Journal of Advanced Research (2016) 7, 185–192

Cairo University

Journal of Advanced Research

REVIEW

TNF-α −308 polymorphisms and male infertility risk: A meta-analysis and systematic review

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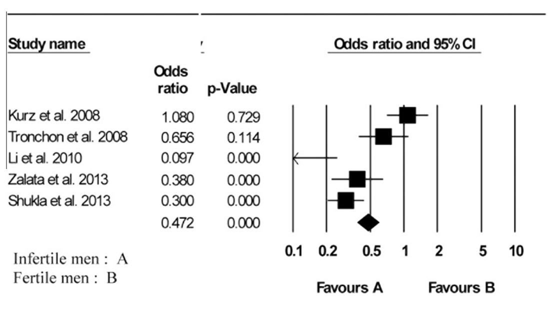
GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 8 May 2015
Received in revised form 8 July 2015
Accepted 9 July 2015
Available online 17 July 2015

Keywords:
Male infertility
TNF-α

ABSTRACT

This study aimed to conduct a systematic review and meta-analysis of prospective studies discussing TNF-α −308 polymorphism and male infertility. This study was conformed to Preferred Reported Items for Systematic Reviews and Meta-Analyses guidelines. PubMed, Embase and Scopus databases were searched to identify relevant studies by two independent reviewers. Hazard ratios were pooled using fixed-effect or random-effects models when appropriate. Q-test was performed to evaluate study heterogeneity and publication bias appraised using funnel plots. The search yielded five studies (three of Caucasians ethnicity and 2 of Asian ethnicity) comprising 2939 men (2262 infertile men and 677 fertile controls). Most of the studied cases were carried out on TNF-α promoter region at positions −308 G/A (four studies) where

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Peer review under responsibility of Cairo University.

ELSEVIER Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jare.2015.07.001

Polymorphism
Meta-analysis
Semen
Sperms

−308 C/T was dealt with in one study. Overall, significant associations between TNF-α −308 gene polymorphisms and idiopathic male infertility risk were observed (fixed effect: OR = 0.472, 95% CI: 0.378–0.589; P = 0.001; random effect: OR = 0.407, 95% CI: 0.211–0.785; P = 0.007) with robust findings according to sensitivity analyses. Funnel plot inspections did not give evidences of publication bias. A stratified analysis performed for ethnic groups revealed significant association in both Caucasian and Asian populations. It is concluded that there are evidences of associations between TNF-α −308 gene polymorphisms and male infertility risk.

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Dr. Mai Taymour was graduated from the Faculty of Medicine, Cairo University 2011. She led her career in Dermatology & Andrology Department, Egypt Air Hospital in Cairo. Her point of interest is bioinformatics and biostatistics. She has 4 international publications with 19 citations and h-index 2.

Introduction

Meta-analysis refers to methods that focus on combining and contrasting results from different studies to identify patterns among study results, sources of disagreement or additional relationships coming in this context [1,2].

Male infertility results from interaction of multi-factorial causes as, endocrinal environmental and/or genetic factors [3–6]. Many genetic studies were carried out to inspect the contribution of encoded genes whereas various studies exposed the association between different genotypes and the disease vulnerability [7–10].

Seminal plasma contains several cytokines that are normally present in the male genital tract. Tumor necrosis factor (TNF)-α is one of the known cytokines regulatory peptides that is produced and secreted by leukocytes being implicated as growth and differentiation factors. In the testes, TNF-α receptors are present in the Sertoli cells and Leydig cells, allowing TNF-α to modulate their functions [11]. In men with unexplained infertility, seminal plasma levels of TNF-α were demonstrated to correlate negatively with progressive sperm motility [12]. In their study, Said et al. [13] demonstrated that exposing sperms to high concentrations of TNF-α results in a significant loss of its functional as well as genomic integrity.

Genetic factors as single nucleotide polymorphisms were revealed to affect TNF-α level, where different polymorphisms in the TNF gene cluster were linked with its modified production. Several single nucleotide polymorphisms in TNF-α promoter region were investigated at positions −1031 T/C, −863 C/A, −857 C/T, −575 G/A, −376 G/A, −308 G/A, −244 G/A, and −238 G/A [14]. Tronchon et al. [15] associated −308 TNF-α A allele with increased expression/production of TNF-α. They pointed that the frequency of −308 allele was significantly higher in infertile men with testicular failure or with altered sperm motility compared with patients with normal sperm parameters (19.4%). Lazaros et al. [16] pointed to the nonsignificant relationship between TNF-α 857C/T polymorphisms and semen quality. Zalata et al. [14] associated the single nucleotide polymorphism in the TNF-α (−308) gene with significantly increased seminal caspase-9 and significant decrease in sperm count, sperm motility, normal sperm morphology, acrosin activity and seminal α-glucosidase. Lately, Shukla et al. [17] designated an association between TNF-α G -308A genotype substitutions with infertile men supported by allele and genotype meta-analysis and thus established it as a risk factor.

This study aimed to assess the relationship of TNF-α polymorphism with male infertility by conducting a meta-analysis of the available case-control studies.

Material and methods

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guiding principle where included studies were retrieved from many electronic databases including PubMed, Scopus and Embase. Combination of search terms was used as (“TNF-alpha” or “TNF-α”), (“male infertility”) and (“polymorphism” or “allele” or “variant” or “mutation” or “gene” or “genotype”). No restrictions were executed on the search in terms of language till June 2015.

Selection criteria

The two investigators (TM, MT) independently assessed the literature eligibility where the discrepancies were resolved by consensus. Articles were considered for inclusion in the systematic review if:

a. Reported data from an original, peer-reviewed study (not conference abstracts, case reports, posters, editorials, review articles or letters to editors).
b. Case-control design.
c. Reported about the TNF-α −308 genotype distribution in cases and corresponding controls.

d. Evaluated TNF-α −308 genotype polymorphism and male infertility risk.
e. All procedures carried out were in accordance with the ethical standards of the responsible committee on humans and with the Helsinki Declaration of 1975, as revised in 2008 and obtained informed consent from all subjects for being incorporated in these studies.

This information was extracted from the studies: first author's name, publication year, country, ethnicity, and genotype frequencies (cases/controls).

Statistical analysis

Comprehensive meta-analysis program (Englewood, NJ, USA) was used for all statistical analyses. Combined odds ratio (OR) with its consequent 95% confidence interval (CI), was used to calculate the strength of the relationship between TNF-α polymorphisms and male infertility risk. Heterogeneity assumption was examined using Q-test [18]. Random-effects model (Der Simonian-Laird method) and fixed-effects model (Mantel–Haenszel method) were used to analyze the pooled effect estimates in the presence ($P \leqslant 0.10$) or absence ($P > 0.10$) of heterogeneity [19]. Publication bias was evaluated through inspection of funnel plots. In case of absent publication bias, the plot resembles a symmetrical inverted funnel [20]. In addition, Hardy–Weinberg equilibrium (HWE) among controls for each study was examined by χ^2 test.

Results

A total of six eligible citations were identified during this search that met our inclusion criteria involving 2939 men in the pooled analyses (2262 cases and 677 controls). These studies were published between 2008 and 2014 (Fig. 1, flowchart). In the articles eligible for the meta-analysis, three were conducted in Caucasian populations, and two studies involved Asian populations. All articles were in English except one in Chinese with English abstract [21]. The controls of all studies mainly came from healthy population from hospital-based populations being matched for sex and age. All included articles used blood samples for genotyping assay.

Applied exclusion criteria included the following: age > 50 years, vasectomy, azoospermia, hypogonadism, varicocele, diabetes, hypertension, chemotherapy, malignancy, tuberculosis, HIV, leukocytospermia, smoking, alcohol or drug abuse, abnormal karyotype, Y chromosome deletions and chronic genital infections.

To assess genetic polymorphism, polymerase chain reaction-restriction fragment length polymorphism was used in every study. Semen samples of cases were carried out according to WHO guidelines 1999 except one paper [14] that used WHO 2010 guidelines. Most of the studied cases were carried out on TNF-α promoter region at positions −308 G/A (3 studies) (GG is the wild and AA is the mutant) where −308 C/T (CC is the wild and TT is the mutant) was dealt with in one study. The characteristics of all case–control studies incorporated for the tested polymorphism were demonstrated (Table 1).

Kurz et al. [22] cases comprised azoospermic, oligozoospermia and teratozoospermia/asthenozoospermia men, Tronchon et al. [15] cases comprised azoospermia and oligozoospermia men, Li et al. [21] cases comprised oligozoospermia, Zalata et al. [14] cases comprised asthenozoospermia, asthenoteratozoospermia and OAT, and Shukla et al. [17] cases comprised oligozoospermic and asthenozoospermic men.

Overall, significant associations between TNF-α gene polymorphisms and male infertility risk were observed (fixed effect: OR = 0.472, 95% CI: 0.378–0.589; P = 0.001; random effect: OR = 0.407, 95% CI: 0.211–0.785; P = 0.007) with strong results according to the sensitivity analyses (Table 2, Fig. 2). Funnel plot assessment did not reveal evidences of publication bias. In the funnel plot, the results of the small studies are shown to be more widely distributed than these of the large one (Fig. 3). Evaluation of heterogeneity was analyzed according to the P-value for heterogeneity indicating a significant heterogeneity (Q-value = 31.969, P = 0.001). Among controls, all studies were in HWE except one [16].

Stratification based on ethnicity demonstrated significant association between TNF-α gene polymorphisms and male infertility risk in Caucasian population (fixed effect: OR = 0.698, 95% CI: 0.526–0.928; P = 0.013; random effect: OR = 0.657, 95% CI: 0.360–1.199; P = 0.171) as well as in Asian population (fixed effect: OR = 0.260, 95% CI: 0.182–0.370; P = 0.001; random effect: OR = 0.194, 95% CI: 0.069–0.541; P = 0.002) (Table 3).

Discussion

Genetic factors may impact TNF-α levels where several polymorphisms in the TNF-α gene cluster have been associated with the modified TNF-α production [23]. Since the original identification of the TNF-α polymorphisms, several studies investigated the genetic effect of these polymorphisms on the susceptibility to different human diseases such as prostate cancer, Crohn's disease, pre-eclampsia and colo-rectal cancer [24,25]. In view of that, the association between TNF-α gene polymorphisms and susceptibility to male infertility was also raised and reported in different populations.

In this meta-analysis, there was a significant association between TNF-α gene polymorphisms and male infertility risk.

Tronchon et al. [15] pointed out, in French population, an increased frequency of the −308 TNF-α A allele in oligozoospermic and asthenozoospermic men compared with normozoospermic men. In oligozoospermic men exhibiting TNF-α A allele, compared with those with G allele, an altered hormonal balance was detected with increased inhibin B hormone levels and subsequent reduced FSH plasma hormone levels, leading to an FSH/inhibin B ratio roughly half as high [15].

Zalata et al. [14] associated, in Egyptian population, that the TNF-α GG genotype was more frequent in fertile men than asthenozoospermic, asthenoteratozoospermic or oligoasthenoteratozoospermic men compared with TNF-α AA genotype. Existence of A allele was significantly greater among infertile patients than fertile controls. Men with the TNF-α AA genotype revealed a significant decrease in the sperm concentration, sperm motility, normal sperm morphology, acrosin activity, and seminal α-glucosidase and demonstrated a

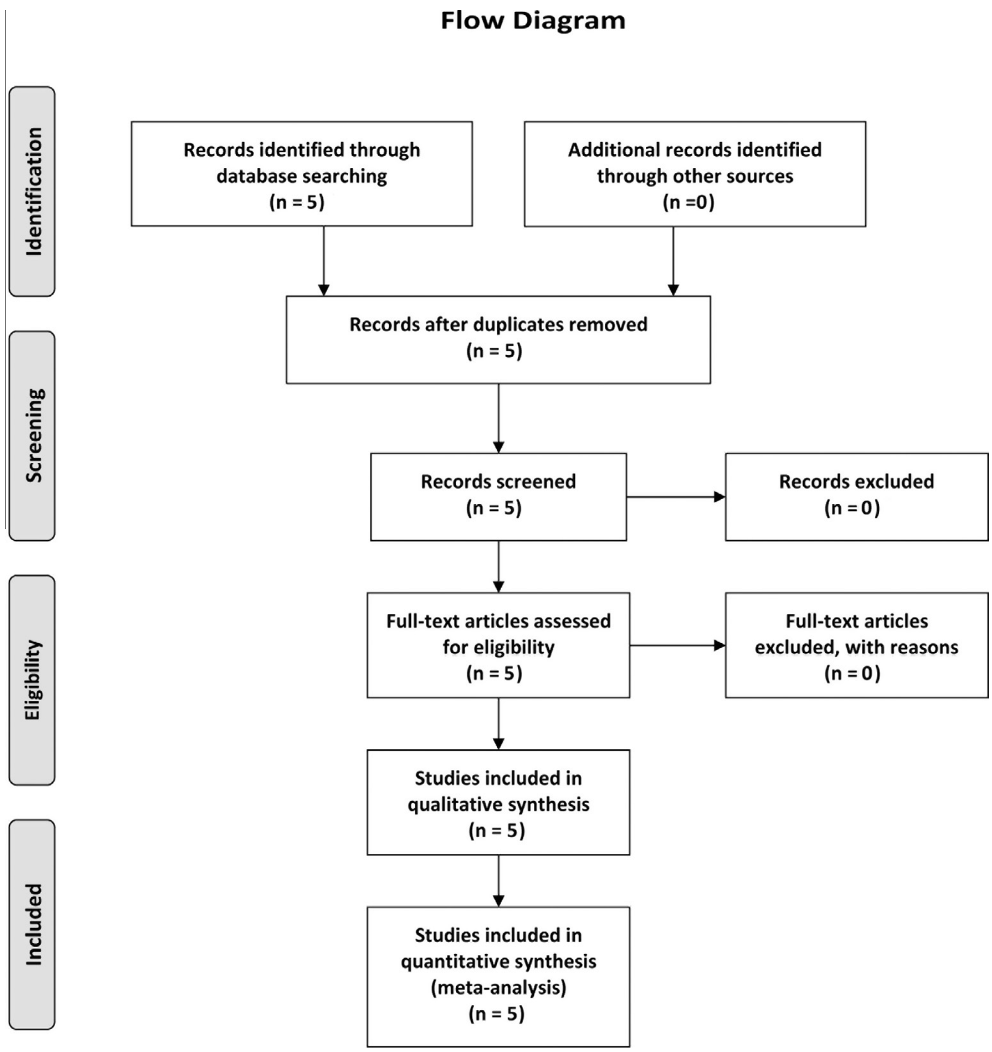

Fig. 1 Flowchart.

significant increase in seminal plasma caspase-9 apoptotic factor compared with these with the TNF-α GG genotype [14].

In Asians, Li et al. [21] in their study on Chinese population, observed that asthenozoospermic and oligoasthenozoospermic men exhibited significant differences from infertile men with normal sperms in the frequency of GA/AA at position −308 in the promoter region of TNF-α gene. They demonstrated negative correlation between the GA + AA type of the TNF-α −308 allele and progressive sperm motility. They pointed that seminal plasma TNF-α level was significantly elevated in asthenozoospermic and oligoasthenozoospermic men compared with infertile men with normal sperms being significantly higher in the GA + AA than in the GG type of the TNF-α −308 allele.

Shukla et al. [17] observed, in Indian population, that the substitution levels from G to A in the TNF-α gene were significantly higher in the infertile subjects compared with the healthy fertile controls. Apoptosis and necrosis levels were also higher in oligozoospermic and asthenozoospermic infertile subjects being associated with increased levels of reactive oxygen species.

However, Kurz et al. [22] demonstrated, in Austrian population, that allele frequencies of TNF-α −308 C → T, −863 C → A polymorphisms were nonsignificantly different between non-normozoospermic and normozoospermic men and that the mutant alleles were not over-represented in oligoasthenoteratozoospermic or asthenozoospermic men. Also, in their study, Lazaros et al. [15] did not associate between TNFα −857C → T polymorphism and semen quality in the Greek population.

Overall, Grataroli et al. [26] noted that TNF-α had a key role in adapting apoptosis throughout binding with type 1 TNF-α receptor, activating a number of transduction pathways leading to the enrollment of adaptor proteins, through interactions between conserved death domains. These adaptor proteins activate caspase-8, that increases mitochondria permeability conversion for releasing cytochrome C, followed by configuration of a high-molecular weight complex (apoptotic protease activating factor-1, cytochrome C, and caspase-9) that activates caspase-3, followed by cell death [27]. In their study, Perdichizzi et al. [28] associated TNF-α with increased sperm DNA damage and phosphatidylserine externalization explaining reduced fertility. Further, the pro-apoptotic effect

Table 1 Characteristics of the included studies on TNF-polymorphisms and male infertility risk.

	Study	Country	Ethnicity	TNF-alpha	Cases/controls	Genotyping	Genotype data (cases)		Genotype data (controls)		Hardy–Weinberg equilibrium
1	Kurz et al. [22]	Austria	Caucasians	−308 CT	446/128	CC, CT/TT	324/446 (72.6%)	123/446 (23.4%)	91/128 (71.1%)	37/128 (28.9%)	Yes
2	Tronchon et al. [15]	France	Caucasians	−308 GA	581/103	GG, GA/AA	425/581 (66.7%)	156/581 (33.3%)	83/103 (80.6%)	20/103 (19.4%)	Yes
3	Li et al. [21]	China	Asians	−308 GA	187/62	GG, GA/AA	98/187 (52.4%)	89/187 (47.6%)	57/62 (91.9%)	5/62 (8.1%)	Yes
4	Zalata et al. [14]	Egypt	Caucasians	−308 GA	268/124	GG, GA/AA	178/268 (66.4%)	90/268 (33.6%)	104/124 (83.9%)	20/124 (16.1%)	Yes
5	Shukla et al. [17]	India	Asians	−308 GA	1040/260	GG, GA/AA	508/780 (65.1%)	172/780 (34.9%)	224/260 (86.2%)	36/260 (34.95%)	Yes

Table 2 Meta-analysis results of the included studies on TNF-polymorphisms and male infertility risk.

		TNF-alpha	Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value	Log odds ratio	SE	Weight (fixed) Relative weight	Weight (Random) Relative weight	Hedges's g	SE
1	Kurz et al. [22]	−308 CT	1.080	0.699	1.669	0.346	0.729	0.077	0.222	25.98	21.42	0.042	0.122
2	Tronchon et al. [15]	−308 GA	0.656	0.390	1.106	−1.582	0.114	−0.421	0.266	18.08	20.57	−0.232	0.147
3	Li et al. [21]	−308 GA	0.97	0.037	0.252	−4.781	0.001	−2.337	0.489	5.38	15.74	−1.258	0.269
4	Zalata et al. [14]	−308 GA	0.380	0.221	0.654	−3.499	0.001	−0.967	0.276	16.80	20.37	−0.532	0.152
5	Shukla et al. [17]	−308 GA	0.300	0.205	0.40	−6.183	0.001	−1.203	0.195	33.77	21.89	−0.663	0.197
	Fixed effect		0.472	0.378	0.589	−6.631	0.001	−0.750	0.113			−0.413	0.062
	Random effect		0.407	0.211	0.785	−2.681	0.007	−0.898	0.335			−0.494	0.184

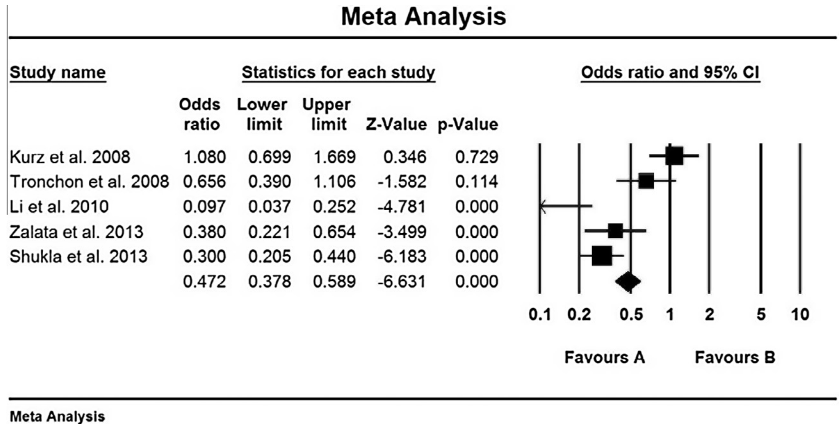

Fig. 2 Forest plot for the association between TNF-α polymorphisms and male infertility [group A (cases) and group B (controls)]. The involvement of each study to the meta-analysis (its weight) is denoted by the area of a box, the center of which represents the size of the estimated OR. The overall OR is shown in the middle of a diamond where the left and right extremes represent the corresponding CI.

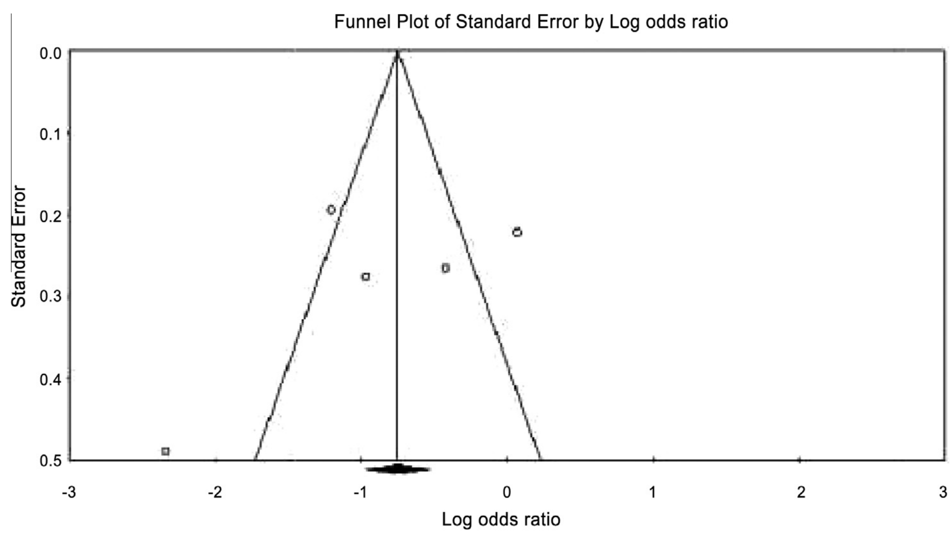

Fig. 3 Begger's funnel plots for TNF-α polymorphisms in male infertility. Vertical axis represents log (OR), and the horizontal axis refers to the standard error of log (OR). The sloping lines designate the expected 95% CI for a given standard error. The area of each circle denotes the impact of the study to the pooled OR.

Table 3 Subgroup meta-analysis results of the included studies on TNF-polymorphisms and male infertility risk according to ethnicity.

		Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value	Log odds ratio	SE	Weight (fixed) relative weight	Weight (random) relative weight	Hedges's g	SE
	Caucasians											
1	Kurz et al. [22]	1.080	0.699	1.669	0.346	0.729	0.077	0.222	42.70	35.30	0.042	0.122
2	Tronchon et al. [15]	0.656	0.390	1.106	−1.582	0.114	−0.421	0.266	29.73	32.66	−0.232	0.147
3	Zalata et al. [14]	0.380	0.221	0.654	−3.499	0.001	−0.967	0.276	27.57	32.04	−0.532	0.152
	Fixed effect	0.698	0.526	0.928	−2.474	0.013					−0.198	0.080
	Random effect	0.657	0.558	1.281	−1.370	0.171					−0.221	0.169
	Asians											
1	Li et al. [21]	1.104	−1.774	0.719	−4.630	0.001	−2.267	0.490	13.64	41.08	−1.246	0.269
2	Shukla et al. [17]	0.300	0.205	0.40	−6.183	0.001	−1.203	0.195	86.63	58.92	−0.663	0.107
	Fixed effect	0.260	0.182	0.370	−4.830	0.001					−0.743	1.00
	Random effect	0.194	0.069	0.541	−2.015	0.002					−0.902	0.287

of TNF-α is demonstrated to be mediated by reactive oxygen species manufacture causing peroxidative damage to sperm plasma membrane and sperm DNA fragmentation correlated with impaired sperm competence [29–33].

Points of limitation in this meta-analysis are the limited available studies and the dealing with only two ethnic races: Caucasians and Asians where other ethnic decent studies were absent e.g., Africans and African–Americans. Moreover, the meta-analysis was limited to available English publications and the possibility of unpublished reports was not yet identified. Also, several models of different alleles were not demonstrated in detail since some of the available papers did not declare these information and fine points clearly.

Conclusions

The current meta-analysis provides evidence of associations between TNF-α gene polymorphisms and male infertility risk. Further studies are warranted to validate associations of TNF-α polymorphisms and male infertility as −363 C/A and −857 G/A.

Funding

None.

Conflict of Interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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