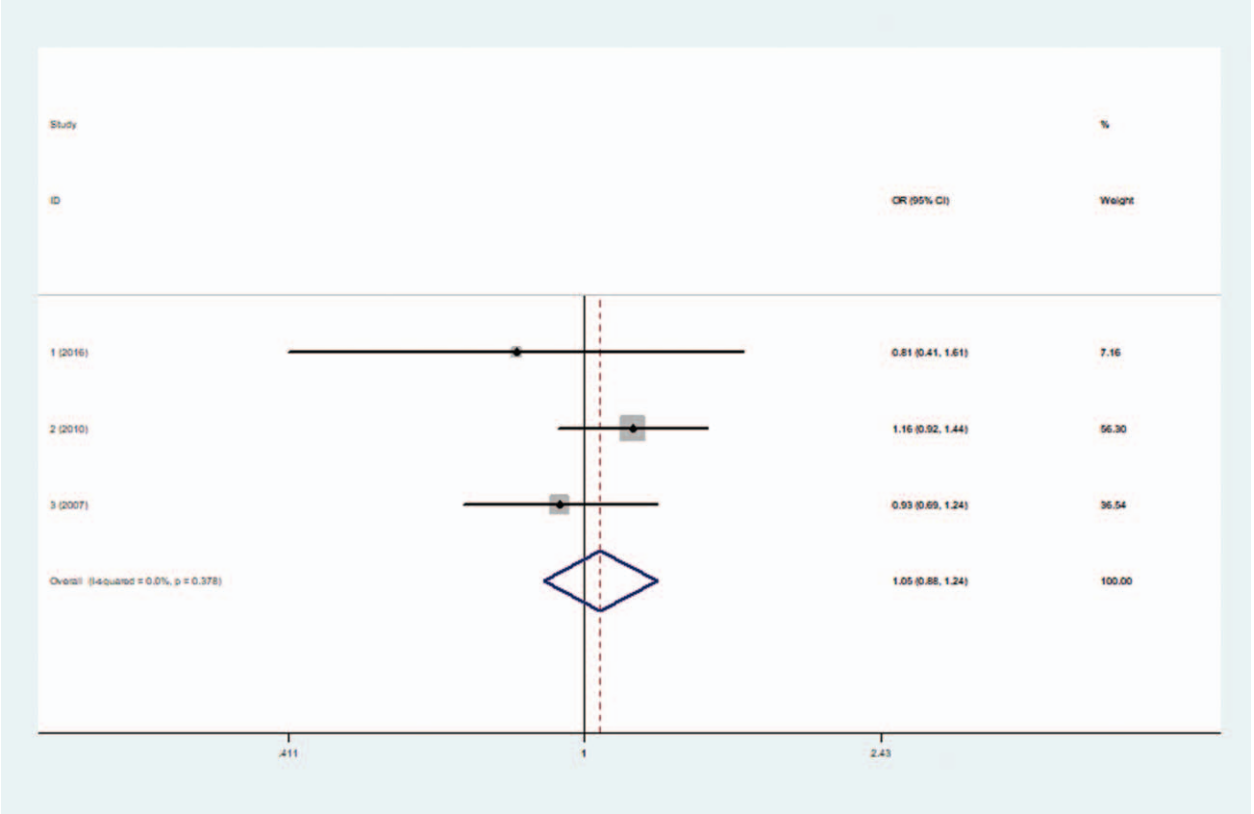

Figure 3. . Forest plot of allele comparison (T vs C) of XRCC1 Arg194Trp for overall comparison, using a fixed-effects model.

heterogeneity does not disappeared. For XRCC1 Arg194Trp, none of the genetic models demonstrated significant heterogeneity, including the allele model (T vs C: $P_h = .378$; $I^2 = 0.0\%$), homozygote comparison model TT vs CC: $P_h = .270$; $I^2 = 17.9\%$), homozygous model (CT vs CC: $P_h = .573$; $I^2 = 0.0\%$), recessive model (TT vs CT+CC: $P_h = .391$; $I^2 = 0.0\%$) and dominant model (CT+TT vs CC: $P_h = .440$; $I^2 = 0.0\%$). In subgroup analysis, no obvious signs of significant heterogeneity were seen in XRCC1 Arg194Trp in any genetic model (detailed in Table 3).

3.4. Sensitivity analyses

We performed sensitivity analysis to assess the influence set by each single study on the pooled ORs for XRCC1 Arg399Gln by deleting individual studies in all genetic models (Fig. 4). Subsequently, highly concordant statistical results were acquired in all genetic model, this finding indicated that the results of our study were statistically reliable. As for XRCC1 Arg194Trp, the primary outcome was still not significant and we obtained consistent results in sensitivity analyses (not shown in the figure).

3.5. Publication bias

To estimate the publication bias of the included studies, Begg's funnel plot and Egger's test were applied. No significant publication bias was observed in accordance with Begg's funnel plot ($P_{Begg} = .091$, GG vs GA+AA, Fig. 5) or Egger's regression test ($P_{Egger} = .154$, GG vs GA+AA). Similarly, these results for the association between XRCC1 Arg399Gln polymorphism and male infertility susceptibility still did not find publication bias in the other genetic models. Because of the limited number of included studies, we did not perform a funnel plot or Egger's test for the association between XRCC1 Arg194Trp and male

Table 3

Meta-analysis of the association between XRCC1 Arg194Trp polymorphism and male infertility.

			Test of association		Test of heterogeneity		
Genetic model XRCC1 Arg194Trp	Population	No. of studies	OR (95%CI)	P	P_h	I^2 (%)	Model
T versus C	Total	3	1.048 (0.884–1.243)	.590	.378	0.0	F
CT versus CC	Total	3	0.942 (0.750–1.183)	.606	.573	0.0	F
TT versus CC	Total	3	1.292 (0.850–1.965)	.231	.270	17.9	F
TT versus CT+CC	Total	3	1.329 (0.888–1.989)	.166	.391	0.0	F
CT+TT versus CC	Total	3	0.991 (0.796–1.234)	.936	.440	0.0	F

F = the fixed-effects model.

P = test for overall effect, $P_h = P$ value of Q-test for heterogeneity test; I^2 = test for heterogeneity in groups.

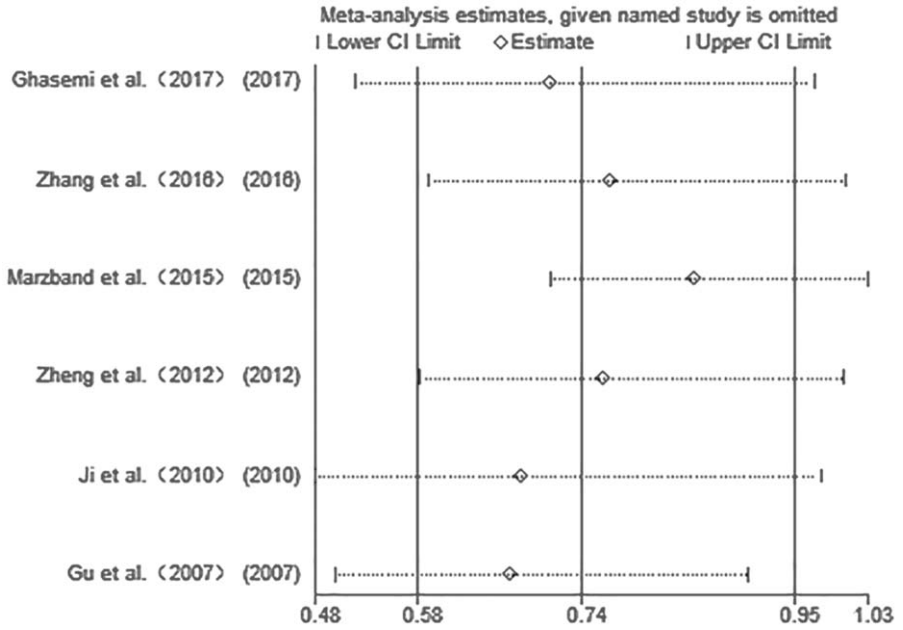

Figure 4. . Results of the sensitivity analysis examining the association between the XRCC1 Arg399Gln polymorphism and male infertility in the heterozygous genetic model.

infertility susceptibility. Consequently, there was no evidence of publication bias observed in this meta-analysis.

4. Discussion

In our present meta-analysis, 6 eligible studies containing 1317 cases and 1115 controls for XRCC1 Arg399Gln and 3 studies involving 953 cases and 686 controls for XRCC1 Arg194Trp were assessed and analyzed. Statistically significant results were observed in the homozygote comparisons (GG vs GA+AA: OR = 0.614, 95% CI: 0.40–0.937, $P = .024$) for the relationship between the XRCC1 Arg399Gln polymorphism and male infertility risk. This negative association was not observed in Asians or Caucasians. Notably, we observed no positive association between XRCC1 Arg194Trp polymorphism and male infertility risk in this meta-analysis.

XRCC1, which is a critical protein in the pathways of DNA repair, is known with other proteins to promote BER or single-strand break repair processes.[34] XRCC1 Arg399Gln is located on the C-terminal side of the PARP (poly-ADP ribose

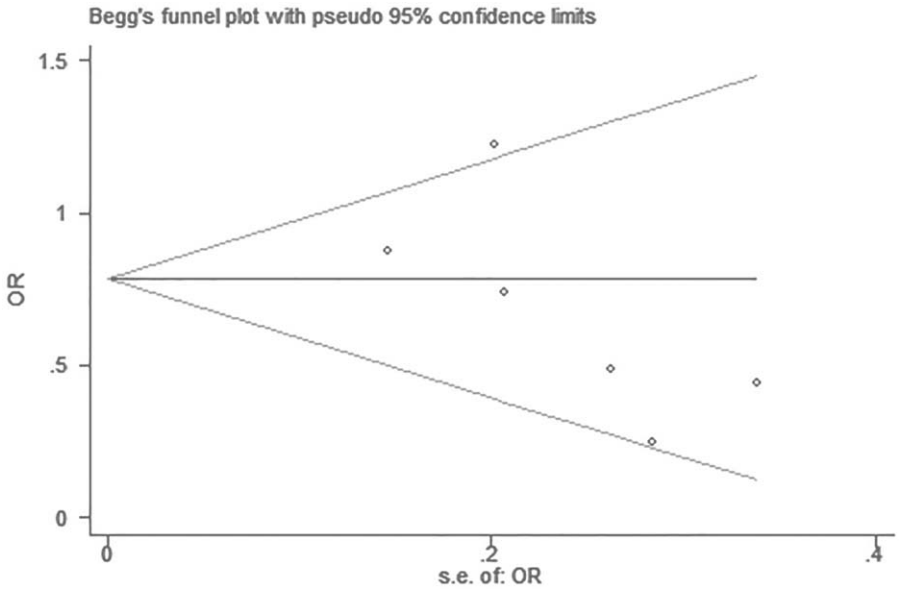

Figure 5. . Begg's funnel plot for publication bias analysis association between the XRCC1 Arg399Gln polymorphism and male infertility risk (GG vs GA+AA).

polymerase) binding domain within the BRCT domain,[35] which suggests potential protein–protein interaction sites. XRCC1 Arg194Trp, which is located at the linker region of DNA that separates the interacting domain of DNA polymerase β(Polβ) from the PARP interacting domain,[36] is also considered to mediate protein-protein interactions.[37] Depending on the type of DNA damage, the strength of the apyrimidinic endonuclease 1 (APE1) interaction with Polβ, XRCC1, and PARP1 is revealed to be modulated by BER intermediates to different extents.[38]

Previously published meta-analysis studies have demonstrated that XRCC1 Arg399Gln and Arg194Trp polymorphisms are involved in the risk of different types of cancers[39–43] and autoimmune diseases.[44] Male infertility, caused by a combination of genetic and paternal age[45] factors, was not performed using the semen parameters alone to predict fertility; as a result, these patients still have an opportunity to become pregnant.[45] It is also important to recognize the impact of genetic factors on male fertility, which contribute to the diagnosis, management, and treatment of this disease.[46] Numerous studies have demonstrated that the two SNPs are associated with male fertility; however, discordant results have been reported.[21,33,47–50] Currently, there are no published articles investigating the association between them. Therefore, we performed this meta-analysis to evaluate the association between the two SNPs and male infertility risk.

Heterogeneity was a major determining factor for the reliability of the results. Significant heterogeneity was observed in the three genetic comparison models, including the allele model (G vs A: $P_h = .004$; $I^2 = 71.5\%$), homozygous model (GG vs AA: $P_h = .079$; $I^2 = 67.6\%$) and recessive model (GG vs GA+AA: $P_h = .000$; $I^2 = 81.8\%$). We used the subgroup analyses to find the source of heterogeneity but failed. For XRCC1 Arg399Gln, no significant association was observed in the all genetic model, and significant heterogeneity was not observed for the overall population. Though heterogeneity existed in this meta-analysis, the results remained stable, and it became more significant in the Asian population. However, for XRCC1 Arg194Trp, no significant heterogeneity was observed for overall comparisons.

In subgroup analysis, we noticed that ethnicity (Caucasian or Asian) had no impact on XRCC1 Arg399Gln polymorphisms in the all genetic model, suggesting that XRCC1 Arg399Gln polymorphism was significantly associated with male infertility in Asian and Caucasian populations. A sensitivity analysis was conducted between XRCC1 Arg399Gln polymorphism and male infertility risk, and highly concordant statistical results were acquired in all genetic model, this finding indicated that the results of our study were statistically reliable. As for XRCC1 Arg194Trp, the pooled estimate remained nonsignificant, and the results of our meta-analysis illustrated the stability with sensitivity analyses. Additionally, we did not observe statistically significant results either in the shape of the funnel plots or the publication bias in this meta-analysis.

Meanwhile, the limitations of the currently meta-analysis must be emphasized. The first limitation is the small number of published studies included in the present meta-analysis. The second limitation is that the included studies only consisted of Asian (China) and Caucasian (Iran) populations; the results may not apply to all populations. Hence, more studies with different ethnicities are required. The third limitation is that one of the eligible studies, namely Ghasemi et al,[31] did not meet the result of HWE, as it was only focused on males and did not include females. The fourth limitation is that significant heterogeneity was observed in the allele model. Finally, due to the lack of necessary information, other clinical data were not analyzed such as the source of control, semen quality, and so on.

5. Conclusions

In conclusion, the results of the current meta-analysis suggest that XRCC1 Arg399Gln polymorphism is significantly associated with decreased male infertility risk. This meta-analysis failed to demonstrate an association between XRCC1 Arg194Trp and male infertility risk.

Author contributions

Data curation: Zhengsheng Liu, Luqi Lin, Xiongbo Yao, Jinchun Xing.
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References

[1] Oliva A, Spira A, Multigner L. Contribution of environmental factors to the risk of male infertility. Hum Reprod 2001;16:1768–76.
[2] Jarow JP, Sharlip ID, Belker AM, et al. Best practice policies for male infertility. J Urol 2002;167:2138–44.
[3] Katz DJ, Teloken P, Shoshany O. Male infertility—the other side of the equation. Aust Fam Physician 2017;46:641–6.
[4] Durairajanayagam D. Lifestyle causes of male infertility. Arab J Urol 2018;16:10–20.
[5] Hayden RP, Flannigan R, Schlegel PN. The role of lifestyle in male infertility: diet, physical activity, and body habitus. Curr Urol Rep 2018;19:56.
[6] Dhamija E, Das CJ, Razik A. Intratesticular varicocele: a rare cause of male factor infertility. BMJ Case Rep 2018;2018.
[7] Fode M. Male factor infertility: varicocele repair in the era of assisted reproductive technology. Nat Rev Urol 2017;14:705–6.
[8] Baazeem A, Belzile E, Ciampi A, et al. Varicocele and male factor infertility treatment: a new meta-analysis and review of the role of varicocele repair. Eur Urol 2011;60:796–808.
[9] Sedaghatpour D, Berookhim BM. The role of varicocele in male factor subfertility. Curr Urol Rep 2017;18:73.
[10] Skowronek MF, Velazquez T, Mut P, et al. Associations between male infertility and ancestry in South Americans: a case control study. BMC Med Gebet 2017;18:78.
[11] Jiang W, Shi L, Liu H, et al. Systematic review and meta-analysis of the genetic association between protamine polymorphism and male infertility. Andrologia 2018;50:e12990.
[12] Rafatmanesh A, Nikzad H, Ebrahimi A. Association of the c.-9C>T and c.368A>G transitions in H2BFWT gene with male infertility in an Iranian population. Andrologia 2018;50: doi: 10.1111/and.12805.
[13] Hu W, Chen M, Wu W, et al. Gene-gene and gene-environment interactions on risk of male infertility: Focus on the metabolites. Environ Int 2016;91:188–95.
[14] Thompson LH, West MG. XRCC1 keeps DNA from getting stranded. Mutat Res 2000;459:1–8.
[15] Fan J, Wilson DM3rd. Protein-protein interactions and posttranslational modifications in mammalian base excision repair. Free Radic Biol Med 2005;38:1121–38.
[16] Zhang X, Miao X, Liang G, et al. Polymorphisms in DNA base excision repair genes ADPRT and XRCC1 and risk of lung cancer. Cancer Res 2005;65:722–6.
[17] Zhang L, Reyes A, Wang X. The role of DNA repair in maintaining mitochondrial DNA stability. Adv Exp Med Biol 2017;1038:85–105.
[18] Moor NA, Lavrik OI. Protein-protein interactions in DNA base excision repair. Biochemistry (Mosc) 2018;83:411–22.
[19] Abbotts R, Wilson DM 3rd. Coordination of DNA single strand break repair. Free Radic Biol Med 2017;107:228–44.

[20] Zhang J, Mo-qi L, Hui-hui H, et al. XRCC1 rs25487 locus genetic polymorphisms and susceptibility to nonobstructive azoospermia in Hui minority ethnic population of Shaanxi province 2016;37:256–9.
[21] Zheng LR, Wang XF, Zhou DX, et al. Association between XRCC1 single-nucleotide polymorphisms and infertility with idiopathic azoospermia in northern Chinese Han males. Reprod Biomed Online 2012; 25:402–7.
[22] Ji G, Gu A, Zhu P, et al. Joint effects of XRCC1 polymorphisms and polycyclic aromatic hydrocarbons exposure on sperm DNA damage and male infertility. Toxicol Sci 2010;116:92–8.
[23] Gu AH, Liang J, Lu NX, et al. Association of XRCC1 gene polymorphisms with idiopathic azoospermia in a Chinese population. Asian J Androl 2007;9:781–6.
[24] Gu A, Ji G, Liang J, et al. DNA repair gene XRCC1 and XPD polymorphisms and the risk of idiopathic azoospermia in a Chinese population. Int J Mol Med 2007;20:743–7.
[25] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg (Lond Engl) 2010;8:336–41.
[26] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
[27] DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clin Trials 1986;7:177–88.
[28] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
[29] Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[30] Zhang J, Lü MQ, Hong HH, et al. XRCC1 rs25487 locus genetic polymorphisms and susceptibility to nonobstructive azoospermia in Hui minority ethnic population of Shaanxi province. J Xi'an Jiaotong Univ (Med Sci) 2016;37:256–9.
[31] Ghasemi H, Khodadadi I, Fattahi A, et al. Polymorphisms of DNA repair genes XRCC1 and LIG4 and idiopathic male infertility. Syst Biol Reprod Med 2017;63:382–90.
[32] Marzband S, Mashayekhi F, Salehi Z, et al. Analysis of XRCC1 Arg194Trp polymorphism and the risk of idiopathic male infertility. Iranian South Med J 2016;19:203–11.
[33] Marzband S, mashayekhi F, Salehi Z, et al. Association of Arg399Gln polymorphism of XRCC1 with idiopathic male infertility in Guilan Province. Arak Med Univ J 2015;18:85–91.
[34] Caldecott KW, Aoufouchi S, Johnson P, et al. XRCC1 polypeptide interacts with DNA polymerase beta and possibly poly (ADP-ribose) polymerase, and DNA ligase III is a novel molecular 'nick-sensor' in vitro. Nucleic Acids Res 1996;24:4387–94.
[35] Zhang X, Morera S, Bates PA, et al. Structure of an XRCC1 BRCT domain: a new protein-protein interaction module. EMBO J 1998; 17:6404–11.
[36] Kubota Y, Nash RA, Klungland A, et al. Reconstitution of DNA base excision-repair with purified human proteins: interaction between DNA polymerase beta and the XRCC1 protein. EMBO J 1996;15: 6662–70.
[37] Masson M, Niedergang C, Schreiber V, et al. XRCC1 is specifically associated with poly(ADP-ribose) polymerase and negatively regulates its activity following DNA damage. Mol Cell Biol 1998; 18:3563–71.
[38] Moor NA, Vasil'eva IA, Anarbaev RO, et al. Quantitative characterization of protein-protein complexes involved in base excision DNA repair. Nucleic Acids Res 2015;43:6009–22.
[39] Goode EL, Ulrich CM, Potter JD. Polymorphisms in DNA repair genes and associations with cancer risk. Cancer Epidemiol Biomarkers Prev 2002;11:1513–30.
[40] Zeng X, Zhang Y, Yue T, et al. Association between XRCC1 polymorphisms and the risk of cervical cancer: a meta-analysis based on 4895 subjects. Oncotarget 2017;8:2249–60.
[41] Yang NN, Huang YF, Sun J, et al. Meta-analysis of XRCC1 polymorphism and risk of female reproductive system cancer. Oncotarget 2017;8:28455–62.
[42] Lu JT, Deng AP, Song J, et al. Reappraisal of XRCC1 Arg194Trp polymorphism and glioma risk: a cumulative meta-analysis. Oncotarget 2017;8:21599–608.
[43] Chen XP, Wen HF, Zhang F, et al. Assessment of the link between XRCC1 Arg399Gln polymorphism and breast cancer: a meta-analysis in a Single Ethnic Group. Clin Lab 2017;63:725–31.
[44] Peng M, Zhou X, Ding X, et al. Association of XRCC1 Arg399Gln and Arg194Trp polymorphisms with susceptibility to multiple autoimmune diseases: a meta-analysis. Rheumatol Int 2017;37:435–44.
[45] Mazur DJ, Lipshultz LI. Infertility in the aging male. Curr Urol Rep 2018;19:54.
[46] Moghbelinejad S, Mozdarania H, Ghoraeian P, et al. Basic and clinical genetic studies on male infertility in Iran during 2000-2016: a review. Int J Reprod Biomed (Yazd, Iran) 2018;16:131–48.
[47] Singh V, Kumar Mohanty S, Verma P, et al. XRCC1 deficiency correlates with increased DNA damage and male infertility. Mutat Res Genet Toxicol Environ Mutagen 2019;839:1–8.
[48] Singh V, Bansal SK, Sudhakar DVS, et al. SNPs in ERCC1, ERCC2, and XRCC1 genes of the DNA repair pathway and risk of male infertility in the Asian populations: association study, meta-analysis, and trial sequential analysis. J Assist Reprod Genet 2019;36:79–90.
[49] Akbas H, Balkan M, Binici M, et al. The possible role of XRCC1 gene polymorphisms with idiopathic non-obstructive azoospermia in Southeast Turkey. Urol J 2019;16:380–5.
[50] Garcia-Rodriguez A, de la Casa M, Serrano M, et al. Impact of polymorphism in DNA repair genes OGG1 and XRCC1 on seminal parameters and human male infertility. Andrologia 2018;50:e13115.