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Association between *CYP1A1* rs4646903 T > C genetic variations and male infertility risk

A meta-analysis

DeHong Cao, MD[a], ZhengJu Ren, MD[a], DongLiang Lu, LiangRen Liu, MD[a], Peng Xu, MD[b], Qin Zhang, MD[c,*], Qiang Wei[a]

Abstract

Background: Number of studies have been performed to investigate the relationship between the *CYP1A1* rs4646903 polymorphism and male infertility risk, but the sample size was small and the results were conflicting. A meta-analysis was performed to assess these associations.

Methods: A systematic search was conducted to identify all relevant studies from Medline, Web of science, Embase, China biology medical literature database (CBM), China National Knowledge Infrastructure (CNKI), WanFang and Weipu (VIP) databases up to June 30, 2018. The odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the strength of associations. All of the statistical analyses were conducted using Revman 5.3 and Stata 14.0.

Results: Ten studies involved 3028 cases and 3258 controls. Overall, significant association was observed between the *CYP1A1* rs4646903 polymorphism and male infertility (C vs T: OR = 1.42, 95%CI = 1.14–1.76; CC vs TT: OR = 2.13, 95%CI = 1.36–3.34; CC vs CT+TT: OR = 1.96, 95%CI = 1.30–2.95; CC+CT vs TT: OR = 1.51, 95%CI = 1.16–1.97). In subgroup analysis by ethnic group, a statistically significant association was observed in Asians (C vs T: OR = 1.59, 95%CI = 1.22–2.08), but not in Non-Asians (C vs T: OR = 1.01, 95%CI = 0.79–1.30). Additionally, none of the individual studies significantly affected the association between *CYP1A1* rs4646903 polymorphism and male infertility, according to sensitivity analysis.

Conclusion: Our meta-analysis supports that the *CYP1A1* rs4646903 polymorphism might contribute to individual susceptibility to male infertility in Asians.

Abbreviations: CBM = China biology medical literature database, CI = confidence interval, CIs = confidence intervals, CNKI = China National Knowledge Infrastructure, HWE = Hardy-Weinberg equilibrium, NOS = Newcastle-Ottawa Scale, OR = odds ratio, ORs = odds ratios, SNP = single-nucleotide polymorphism, SNPs = single-nucleotide polymorphisms, VIP = Weipu.

Keywords: CYP1A1, male infertility, meta-analysis, polymorphism

1. Introduction

Infertility is the inability of a couple to conceive pregnancy after 1 year of unprotected, regular sexual intercourse and affects approximately 10% to 20% of couples.[1,2] Among them, approximately 50% of the cases are associated with male factors.[3] It is thought that lifestyle factors and environmental factors such as cigarette, smoking, and exposure to certain chemicals, are potential causes of male infertility.[4,5] In addition, genetic factors, such as chromosomal aberrations, gene mutations, and polymorphisms, can also be associated with male infertility.[6–8] Several studies suggest the *CYP1A1* gene as a candidate gene for male infertility.[9,10]

Cytochrome P4501A1 gene, located on chromosome 15q22-q24, is 5987-bp long and encodes a 512 amino acid protein.[11,12] CYP1A1, a member of the CYP1 family, involved in the metabolism of a vast number of xenobiotics and endogenous substrates.[13] The disturbed testicular expression of CYP1A1 is responsible for producing hydroxyestradiols and/or methoxyestradiols, and the increased intratesticular hydroxyestradiols and methoxyestradiols concentrations could elicit an impaired Sertoli cell function, this could ultimately lead to male infertility.[14] Several single-nucleotide polymorphisms (SNPs) of *Cytochrome* P4501A1 gene have been identified, including T3801C, T3205C, A2455G.[13] Among them, *P4501A1* MspI (3798 T > C; *CYP1A1**2A; rs4646903) polymorphism is one of the most-studied single-nucleotide polymorphism (SNP). Recently, many genetic studies have investigated the association between the *CYP1A1* rs4646903 polymorphism and the risk of male

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DC and ZR have contributed equally to this work and should be considered co-first authors.

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DC, ZR, LL, PX, and QZ declare that they have no conflicts of interest.

[a] Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu, [b] Department of Urology, [c] Department of Radiology, Chongqing Traditional Chinese Medicine Hospital, Chongqing, China.

[*] Correspondence: Qin Zhang, Chongqing Traditional Chinese Medicine Hospital, Chongqing, China (e-mail: zqfamilylove@163.com).

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infertility. However, these studies have relatively sample size and the results remain controversial. In 2013, a meta-analysis based on 6 case-control studies including 1060 cases and 1225 controls was conducted, the authors concluded that the *CYP1A1* rs4646903 polymorphism is capable of causing male infertility susceptibility in Asians, but not in Caucasians.[15] In 2014, a meta-analysis conducted by Luo et al[16] demonstrated that the *CYP1A1* rs4646903 polymorphism was associated with male infertility in overall population, however, no association was observed between *CYP1A1* rs4646903 polymorphism and male infertility in both Asians and Caucasians. In addition, several novel related studies of male infertility risk have since been published. Therefore, in the present study, we performed an updated meta-analysis based on 10 studies of the *CYP1A1* rs4646903 polymorphism (3028 cases and 3258 controls) to elucidate the relationship between the *CYP1A1* rs4646903 polymorphism and male infertility risk.

2. Methods

2.1. Search strategy

To assess the complete evidence of an association between the *CYP1A1* rs4646903 polymorphism and male infertility, we performed the present comprehensive meta-analysis of published studies. Medline, Web of science, Embase, CBM, CNKI, WanFang, and VIP databases were searched for relevant articles up to June 30, 2018. The following search terms and keywords were used: "*CYP1A1* gene" or "Cytochrome P450 1A1 gene," and "SNP" or "polymorphism" or "mutation" or "variant" and "male infertility". References of all relevant studies were reviewed to obtain additional references. All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

2.2. Inclusion and exclusion criteria

Studies were considered eligible if they met the following criteria: case-control study; full text of the article was available; available data to estimate an odds ratio (OR) with 95% confidence interval (CI); the genetypes in cases and controls were available. Exclusion criteria included: studies not concerning association between the *CYP1A1* rs4646903 polymorphism and male infertility risk; repeated or overlapping publications; and animal studies, review articles, meta-analysis, and conference abstracts or editorial articles.

2.3. Quality assessment and data extraction

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of included studies by 2 authors.[17] This scale assesses the quality of case-control studies included 3 areas: selection, comparability, and exposure. A star rating system was used to judge methodological quality. Scores range from 0 stars (worst) to 9 stars (best), and studies with a score ≥ 7 were defined as high quality. Discrepant opinions were resolved by discussion and consensus. Two investigators extracted the data using a standardized data extraction form independently. Discrepancies were resolved by discussion with a third investigator. The following information was extracted from each study: first author, year of publication, sample size, geographical location, genotype frequencies of CYP1A1.

2.4. Statistical analysis

Odds ratios (ORs) with 95% CIs were used to assess the strength of association between *CYP1A1* rs4646903 polymorphism and male infertility risk. The pooled ORs were performed for *CYP1A1* rs4646903 polymorphism under the allele comparison model (C vs T), additive model (CC vs TT), recessive model (CC vs CT+TT), and dominant model (CC+CT vs TT), respectively. The significance of the pooled OR was analyzed by the Z test, and $P < .05$ was considered statistically significant. The Chi-square-based Q-test and I^2 statistics were used to calculated heterogeneity among included studies. The $P > .05$ for Q test or $I^2 < 50\%$ indicated a statistically significant degree of heterogeneity among studies. In contrast, the random-effects model was used. All statistical analyses were performed by using Revman 5.3 and Stata 14.0. Publication bias was investigated with the funnel plot, Begg test, and Egger test. Sensitivity analysis was conducted to assess the stability of the results by sequentially omitted individual studies.

3. Results

3.1. Description of included studies

A total of 131 studies were retrieved from online databases. Of these, after the first screening, 121 studies were excluded based on inclusion and exclusion criteria. Finally, 10 studies including 3028 cases and 3258 controls were included in this meta-analysis.[9,17–25] A detailed flow chart of the study selection is shown in Fig. 1. The years of publication ranged from 2008 to 2017, and there were 7 studies of Asian descendants and 3 studies of Non-Asian descendants. The Hardy-Weinberg test (HWE) was performed on all of the included studies, and the results showed that the *CYP1A1* rs4646903 gene genotype frequencies of all 10 studies were in HWE in the controls (Table 1).

3.2. Meta-analysis of CYP1A1 rs4646903 polymorphism in male infertility susceptibility

Ten studies involving a total of 6286 individuals evaluated the influence of the *CYP1A1* gene variant rs4646903 polymorphism on the risk of male infertility. Figures 2–5 show the meta-analysis results for the allele model, additive model, recessive model, and dominant model, for which the I^2 value was 78%, 69%, 67%, and 75%, respectively. Thus, the random effect model was used to synthesize the data. Overall, pooled risk estimates indicated that *CYP1A1* rs4646903 polymorphism was associated with an increased risk of male infertility (C vs T: OR = 1.42, 95%CI = 1.14–1.76; CC vs TT: OR = 2.13, 95%CI = 1.36–3.34; CC vs CT +TT: OR = 1.96, 95%CI = 1.30–2.95; CC+CT vs TT: OR = 1.51, 95%CI = 1.16–1.97).

Subgroup analysis based on ethnicity indicated that the *CYP1A1* rs4646903 polymorphism was associated with increased susceptibility to male infertility in Asians (C vs T: OR = 1.59, 95%CI = 1.22–2.08; CC vs TT: OR = 2.58, 95%CI = 1.46–4.56; CC vs CT+TT: OR = 2.33, 95%CI = 1.38–3.91; CC+CT vs TT: OR = 1.58, 95%CI = 1.11–2.26), however, no association was found between the *CYP1A1* rs4646903 polymorphism and male infertility risk in Non-Asians (C vs T: OR = 1.01, 95%CI = 0.79–1.30; CC vs TT: OR = 1.22, 95%CI = 0.66–2.25; CC vs CT +TT: OR = 1.15, 95%CI = 0.64–2.05; CC+CT vs TT: OR = 0.98, 95%CI = 0.72–1.34) (Table 2).

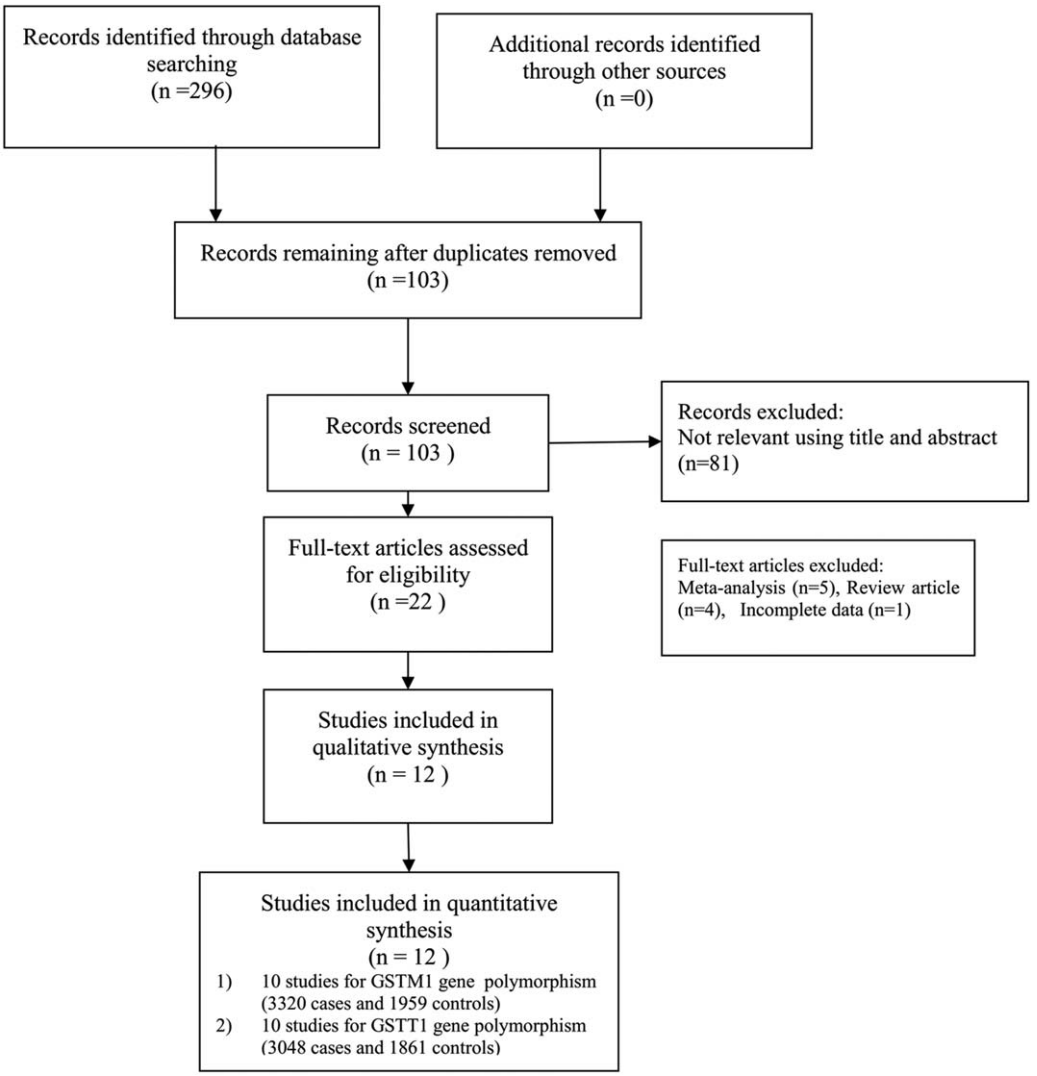

Figure 1. Flowchart showing the study selection.

3.3. Publication bias and sensitivity

There was no evidence of obvious asymmetry in the funnel plots (Fig. 6). The Begg test and Egger test were also performed to access publication bias in the articles included in this meta-analysis. No significant publication bias was observed under all the genetic models, as shown in Fig. 6 and Table 3. Sensitivity analyses were conducted to calculate pooled ORs by omitting one study each time. Results showed that no individual study

Table 1

Characteristics of the studies included in the meta-analysis and their genotype distributions of the *CYP1A1* rs4646903 polymorphism.

				Genotyping			Case			Control				
Author	Year	Region	Ethnicity	Method	Case	Control	TT	CT	CC	TT	CT	CC	HWE	NOS
Chen	2010	China	Asian	PCR	105	140	35	47	23	88	45	7	Y	6
Flórez	2015	Colombia	Non-Asian	PCR-RFLP	31	20	25	5	1	16	4	0	Y	5
Liu	2010	China	Asian	PCR	60	60	26	14	20	27	26	7	Y	7
Lu	2008	China	Asian	PCR-RFLP	192	226	69	96	27	95	104	27	Y	7
Peng	2012	China	Asian	PCR	202	249	72	93	39	78	94	30	Y	5
Ramgir	2017	India	Asian	PCR	120	80	40	70	10	52	27	1	Y	6
Salehi	2012	Iran	Non-Asian	PCR	150	200	58	72	20	85	91	24	Y	7
Vani	2009	India	Asian	PCR	206	230	108	80	18	146	80	4	Y	8
Wang	2017	China	Asian	PCR-RFLP	1759	1826	625	860	274	723	849	254	Y	7
Yarosh	2013	Russian	Non-Asian	PCR	203	227	165	35	3	176	48	3	Y	8

HWE = Hardy-Weinberg equilibrium, NOS = Newcastle-Ottawa Scale, PCR = polymerase chain reaction, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism.

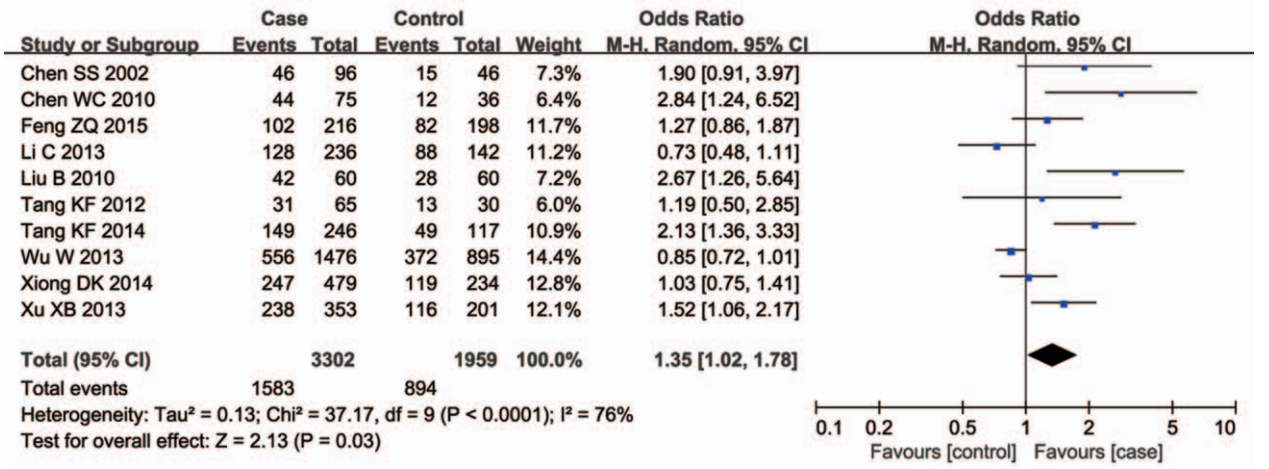

Figure 2. Forest plot of the studies assessing the association between *CYP1A1* rs4646903 polymorphism and male infertility. (Allelic model: C vs T).

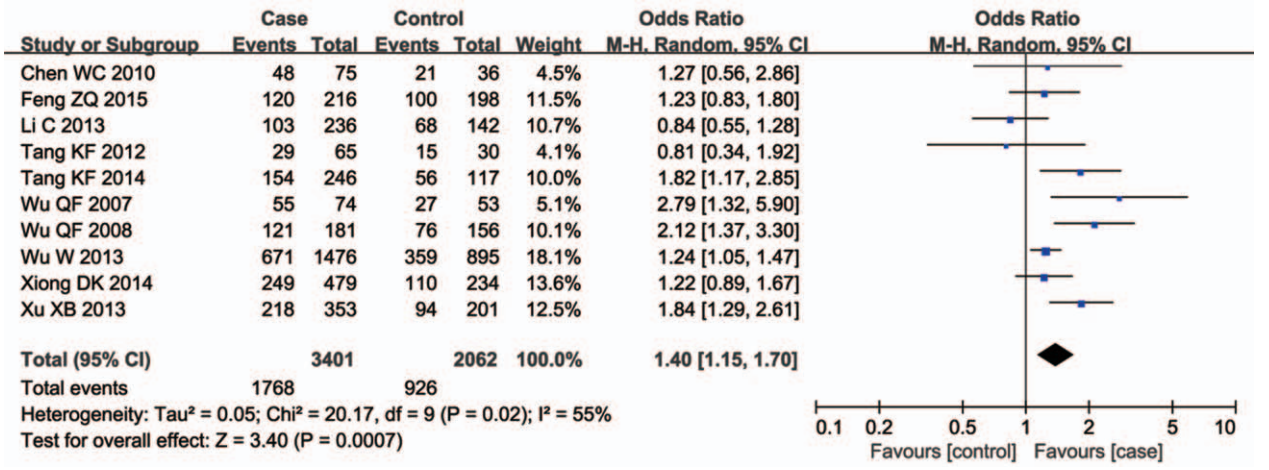

Figure 3. Forest plot of the studies assessing the association between *CYP1A1* rs4646903 polymorphism and male infertility. (Additive model: CC vs TT).

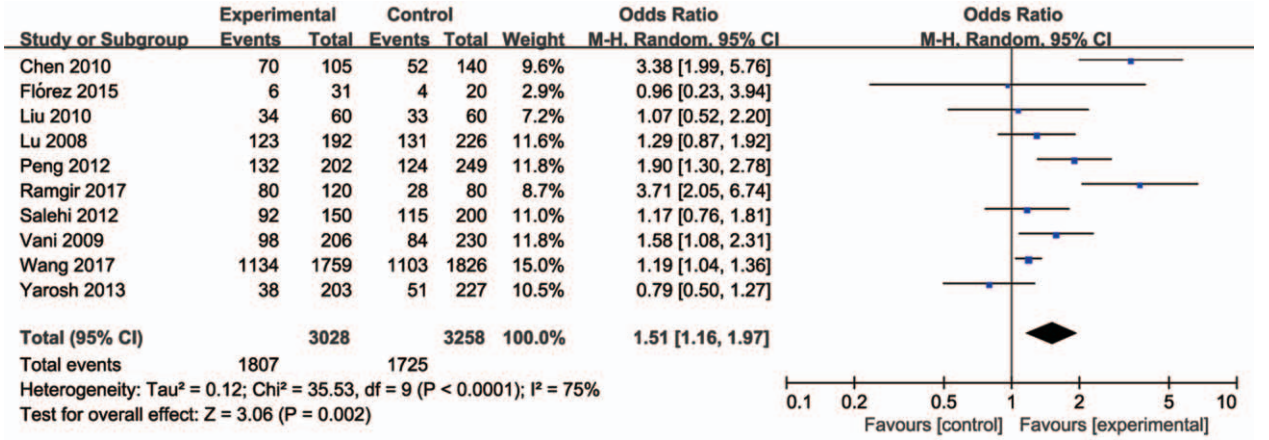

Figure 4. Forest plot of the studies assessing the association between *CYP1A1* rs4646903 polymorphism and male infertility. (Dominant model: CC+CT vs TT).

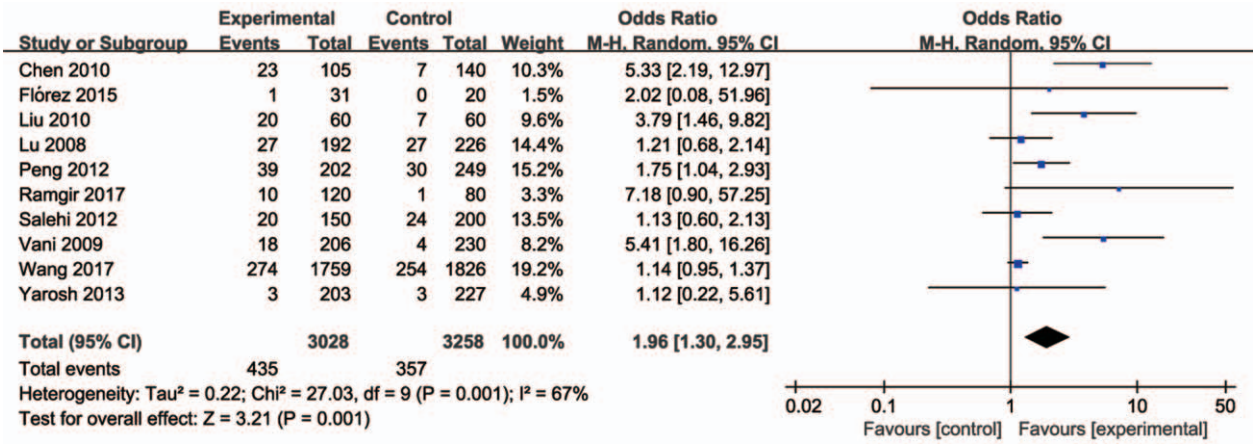

Figure 5. Forest plot of the studies assessing the association between *CYP1A1* rs4646903 polymorphism and male infertility. (Recessive model: CC vs CT+TT).

Table 2

Meta-analysis of the association of *CYP1A1* rs4646903 polymorphism with male infertility.

CYPA1 rs4646903	N	C vs T (OR, 95%CI)	CC vs TT (OR, 95%CI)	CC+CT vs TT (OR, 95%CI)	CC vs CT+TT (OR, 95%CI)
Asian	7	1.59 [1.22, 2.08]	2.58 [1.46, 4.56]	1.75 [1.27, 2.42]	2.33 [1.38, 3.91]
Non-Asian	3	1.01 [0.79, 1.30]	1.22 [0.66, 2.25]	0.98 [0.72, 1.34]	1.15 [0.64, 2.05]
Overall	10	1.42 [1.14, 1.76]	2.13 [1.36, 3.34]	1.51 [1.16, 1.97]	1.96 [1.30, 2.95]

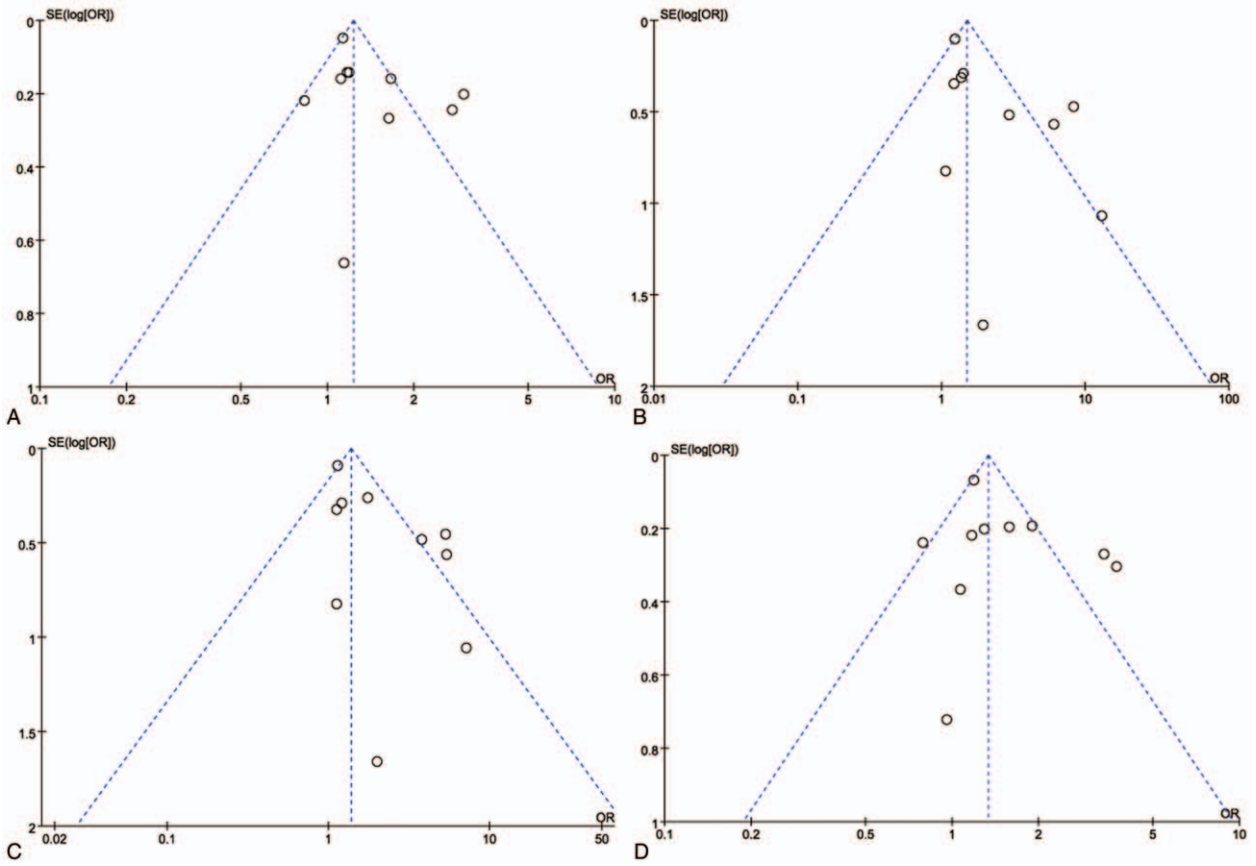

Figure 6. Funnel plot for the *CYP1A1* rs4646903 polymorphism and male infertility risk. (A. Allelic model: C vs T; B. additive model: CC vs TT; C. dominant model: CC+CT vs TT; D. recessive model: CC vs CT+TT).

Table 3

Publication bias test for *CYP1A1* rs4646903 polymorphism.

Comparisons	Egger test			Begg test
	Coefficient	*P* value	95% CI	*P* value
CYPA1 rs4646903				
C vs T	1.644	.153	−0.759 to 4.047	.210
CC vs TT	1.624	.045	0.043–3.206	.283
CC + CT vs TT	1.026	.362	−1.422 to 3.475	.721
CC vs CT + TT	0.211	.533	−0.535 to 0.958	.721

influenced overall pooled ORs (Fig. 7), indicating that the results of this meta-analysis are relatively stable.

4. Discussion

In the present study, significant associations with the risk of male infertility were detected for the *CYP1A1* rs4646903 polymorphism. Further subgroup analyses based on ethnicity of study subjects revealed that genetic variations of *CYP1A1* gene rs4646903 may contribute to susceptibility to male infertility in Asians, but not in Non-Asians.

Cytochrome P4501A1, an important phase I enzyme, plays an essential role in the metabolism of polycyclic aromatic hydrocarbons (PAHs).[21,26] PAHs are able to form DNA adducts once it has been activated to DNA reactive metabolites.[27] DNA adducts could be considered as a sign of severe DNA damage in sperm cells, which played an essential role in meiotic division during spermatogenesis and associated with male infertility.[18,28] It has been suggested that the SNPs of the *CYP1A1* gene could determine the activity and/or inducibility of *CYP1A1*.[19,29] Recent studies have revealed that *CYP1A1* rs4646903 polymorphism was associated with an increased risk of male infertility, but the results of these studies were inconsistent. Lu et al[17] reported that no significant association was detected between *CYP1A1**2A polymorphism and male infertility in Chinese population. Similarly, a case-control study conducted by Yarosh et al[20] revealed that *CYP1A1**2A polymorphism do not contribute to male infertility of Colombian Caribbean men. However, Flórez et al[21] reported that CC genotype of *CYP1A1* is associated in the pathogenesis of male infertility in Indian population. The difference between the studies could arise from race, geography, or genetic background of the study population. Subsequently, two meta-analysis, included 6 studies involving 1060 cases and 1225 controls, comprehensively evaluated the associations between *CYP1A1* rs4646903 polymorphism and male infertility risk, but there results were still inconsistent.[14,15] This inconsistent result may arise from different search strategies, and the 2 meta-analyses do not include all relevant studies.

In the present study, 10 studies including 3028 cases and 3258 controls were included, the overall results showed that *CYP1A1* rs4646903 polymorphism could increase the risk of male infertility (C vs T: OR = 1.42, 95%CI = 1.14–1.76; CC vs TT: OR = 2.13, 95%CI = 1.36–3.34; CC vs CT+TT: OR = 1.96, 95% CI = 1.30–2.95; CC+CT vs TT: OR = 1.51, 95%CI = 1.16–1.97).

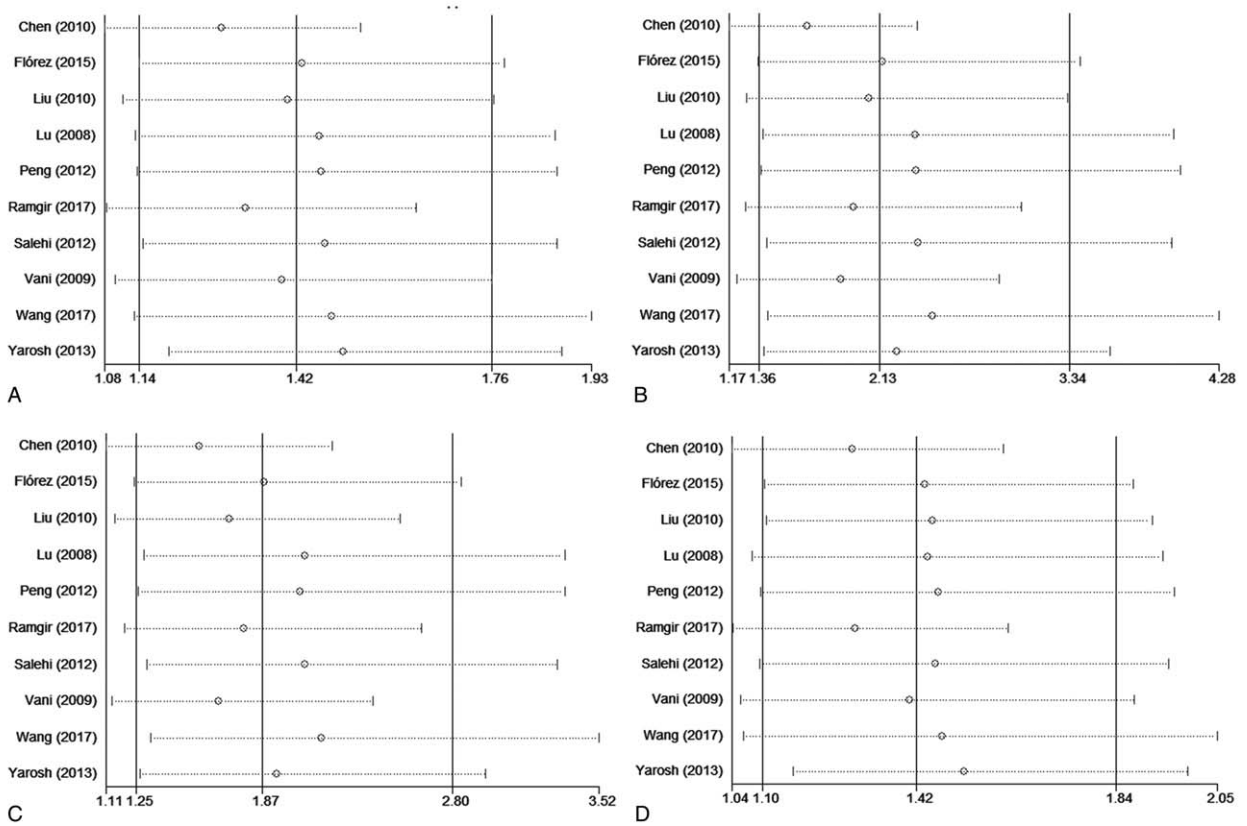

Figure 7. Sensitivity analysis diagram for each study used to assess the relative risk estimates for the *CYP1A1* rs4646903 polymorphism and male infertility in all of the included studies. (A. Allelic model: C vs T; B. additive model: CC vs TT; C. dominant model: CC+CT vs TT; D. recessive model: CC vs CT+TT).

It reveals that individuals with the variant C allele may have a higher risk for male infertility than those carrying T homozygote. Nevertheless, in the subgroup analysis of ethnicity, we found that *CYP1A1* rs4646903 polymorphism had an effect on increase in the male infertility risk in Asians, while the susceptibility to male infertility was not observed in Non-Asian population. However, only 3 studies reported the relationship between the *CYP1A1* rs4646903 polymorphism and male infertility risk in Non-Asians and 5 studies for Asian population were included in the present meta-analysis. The sample size was small, thus, studies with larger sample sizes are needed to further investigate the potential relationships of *CYP1A1* rs4646903 polymorphism with male infertility risk.

When interpreting the results of the current study, there are still several limitations should be considered. First, only 10 studies were incorporated in the meta-analysis, the sample size of included published articles was small. Second, subgroup analyses such as by infertility type and source of control group were not performed, due to the lack of information. Third, the effects of gene–gene and gene–environment interactions on male infertility susceptibility were not estimated, as the studies enrolled lacked of information. Finally, our results were based on unadjusted estimates, due to the lack of data of smoking, age, and other environmental exposure factors.

5. Conclusions

This meta-analysis result suggests that the *CYP1A1* rs4646903 polymorphism may increase the risk of male infertility, especially in Asians. However, large sample size, well-designed, and population-based studies are necessary to comprehensively verify the association between *CYP1A1* gene variant rs4646903 polymorphism and male infertility risk.

Author contributions

Conceptualization: Qin Zhang, DeHong Cao.
Data curation: DeHong Cao.
Formal analysis: DongLiang Lu.
Funding acquisition: Qiang Wei.
Methodology: ZhengJu Ren.
Software: Qin Zhang, ZhengJu Ren, Peng Xu.
Supervision: DongLiang Lu, LiangRen Liu, Qiang Wei.
Writing – original draft: DeHong Cao, ZhengJu Ren.
Writing – review & editing: Qin Zhang, DongLiang Lu, LiangRen Liu, Peng Xu.

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