Evaluation of genetic polymorphisms in TNF-α-308G/A rs1800629 associated with susceptibility and severity of rheumatoid arthritis: A systematic review and meta-analysis

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Abstract. To investigate the association of gene polymorphisms of TNF-α-308G/A rs1800629 with the susceptibility and severity of rheumatoid arthritis (RA), literature from PubMed, EMBASE, Web of Science and CNKI databases was searched. Two authors screened the literature independently, extracted data and evaluated the risk of bias of the included studies. According to the inclusion and exclusion criteria, five genetic models were established: The allelic model (A vs. G), dominant model (GA + AA vs. GG), recessive model (AA vs. GG + GA), co-dominant model (AA vs. GG) and super-dominant model (GG + AA vs. GA). Stata 17.0 software was used for the meta-analysis. A total of 34 eligible studies with 12,611 subjects were included, including 6,030 cases in the RA group and 6,581 controls. Meta-analysis calculations revealed that the genetic polymorphisms of TNF-α-308G/A rs1800629 were not significantly associated with susceptibility to RA, with an odds ratio and 95% confidence interval (CI) for each genetic model [A vs. G: 0.937 (0.762-1.152); GA + AA vs. GG: 0.918 (0.733-1.148); AA vs. GG + GA: 1.131 (0.709-1.802); AA vs. GG: 1.097 (0.664-1.813); and GG + AA vs. GA: 1.108 (0.894-1.373)]. For the association between TNF-α-308G/A rs1800629 gene polymorphisms and the severity of RA, the results of subgroup analysis calculations showed that TNF-α-308G/A rs1800629 gene polymorphisms were associated with the severity of RA in European populations, with the gene model and 95% CI [GA + AA vs. GG: 0.503 (0.297-0.853); and GG + AA vs. GA: 2.268 (1.434-3.590)]. When assessing the confidence in the positive results of the present study through the false-positive report probability, the positive results were observed to be reliable. No significant association was observed between genetic polymorphisms in TNF-α-308G/A rs1800629 and susceptibility to RA. However, a significant association exists with the severity of RA in European populations.

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Abbreviations: RA, rheumatoid arthritis; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; CI, confidence interval; NOS, Newcastle-Ottawa-Scale; FPRP, false-positive report probability

Key words: TNF-α-308G/A, gene polymorphisms, RA, meta-analysis

Introduction

Rheumatoid arthritis (RA) is a common, chronic autoimmune joint disease characterized by synovial inflammation, pannus formation and joint damage as major pathological features. The global incidence of RA is 0.5-1% (1). RA is characterized by chronic systemic inflammation, which mainly affects the joint synovial tissue, eventually leading to joint destruction, functional disability and even death, severely affecting the quality of life of patients (2). The etiology and pathogenesis of RA remain largely unknown. Currently, it is considered by most scholars that this is the result of the combined effects of genetics, environment, infection and other factors, leading to an imbalance in immune regulation and the induction of a series of joint tissue inflammations (3). It has been hypothesized that TNF-α-308G/A rs1800629 is closely related to the pathogenesis and severity of RA (4,5), while other studies consider that there is no relationship between the two (6,7). Different studies produced different results (4-7), which may be related to the sample size, quality and whether the frequency of the control genotype conformed to the Hardy-Weinberg equilibrium (HWE) (8). Therefore, the current meta-analysis of the two aspects of susceptibility and severity of TNF-α-308G/A rs1800629 and RA was conducted to obtain reliable theoretical support and research results and provide evidence-based medical evidence for in-depth research on genetic susceptibility.

Materials and methods

Search policy. The PubMed (https://pubmed.ncbi.nlm.nih.gov), EMBASE (https://www.embase.com), Web of Science (https://www. webofscience.com/wos) and CNKI (https://www.cnki.net/) databases were employed. The key words searched were: 'rheumatoid arthritis', 'TNF-α' and 'polymorphism'. The search strategy was as follows: (polymorphism or variant or variation or mutation or SNP or genome-wide association study or genetic association study or genotype or allele) AND (rheumatoid arthritis) OR (RA) AND (Tumor Necrosis Factor-alpha) OR (Tumor Necrosis Factor alpha) OR (Cachectin) OR (Cachectin-Tumor Necrosis Factor) OR (Tumor Necrosis Factor Ligand Superfamily Member 2) OR (Tumor Necrosis Factor) OR (TNFalpha) OR (TNF-alpha) OR (TNF-α). The search period ranged from the establishment of each database until May 2023.

Inclusion and exclusion criteria. The inclusion criteria were as follows: i) The study participants were patients with RA, and there were clear diagnostic criteria; ii) the type of study was a case-control study or a cohort study; iii) the research content was the relationship between TNF-α-308G/A rs1800629 gene polymorphisms and the susceptibility or severity of RA; iv) the study included complete genotype and allele frequency data and inclusion or availability to calculate odds ratio (OR) and 95% confidence intervals (CI); v) the control group conformed to HWE.

The exclusion criteria were as follows: i) Duplicate publications; ii) no health control studies; iii) studies with incomplete data or an inability to calculate OR and 95% CI; and iv) animal experimental literature.

Data extraction. Two authors independently screened and extracted the data; in cases of disagreement, a third author decided. Missing data were supplemented as much as possible by contacting the authors of the studies. The data extracted included: i) First author and year of publication; ii) country, geographic region, sex composition, mean age and diagnostic criteria of the study subjects; iii) sample size, allele and genotype frequency of the RA and control groups; and iv) whether they conformed to the HWE.

Literature quality evaluation criteria. The Newcastle-Ottawa Scale (NOS) evaluated the quality of the literature. The NOS scale includes three dimensions with a total of eight items: Four items for study object selection, one item for intergroup comparability and three items for outcome measurement. In addition to the comparability item, the highest score was two points, and the other items could reach up to one point, with a score range of 0 to 9 points. The higher the overall score, the higher the quality of the study. The NOS score is divided into three grades: Low, medium and high quality, namely <5 points, 5-7 points and ≥8 points (9).

Statistical methods. The present study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (10). The meta-analysis was performed using Stata 17.0 (StataCorp LP). Using OR and its 95% CI to assess the strength of the association between

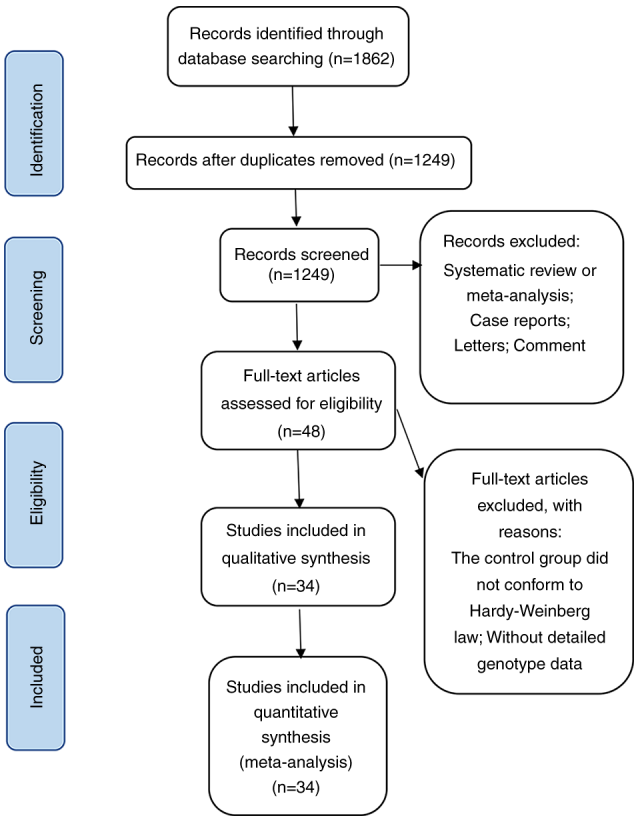

Figure 1. Flow diagram of study identification and selection.

TNF-α-308G/A rs1800629 gene polymorphisms and the risk and severity of RA, P<0.05 was considered statistically significant. Heterogeneity was assessed using Cochrane's Q test and I^2 values, and pooled analyses were performed using a random-effects model when $I^2 \leq 50\%$ between study groups. When heterogeneity could not be completely eliminated, a random-effects model was also used. The following five genetic models were used for comparison: Allele, dominant, recessive, co-dominant and super-dominant models. Subgroup analysis was carried out for further research. The subgroups were divided into: Asian, South American, European, North American and African groups according to the source of the patient. Sensitivity analyses were conducted by excluding literature on a case-by-case basis to observe the effect of each study on the overall effect size or by using Stata 17.0 to assess the robustness of the results. Funnel plots were only used to visualize publication bias for the number of included studies ≥10. Publication bias was detected using Egger's test, and no publication bias was considered when P>0.05 (11).

Results

Search results. According to the search strategy, 1,862 relevant studies were retrieved from the databases, duplicate publications were removed, and 34 studies were screened in combination with the aforementioned inclusion and exclusion criteria. The study of TNF-α-308G/A rs1800629 gene polymorphisms and susceptibility to RA included 6,030 cases in the RA group and 6,581 cases in the control group. TNF-α-308G/A rs1800629 gene polymorphisms and the severity of RA included

Table I. Basic characteristics of the included studies and NOS scores.

				Cases				Controls					
First author/year	Country	Ethnicity	Sex	N	Age	Diagnosis	Matching	N	Age	HWE	Healthy	NOS score	(Refs.)
Al-rayes *et al*, 2011	Saudi Arabia	Asia	M&F	106	49.0±12.9	ACR	Age and Sex	126	48.0±11.5	Y	Y	8	(12)
Aranda *et al*, 2014	Argentina	South America	M&F	223	56.0±60.6	ACR	Age and Sex	111	NA	Y	Y	7	(13)
Ates *et al*, 2008	Turkey	Europe	M&F	98	50.8±12.0	ACR	Age and Sex	122	57.0±6.0	Y	Y	8	(14)
Boechat *et al*, 2013	Brazil	South America	M&F	131	48.5±12.4	ACR	Age and Sex	192	49.2±12.1	Y	Y	8	(5)
Brinkman *et al*, 1997	Netherlands	Europe	M&F	283	NA	ACR	Sex	116	NA	Y	Y	7	(15)
Carreón *et al*, 2005	Mexico	North America	M&F	133	NA	ACR	Sex	162	NA	Y	Y	7	(16)
Chen *et al*, 2007	China	Asia	M&F	367	51.8±13.8	ACR	Age and Sex	271	46.2±3.9	Y	Y	8	(17)
Correa *et al*, 2005	Colombia	South America	M&F	165	46.0±12.7	ACR	Age and Sex	430	49.0±15.0	Y	Y	8	(18)
Cuenca *et al*, 2003	Chile	South America	M&F	92	51.1±11.7	ACR	Age and Sex	42	36.3±16.5	Y	Y	8	(19)
Danis *et al*, 1994	Britain	Europe	M&F	34	NA	ARA	Sex	57	NA	Y	Y	7	(20)
Das *et al*, 2019	India	Asia	M&F	126	45.96±12.0	ACR and EULAR	Age and Sex	160	24.63±10.0	Y	Y	8	(21)
Emonts *et al*, 2011	Netherlands	Europe	M&F	375	59.3±13.7	ACR	Age and Sex	461	39.1±8.5	Y	Y	8	(22)
Fugger *et al*, 1989	Denmark	Europe	M&F	24	NA	ARA	Sex	131	NA	Y	Y	7	(23)
Guo *et al*, 2012	China	Asia	M&F	452	47.12±15.36	ACR	Age and Sex	356	47.65±13.25	Y	Y	8	(24)
Hussein *et al*, 2011	Saudi Arabia	Asia	F	172	47.39±9.3	ACR	Age and Sex	160	49.35±8.7	Y	Y	6	(25)
Jahid *et al*, 2017	India	Asia	M&F	187	37.6±9.1	ACR	Age and Sex	214	38.4±10.1	Y	Y	8	(4)
Li *et al*, 2014	China	Asia	M&F	256	50.26±12.86	ACR and EULAR	Age and Sex	331	48.08±13.92	Y	Y	8	(26)
Li *et al*, 2015	China	Asia	M&F	112	49.66±12.02	ACR	Age and Sex	129	47.92±8.27	Y	Y	8	(27)
Lv *et al*, 2011	China	Asia	M&F	98	40.3±4.8	ACR	Age and Sex	100	NA	Y	Y	7	(28)
Manolova *et al*, 2014	Bulgaria	Europe	M&F	108	55.0±11.2	ACR	Age and Sex	177	47.5±14.0	Y	Y	8	(29)
Nemec *et al*, 2008	Czech Republic	Europe	M&F	130	NA	ACR	Sex	150	NA	Y	Y	7	(30)
Pawlik *et al*, 2005	Poland	Europe	M&F	91	51.7±147.4	ACR	Age and Sex	105	48.9±154.5	Y	Y	8	(31)
Pérez *et al*, 2017	Mexico	North America	M&F	80	47.21±13.3	ACR	Age and Sex	80	48.8±9.86	Y	Y	8	(32)
Rezaieyazdi *et al*, 2007	Iran	Asia	M&F	34	47.3±13.8	ACR	Age and Sex	30	NA	Y	Y	7	(33)
Sandoval *et al*, 2017	Mexico	North America	M&F	499	51.0±12.6	ACR-EULAR	Age and Sex	492	50.0±7.8	Y	Y	8	(7)
Shafia *et al*, 2016	India	Asia	M&F	150	NA	ACR	Sex	200	NA	Y	Y	7	(34)
Snezhana *et al*, 2009	Republic of Macedonia	Europe	M&F	84	NA	ACR	Sex	301	NA	Y	Y	7	(35)
Sun *et al*, 2013	China	Asia	M&F	519	54.72±15.27	ACR	Age and Sex	520	54.17±10.50	Y	Y	8	(6)
Vinasco *et al*, 1997	Spain	Europe	M&F	60	NA	ACR	Sex	102	NA	Y	Y	7	(36)
Wang *et al*, 2015	China	Asia	M&F	113	45.0±10.0	ACR	Age and Sex	126	NA	Y	Y	7	(37)

Table I. Continued.

			Cases					Controls					
First author/year	Country	Ethnicity	Sex	N	Age	Diagnosis	Matching	N	Age	HWE	Healthy	NOS score	(Refs.)
Wang *et al*, 2022	China	Asia	M&F	144	51.0±66.7	ACR	Age and Sex	122	42.0±50.2	Y	Y	8	(38)
Yen *et al*, 2013	China	Asia	M&F	97	NA	ACR	Sex	97	NA	Y	Y	7	(39)
You *et al*, 2013	China	Asia	M&F	452	47.08+15.36	ACR-EULAR	Age and Sex	373	47.35+14.37	Y	Y	8	(40)
Zaghlol *et al*, 2018	Egypt	Africa	M&F	35	45.63±13.93	ACR-EULAR	Age and Sex	35	40.51±12.63	Y	Y	8	(41)

M, Male; F, Female; NA, not available; ACR, American College of Rheumatology, ARA, American Rheumatism Association, EULAR, European League Against Rheumatism; HWE, Hardy-Weinberg equilibrium; Y, Yes.

483 cases in the RA group and 545 cases in the control group. The selection process and results of the included studies are demonstrated in Fig. 1.

Basic information included in the literature. The basic characteristics of the included studies and the NOS score results are presented in Table I. The specific sample size, genotype and allele frequency included in the study of TNF-α-308G/A rs1800629 polymorphisms and susceptibility to RA are shown in Table II. Of the studies included in the meta-analysis, 16 were conducted in the Asian population, four in the South American population, 10 in the European population, three in the North American population and one in the African population. The specific sample size, genotype and allele frequency included in the study of TNF-α-308G/A rs1800629 polymorphisms and the severity of RA are presented in Table III. Of the studies included in the meta-analysis, one was conducted in North Americans, three in Asians and two in Europeans.

Results of the meta-analysis

TNF-α-308G/A rs1800629 polymorphisms and susceptibility to RA. A total of 34 studies were included in the present analysis. Significant study heterogeneity was observed in allele, dominant and super-dominant models ($I^2 \geq 50\%$, $P<0.05$); therefore, random-effect models were used for analysis. Other genetic models were less heterogeneous and were also analyzed using random-effect models ($I^2<50\%$, $P>0.05$). No significant association between TNF-α-308G/A rs1800629 gene polymorphisms and susceptibility to RA was observed in the five gene models ($P>0.05$). After subgroup analysis, no clear association was observed among the different geographic regions. Detailed data is listed in Table IV.

TNF-α-308G/A rs1800629 polymorphisms and severity of RA. A total of six studies were included in the meta-analysis. Significant study heterogeneity was observed in allele models, dominant gene models and super-dominant models ($I^2 \geq 50\%$, $P<0.05$); therefore, random-effect models were used for analysis. Recessive and co-dominant models were also analyzed using random-effect models. In the overall calculation, TNF-α-308G/A rs1800629 polymorphisms were not statistically significantly associated with the severity of RA. After subgroup analysis by geographic region, TNF-α-308G/A rs1800629 polymorphisms were significantly associated with RA severity in European populations, GA + AA vs. GG: (OR=0.503, 95% CI: 0.297-0.853 and P=0.011); GG + AA vs. GA: (OR=2.268, 95% CI: 1.434-3.590 and P<0.001). No other models were statistically significant. Forest plots of the dominant gene models and super-dominant models are illustrated in Figs. 2 and 3, and detailed data are revealed in Table V.

Heterogeneity and sensitivity analyses. Heterogeneity between the studies was observed in the current meta-analysis. Subgroup analyses were performed to explore the sources of heterogeneity. For the study of TNF-α-308G/A rs1800629 polymorphism and RA susceptibility, subgroup analysis by geographical region showed no significant statistical significance in the overall and subgroup results of the five gene models. For the study of TNF-α-308G/A rs1800629 polymorphisms and RA severity, the overall results of the five gene models were not statistically significant, but TNF-α-308G/A

Table II. Sample size, genotype and allele frequency in rheumatoid arthritis and control groups in susceptibility studies.

First author/Year	Country	Ethnicity	Number of samples			Genotypes of cases			Alleles of cases		Minor allele frequency	Genotypes of controls			Alleles of controls		Minor allele frequency	(Refs.)
			Cases	Controls	Total	G/G	G/A	A/A	G	A		G/G	G/A	A/A	G	A		
Al-rayes *et al*, 2011	Saudi Arabia	Asia	106	126	232	68	35	3	171	41	0.239766082	63	48	15	174	78	0.448275862	(12)
Aranda *et al*, 2014	Argentina	South America	223	111	334	174	45	4	393	53	0.134860051	86	24	1	196	26	0.132653061	(13)
Ates *et al*, 2008	Turkey	Europe	98	122	220	73	25	0	171	25	0.14619883	101	21	0	223	21	0.094170404	(14)
Boechat *et al*, 2013	Brazil	South America	131	192	323	109	22	0	240	22	0.091666667	159	33	0	351	33	0.094017094	(5)
Brinkman *et al*, 1997	Netherlands	Europe	283	116	399	195	77	11	467	99	0.211991435	66	45	5	177	55	0.310734463	(15)
Carreón *et al*, 2005	Mexico	North America	133	162	295	113	17	3	243	23	0.094650206	148	14	0	310	14	0.04516129	(16)
Chen *et al*, 2007	China	Asia	367	271	638	338	29	0	705	29	0.041134752	232	36	3	500	42	0.084	(17)
Correa *et al*, 2005	Colombia	South America	165	430	595	109	52	4	270	60	0.222222222	338	87	5	763	97	0.127129751	(18)
Cuenca *et al*, 2003	Chile	South America	92	42	134	71	20	1	162	22	0.135802469	38	4	0	80	4	0.05	(19)
Danis *et al*, 1994	Britain	Europe	34	57	91	17	13	4	47	21	0.446808511	44	13	0	101	13	0.128712871	(20)
Das *et al*, 2019	India	Asia	126	160	286	68	58	0	194	58	0.298969072	120	40	0	280	40	0.142857143	(21)
Emonts *et al*, 2011	Netherlands	Europe	375	461	836	248	119	8	615	135	0.219512195	300	147	14	747	175	0.234270415	(22)
Fugger *et al*, 1989	Denmark	Europe	24	131	155	15	6	3	36	12	0.333333333	63	60	8	186	76	0.408602151	(23)
Guo *et al*, 2012	China	Asia	452	356	808	422	30	0	874	30	0.034324943	307	49	0	663	49	0.073906486	(24)
Hussein *et al*, 2011	Saudi Arabia	Asia	172	160	332	134	36	2	304	40	0.131578947	150	10	0	310	10	0.032258065	(25)
Jahid *et al*, 2017	India	Asia	187	214	401	108	69	10	285	89	0.312280702	147	62	5	356	72	0.202247191	(4)
Li *et al*, 2014	China	Asia	256	331	587	246	10	0	502	10	0.019920319	290	40	1	620	42	0.067741935	(26)
Li *et al*, 2015	China	Asia	112	129	241	104	8	0	216	8	0.037037037	104	23	2	231	27	0.116883117	(27)
Lv *et al*, 2011	China	Asia	98	100	198	94	4	0	192	4	0.020833333	86	14	0	186	14	0.075268817	(28)
Manolova *et al*, 2014	Bulgaria	Europe	108	177	285	83	24	1	190	26	0.136842105	135	40	2	310	44	0.141935484	(29)
Nemec *et al*, 2008	Czech Republic	Europe	130	150	280	93	36	1	222	38	0.171171171	121	29	0	271	29	0.10701107	(30)
Pawlik *et al*, 2005	Poland	Europe	91	105	196	74	17	0	165	17	0.103030303	77	25	3	179	31	0.173184358	(31)
Pérez *et al*, 2017	Mexico	North America	80	80	160	66	14	0	146	14	0.095890411	68	12	0	148	12	0.081081081	(32)
Rezaieyazdi *et al*, 2007	Iran	Asia	34	30	64	29	5	0	63	5	0.079365079	29	1	0	59	1	0.016949153	(33)
Sandoval *et al*, 2017	Mexico	North America	499	492	991	457	39	3	953	45	0.047219307	447	43	2	937	47	0.050160085	(7)
Shafia *et al*, 2016	India	Asia	150	200	350	129	21	0	279	21	0.075268817	166	34	0	366	34	0.092896175	(34)
Snezhana *et al*, 2009	Republic of Macedonia	Europe	84	301	385	67	15	2	149	19	0.127516779	231	66	4	528	74	0.140151515	(35)
Sun *et al*, 2013	China	Asia	519	520	1039	456	63	0	975	63	0.064615385	446	70	4	962	78	0.081081081	(6)
Vinasco *et al*, 1997	Spain	Europe	60	102	162	43	14	3	100	20	0.2	84	16	2	184	20	0.108695652	(36)
Wang *et al*, 2015	China	Asia	113	126	239	90	23	0	203	23	0.113300493	104	22	0	230	22	0.095652174	(37)

Table II. Continued.

First author/Year	Country	Ethnicity	Number of samples			Genotypes of cases			Alleles of cases		Minor allele frequency	Genotypes of controls			Alleles of controls		Minor allele frequency	(Refs.)
			Cases	Controls	Total	G/G	G/A	A/A	G	A		G/G	G/A	A/A	G	A		
Wang *et al*, 2022	China	Asia	144	122	266	135	9	0	279	9	0.032258065	114	8	0	236	8	0.033898305	(38)
Yen *et al*, 2013	China	Asia	97	97	194	94	3	0	191	3	0.015706806	72	23	2	167	27	0.161676647	(39)
You *et al*, 2013	China	Asia	452	373	825	422	30	0	874	30	0.034324943	323	50	0	696	50	0.07183908	(40)
Zaghlol 2018	Egypt	Africa	35	35	70	30	3	2	63	7	0.111111111	19	16	0	54	16	0.296296296	(41)

Table III. Sample size, genotype and allele frequency in RA and control groups in the severity study.

First author/Year	Country	Ethnicity	Number of samples			Genotypes of Severe RA			Alleles of Severe RA		Minor allele frequency	Genotypes of non-severe RA			Alleles of non-severe RA		Minor allele frequency	(Refs.)
			Severe RA	Non-severe RA	Total	G/G	G/A	A/A	G	A		G/G	G/A	A/A	G	A		
Carreón *et al*, 2005	Mexico	North America	46	87	133	35	8	3	78	14	0.179487179	78	9	0	165	9	0.054545455	(16)
Das *et al*, 2019	India	Asia	112	14	126	59	53	0	171	53	0.30994152	9	5	0	23	5	0.217391304	(21)
Emonts *et al*, 2011	Netherlands	Europe	120	250	370	89	26	5	204	36	0.176470588	156	91	3	403	97	0.240694789	(22)
Hussein *et al*, 2011	Saudi Arabia	Asia	60	112	172	52	8	0	112	8	0.071428571	82	28	2	192	32	0.166666667	(25)
Lv *et al*, 2011	China	Asia	31	67	98	30	1	0	61	1	0.016393443	64	3	0	131	3	0.022900763	(28)
Nemec *et al*, 2008	Czech Republic	Europe	114	15	129	85	28	1	198	30	0.151515152	7	8	0	22	8	0.363636364	(30)

RA, rheumatoid arthritis.

Table IV. Summary of associations between TNF-α-308G/A rs1800629 gene polymorphisms and rheumatoid arthritis.

			Test of association		Tests for heterogeneity		Egger's test
Genetic model	Population	Number of studies	OR (95% CI)	P-value	P_h	I^2 (%)	P_E
A vs. G	Overall	34	0.937 (0.762-1.152)	0.539	<0.001	79.1	0.769
	Asia	16	0.720 (0.494-1.050)	0.088	<0.001	85.2	
	South America	4	1.357 (0.916-2.010)	0.128	0.107	50.8	
	Europe	10	1.100 (0.837-1.447)	0.494	0.002	65.0	
	North America	3	1.261 (0.770-2.064)	0.357	0.148	47.6	
	Africa	1	0.375 (0.144-0.979)	0.045	-	-	
GA + AA vs. GG	Overall	34	0.918 (0.733-1.148)	0.452	<0.001	78.7	0.695
	Asia	16	0.731 (0.490-1.091)	0.125	<0.001	85.0	
	South America	4	1.383 (0.881-2.171)	0.159	0.078	56.0	
	Europe	10	1.060 (0.786-1.430)	0.704	0.005	62.2	
	North America	3	1.174 (0.762-1.809)	0.466	0.249	28.0	
	Africa	1	0.198 (0.062-0.629)	0.006	-	-	
AA vs. GG + GA	Overall	34	1.131 (0.709-1.802)	0.605	0.132	25.4	0.849
	Asia	16	0.457 (0.148-1.413)	0.174	0.054	49.5	
	South America	4	1.993 (0.682-5.823)	0.207	0.973	0.0	
	Europe	10	1.198 (0.686-2.092)	0.526	0.364	8.5	
	North America	3	2.379 (0.512-11.044)	0.269	0.317	0.1	
	Africa	1	5.299 (0.245-114.465)	0.288	-	-	
AA vs. GG	Overall	34	1.097 (0.664-1.813)	0.718	0.062	33.3	0.853
	Asia	16	0.426 (0.123-1.473)	0.178	0.020	57.8	
	South America	4	2.241 (0.765-6.568)	0.141	0.964	0.0	
	Europe	10	1.148 (0.628-2.098)	0.654	0.299	16.1	
	North America	3	2.458 (0.489-12.357)	0.275	0.301	6.4	
	Africa	1	3.197 (0.146-70.190)	0.461	-	-	
GG + AA vs. GA	Overall	34	1.108 (0.894-1.373)	0.348	<0.001	75.7	0.467
	Asia	16	1.314 (0.898-1.923)	0.159	<0.001	83.1	
	South America	4	0.750 (0.482-1.167)	0.202	0.094	53.1	
	Europe	10	0.997 (0.759-1.310)	0.982	0.027	52.1	
	North America	3	0.946 (0.666-1.345)	0.758	0.431	0.0	
	Africa	1	8.982 (2.311-34.910)	0.002	-	-	

OR, odds ratio; CI, confidence interval.

rs1800629 polymorphisms were observed to be significantly associated with the severity of RA in the European population after subgroup analysis; therefore, geographical regions may be the source of heterogeneity in TNF-α-308G/A rs1800629 polymorphisms and RA severity studies. In both studies, sensitivity analyses were performed using the two methods. First, a sensitivity analysis was conducted by eliminating them individually. The results showed no significant change in the OR or 95% CI values for the overall outcome after the sequential removal of each study. Second, Stata 17.0 software performed a sensitivity analysis of the results of the meta-analysis. The results revealed that none of the 34 studies on RA susceptibility affected the stability of the results (Fig. 4). Similarly, none of the six studies on the severity of RA affected the stability of the results (Fig. 5). The results of sensitivity analysis indicated that the present meta-analysis was reliable.

Analysis of publication bias. In the study of TNF-α-308G/A rs1800629 polymorphisms and susceptibility to RA, the funnel plot method was used to test for publication bias. A publication bias funnel plot, which is visually asymmetric, is illustrated in Fig. 6, and there may be bias. After the Egger method test, P>0.05 in all genetic models indicated that there was no publication bias in the present study, and the detailed data are presented in Table IV. For the study of TNF-α-308G/A rs1800629 polymorphisms and RA severity, no publication bias funnel was used for publication bias because the number of studies was <10. Publication bias was assessed using Egger's test. According to the results of the Egger test, P>0.05 in all genetic models indicated that there was no publication bias in the present study. Detailed data is listed in Table V.

Positive result confidence test. Based on the OR value and 95% CI of the aforementioned results, the false-positive

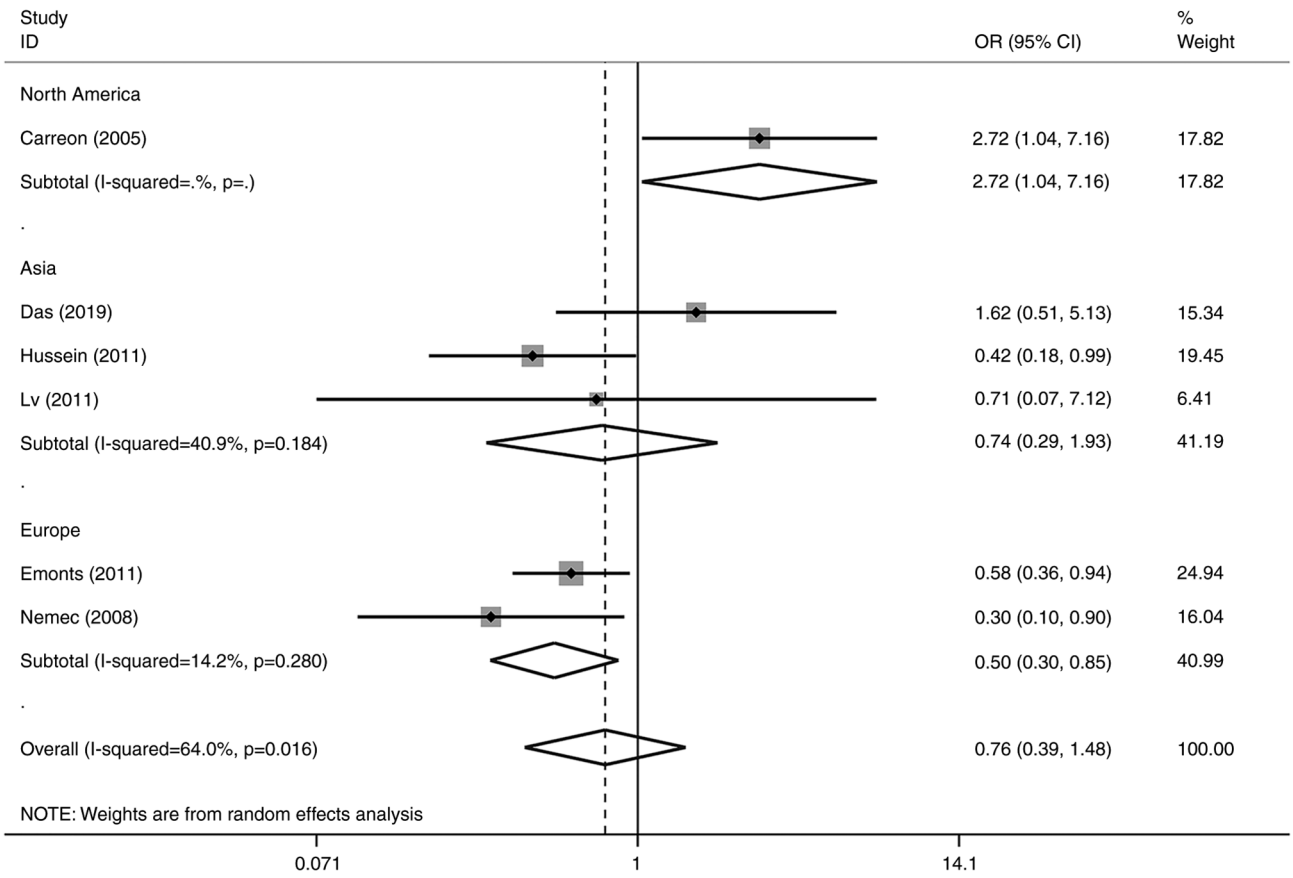

Figure 2. The forest plots of dominant gene models in TNF-α-308G/A rs1800629 polymorphisms and severity of rheumatoid arthritis. OR, odds ratio; CI, confidence interval.

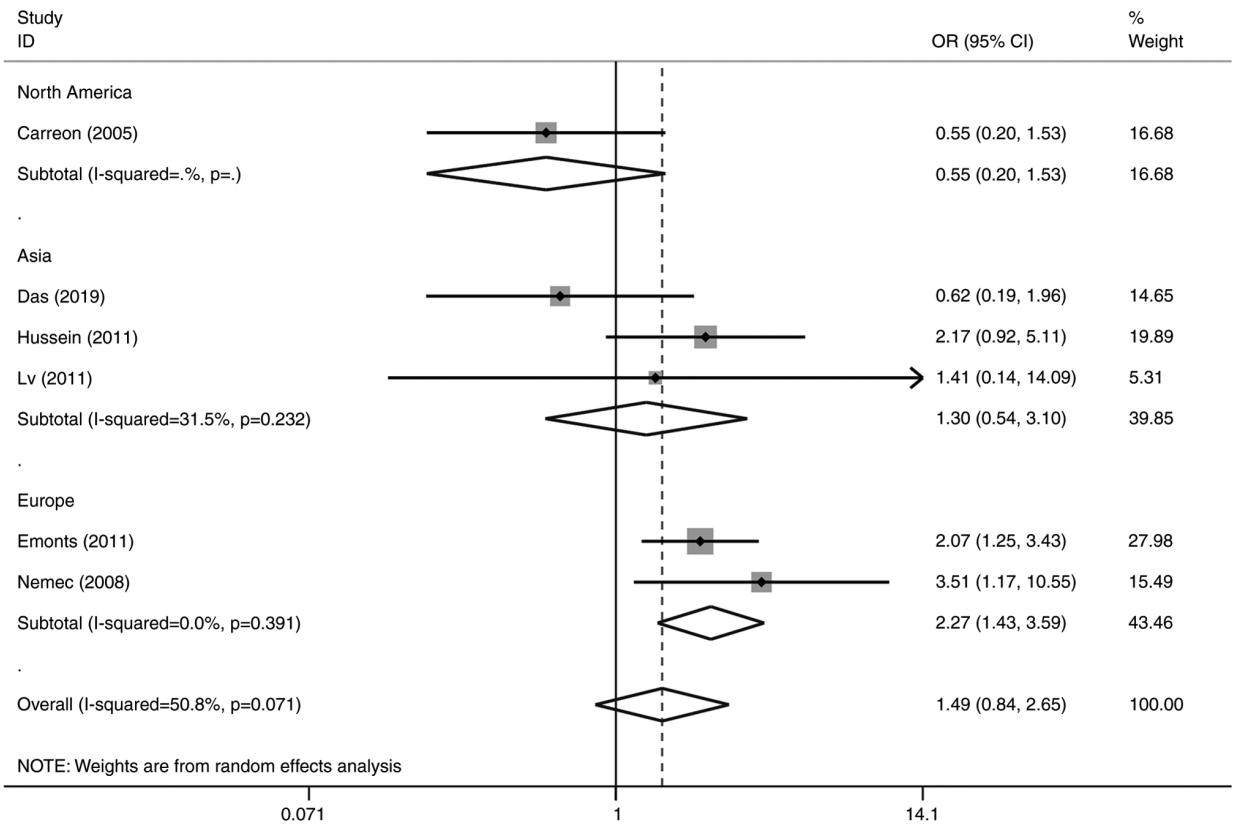

Figure 3. The forest plots of super-dominant gene models in TNF-α-308G/A rs1800629 polymorphisms and severity of rheumatoid arthritis. OR, odds ratio; CI, confidence interval.

Table V. Summary of associations between TNF-α-308G/A rs1800629 gene polymorphisms and rheumatoid arthritis.

			Test of association		Tests for heterogeneity		Egger's test
Genetic model	Population	Number of studies	OR (95% CI)	P-value	P_h	I^2 (%)	P_E
A vs. G	Overall	6	0.870 (0.464-1.629)	0.663	0.008	68.1	0.756
	North America	1	3.291 (1.365-7.930)	0.008	-	-	
	Asia	3	0.730 (0.307-1.737)	0.477	0.192	39.4	
	Europe	2	0.638 (0.396-1.029)	0.066	0.261	20.8	
GA + AA vs. GG	Overall	6	0.764 (0.394-1.482)	0.426	0.016	64.0	0.640
	North America	1	2.724 (1.036-7.164)	0.042	-	-	
	Asia	3	0.745 (0.288-1.928)	0.543	0.184	40.9	
	Europe	2	0.503 (0.297-0.853)	0.011	0.280	14.4	
AA vs. GG + GA	Overall	6	2.129 (0.483-9.386)	0.318	0.237	29.3	0.557
	North America	1	14.080 (0.711-278.718)	0.083	-	-	
	Asia	3	0.365 (0.017-7.733)	0.518	-	-	
	Europe	2	2.009 (0.307-13.144)	0.467	0.232	30.1	
AA vs. GG	Overall	6	1.721 (0.336-8.825)	0.515	0.177	39.1	0.601
	North America	1	15.479 (0.779-307.680)	0.072	-	-	
	Asia	3	0.314 (0.015-6.676)	0.458	-	-	
	Europe	2	1.402 (0.160-12.305)	0.760	0.189	42.0	
GG + AA vs. GA	Overall	6	1.490 (0.838-2.651)	0.174	0.071	50.8	0.472
	North America	1	0.548 (0.196-1.533)	0.252	-	-	
	Asia	3	1.300 (0.545-3.103)	0.554	0.232	31.5	
	Europe	2	2.268 (1.434-3.590)	<0.001	0.391	0	

OR, odds ratio; CI, confidence interval.

report probability (FPRP) values of the dominant and super-dominant models were calculated under a series of prior probability conditions, and the results are shown in Table VI. An FPRP value of <0.2 was used as the standard to judge the reliability of the correlation (42). Confidence assessment determined that the statistically significant association in this meta-analysis was reliable for TNF-α-308G/A rs1800629.

Discussion

RA is a typical chronic inflammatory disease, and genetic factors are extremely important in the pathogenesis of RA. Individuals with predisposing genes are exposed to specific environments that cause immune regulation in the body, thereby triggering the entire inflammatory process. During this process, the oxidative stress that occurs in the body accelerates the inflammatory process, aggravates immune system disorders and promotes the occurrence of diseases (43). In addition, RA is a heterogeneous disease, and genetic and environmental factors influence its incidence in different ethnic groups. According to the current results, genetic heterogeneity is manifested by different susceptibility gene loci in different races, and even if individual sites are the same, allele frequency and genetic contribution are different (44).

The TNF-α gene, located in a highly polymorphic region, human chromosome 6 short arm 6p21.3, is a pro-inflammatory cytokine produced primarily by macrophages and monocytes and is involved in normal inflammatory and immune responses (45). TNF-α has two different receptors (TNFR1 and TNFR2). TNF-α binds to cell surface TNFR1 and TNFR2, respectively, to regulate apoptosis, proliferation and differentiation. Most cell surfaces express TNFR1; however, TNFR2 expression is limited to immune cells (46). TNF-α has numerous biological effects, such as activation, proliferative and differentiation of immune cells; inducing apoptosis in certain non-tumor cells and most tumor cells; playing an important role in antitumor, immune defense and inflammatory response; and is an important biological mediator for maintaining the immune balance of the body (47). TNF can be detected in the synovial fluid of patients with RA; therefore, it is important to investigate whether there is an association between TNF-α-308G/A rs1800629 gene polymorphisms and RA susceptibility and severity. The results of Jahid *et al* (4) demonstrated that TNF-α-308G/A rs1800629 was strongly associated with the onset of RA in the Indian population. Li *et al* (26) showed that TNF-α-308G/A rs1800629 gene polymorphisms were significantly associated with the occurrence of RA in the Han Chinese population. By contrast, the results of Sun *et al* (6) demonstrated that TNF-α-308G/A rs1800629 gene polymorphisms are not associated with the pathogenesis of RA. In addition, Boechat *et al* (5) reported through a controlled study of 131 patients with RA and 192 healthy volunteers that TNF-α-308G/A rs1800629 gene

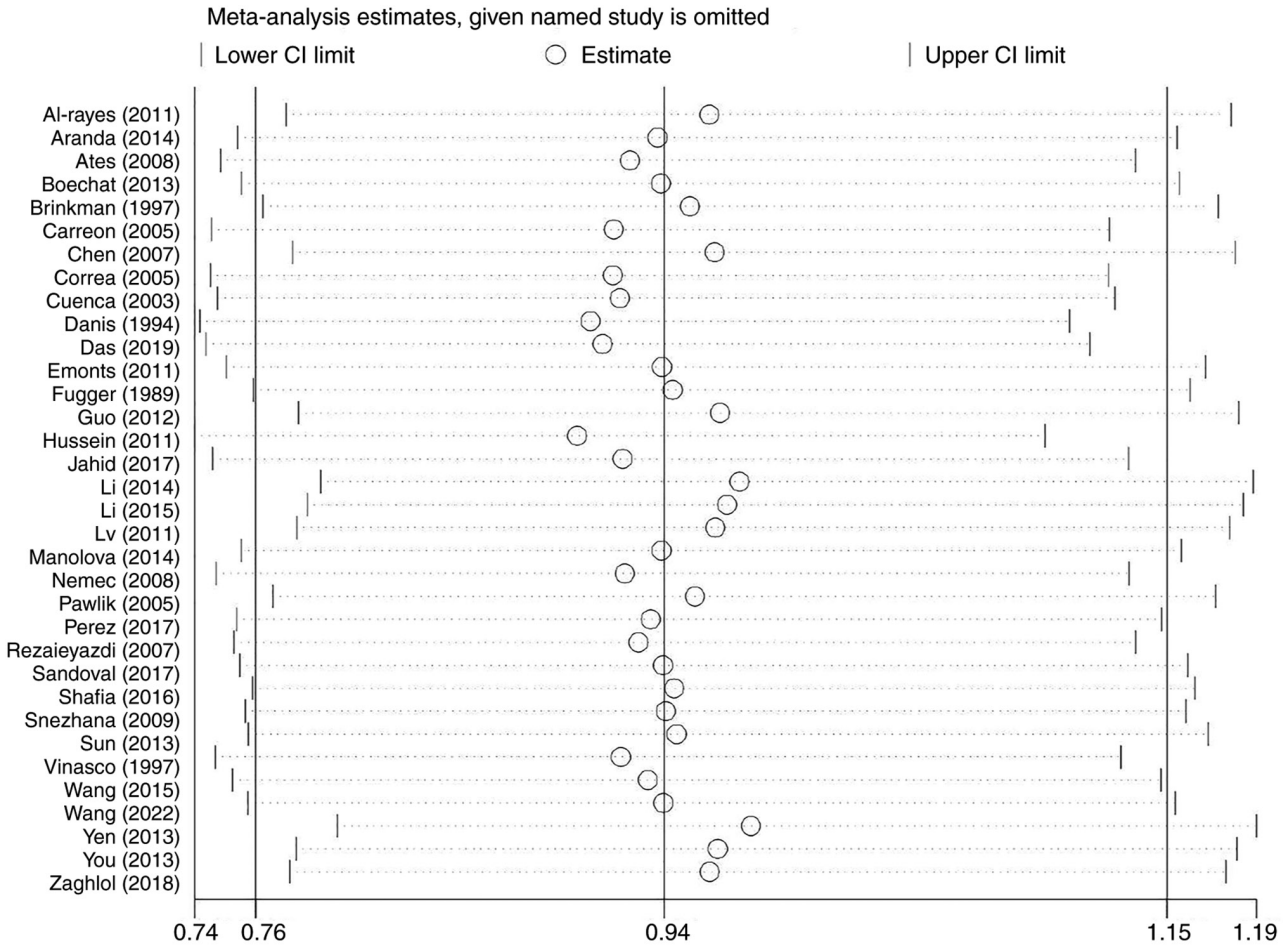

Figure 4. Sensitivity analysis of TNF-α-308G/A rs1800629 gene polymorphisms and rheumatoid arthritis susceptibility. CI, confidence interval.

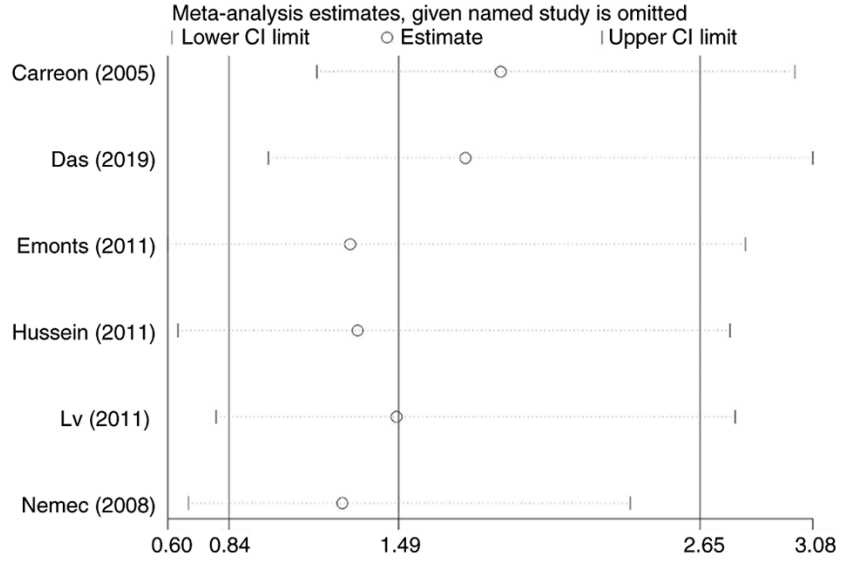

Figure 5. Sensitivity analysis of TNF-α-308G/A rs1800629 gene polymorphisms and rheumatoid arthritis severity. CI, confidence interval.

polymorphisms in the Brazilian population were not associated with the occurrence of RA but were related to the severity of the disease. Nemec *et al* (30) reported that patients with RA and the GG genotype of the promoter polymorphism of the TNF-α-308G/A rs1800629 had a more severe disease course. In addition, they observed that the G allele of the TNF-α-308G/A rs1800629 promoter polymorphism in this cohort was associated with decreased functional ability in patients with RA. In a previous meta-analysis, Song *et al* (48) included 19 studies suggesting that TNF-α-308G/A rs1800629

Table VI. False-positive report probability values for meta-analysis results.

Positive result	Subgroup	Genetic model	OR (95% CI)	I^2 (%)	P-value	Power	Prior probability				
							0.25	0.1	0.01	0.001	0.0001
TNF-α-308G/A rs1800629 and RA severity	Europe	GA + AA vs. GG	0.503 (0.297-0.853)	14.4	0.011	0.148	0.179[a]	0.396	0.878	0.986	0.999
	Europe	GG + AA vs. GA	2.268 (1.434-3.590)	0	<0.001	0.039	0.035[a]	0.099[a]	0.547	0.924	0.992

[a]indicates statistically significant values. OR, odds ratio; CI, confidence interval; RA, rheumatoid arthritis.

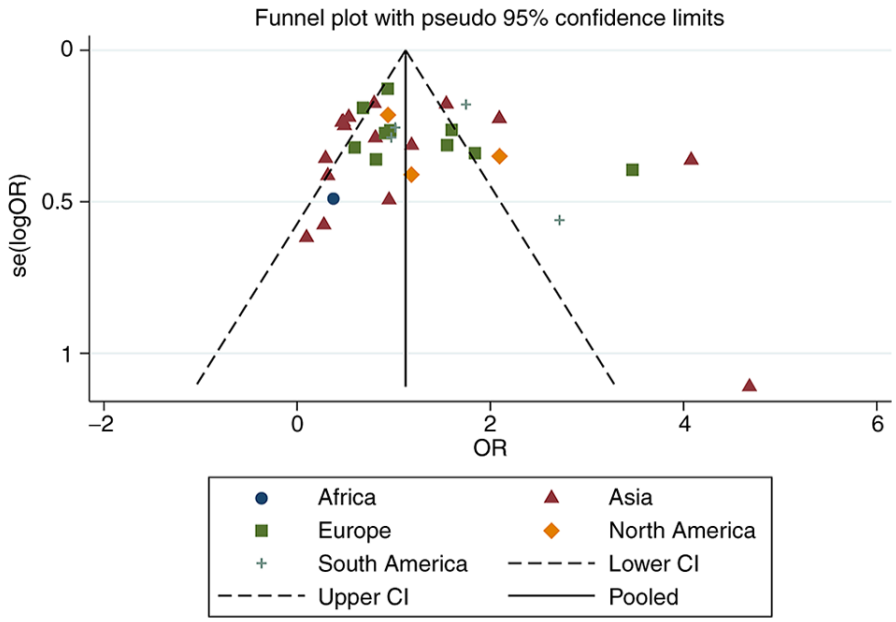

Figure 6. Publication bias funnel plot for TNF-α-308G/A rs1800629 gene polymorphisms and rheumatoid arthritis susceptibility. CI, confidence interval; OR, odds ratio.

gene polymorphisms are associated with susceptibility to RA. This meta-analysis excluded the literature that the genotype frequency of the control group did not conform to HWE, included a total of 34 relevant literature, analyzed by five gene models, and finally reported that TNF-α-308G/A rs1800629 gene polymorphisms were associated with the severity of RA in the European population in the dominant model and the super-dominant model, and the results were reliable after FPRP testing.

The present meta-analysis had certain limitations. First, the current study included 34 articles, but the sample size of certain single nucleotide polymorphism analyses was small, and most of them were single-center studies. More high-quality, multicenter and large-sample studies are required for further analysis and verification. Second, a few studies did not provide long-term follow-up data, making it difficult to assess the durability and stability of the results. Thirdly, in the subgroup analyses, the sample sizes were insufficient for a few ethnic groups, resulting in a slight lack of diversity in the results. Fourth, only the relationship between TNF-α-308G/A rs1800629 gene polymorphisms and the susceptibility and severity of RA was studied, and further research on other related genes is necessary to fully elucidate the pathogenesis of RA. Fifth, meta-analysis is a descriptive secondary analysis that builds on existing research; therefore, the heterogeneity of the selected literature, study design of variables, different judgment criteria and statistical methods may affect the results of the meta-analysis.

In summary, it was observed that TNF-α-308G/A rs1800629 gene polymorphisms were not associated with susceptibility to RA. However, TNF-α-308G/A rs1800629 gene polymorphisms were significantly associated with the severity of RA in the European population, and FPRP testing suggested reliable results.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

YLW and XYL participated in the design of the present study, and both performed statistical analyses. LL and SFL conducted the study and collected important background information. PFH and XDL drafted the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

All procedures involving human participants performed in the present study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent was not required.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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