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THE ASSOCIATION BETWEEN TNFα POLYMORPHISMS AND SUSCEPTIBILITY TO RHEUMATOID ARTHRITIS: A META-ANALYSIS

Rheumatology

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ABSTRACT

Objective: The goal of this study was to investigate whether the tumor necrosis factor- α (TNF- α) -308 G/A and -238 G/A promoter polymorphisms are associated with the risk of developing Rheumatoid arthritis (RA).

Methods: The authors conducted a comparative meta-analysis, incorporating 3131 RA patients and 3490 healthy controls from a total of 18 studies consisting of 29 separate comparisons. The tests were performed by the using fixed or random effects models.

Results: A positive association was found between TNFα-308G/A polymorphism (OR =0.845, 95%CI =0.752-0.949, P = 0.005) and TNFα -238 G/A polymorphism and RA risk by meta-analysis (OR = 0.744, 95% CI = 0.602- 0.920, P = 0.006) in the overall population. On stratification by ethnicity a significant association was found between TNFα-308G/A polymorphism and RA risk in Latin American (OR=1.578, 95%CI=1.073 - 2.320, P=0.020) and Asian (OR=0.644, 95%CI=0.501-0.828,P= 0.001) and for TNFα -238 G/A in Europeans (OR=0.595, 95%CI=0.435-0.815, P=0.001) and Latin Americans (OR=0.493, 95%CI=0.245-0.992, P=0.047).

Conclusion: Meta-analysis of available data revealed that the TNFα-308G/A polymorphisms is a susceptibility factor for developing RA in Latin Americans and Asians but not in Europeans and TNFα-238 polymorphism is susceptibility factor for RA in Latin Americans and Europeans but not in Asian population.

KEYWORDS

Meta-analysis, Rheumatoid arthritis, TNFα

Introduction:

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic inflammation of the synovial joints, hyperplasia and overgrowth of synoviocytes, with ensuing destruction of articular cartilage [1,2]. RA is associated with progressive disability, systemic complications, premature mortality, and socioeconomic costs [3]. It affects approximately 1 per cent of world population including India [4, 5]. RA is a complex multi-factorial disease in which multiple genetic and environmental factors modulate disease occurrence and severity [6]. The main genetic factor for RA is HLA-DRB1 alleles, but the HLA genes account only for an estimated 37% of the total genetic risk in RA [7]. Other than that for the shared epitope alleles at the HLA locus, non- HLA genes have also been implicated in disease susceptibility e.g., *PTPN22, TNFAIP3, STAT4, TRAF1/C5, IL2RB, AFF3, CD40, CTLA4, MMEL1, PADI4* [8,9].

Apart from the *HLA-DRB1* alleles, another genetic factor within the MHC region that is an attractive candidate for additional susceptibility and progression for RA is tumor necrosis factor α *(TNFα)*. *TNFα* has been suggested to be the central mediator of joint inflammation and destruction in RA [10]. Studies have revealed that *TNFα* has a pivotal role to play in the pathophysiology of RA by mediating a broad range of proinflammatory and immunostimulatory activities [11]. Increased levels of TNFα are found in the synovial fluid and synovial tissue of RA patients [12]. Studies have also indicated that the persistent expression of *TNFα* alone may be sufficient to induce chronic arthritis in a transgenic mouse model that resembles human RA [13]. Furthermore, the treatment of RA patients with anti-TNFα monoclonal antibodies in two placebo controlled double blind trials has proven to be significantly beneficial [14,15]. Within the *TNFα* gene there are several high degree sequence variations and these may be important for the susceptibility to RA. Studies have indicated that the polymorphisms in the *TNFα* promoter gene may modulate the magnitude of the secretory response of this cytokine and thereby affect the disease susceptibility and severity [16,17,18]. These polymorphisms mediate their influence on transcription by modifying the binding site of specific transcription factors [19,20]. Several polymorphisms have been found in the *TNFα* gene promoter, including *-308* and *-238* positions , in both cases, a guanine *(G)* is substituted by an adenine *(A)*[21]. Many studies have reported an association of these two genetic polymorphisms with susceptibility to RA, albeit with contradictory conclusions for different populations [22-39] **See Table 1**. These result discrepancies may be due to small sample sizes, low statistical power, or clinical heterogeneity. In the present study, we adopted a meta-analysis approach to overcome the limitations of individual studies and resolve these disparities and to draw a more definitive conclusion on the role of the *TNFα* promoter -*308G/A* and *-238G/A* polymorphisms as a risk factor for the development of RA.

Methods:

Identification of eligible studies and data extraction:

We performed a search for studies that examined associations between *TNFα* promoter *–308G/A* and *– 238G/A* polymorphisms and RA. A literature search was conducted manually and on Google Scholar and PubMed database (up to May 31, 2017) using the following key words 'rheumatoid arthritis' and '*TNFα–308G/A* and *–238 G/A* polymorphism'. Language of origin was not restricted. Studies were included in the analysis if; (1) they were case-control and cohort studies, (2) they contained original data, (3) they provided enough data to calculate odds ratios (ORs). The following information was extracted from each study; first author, year of publication, racial makeup of the study population, numbers of cases and controls, and genotypic frequency information for *TNF- α* polymorphisms. The compliance of the study with the MOOSE checklist was also checked [40].

Evaluation of publication bias

Funnel plots are used to detect publication bias, but they require a range of studies of varying sizes and subjective judgements, and thus, we evaluated publication bias using Egger's linear regression test [41], which measures funnel plot asymmetry on a natural logarithm scale of Ors.

Evaluation of statistical associations

Because of the low frequency of the *A/A* genotypes of the 2 *TNF-α*

promoter polymorphisms, the overall estimate of risk of *TNF-α G/A + A/A* was calculated. We performed the meta-analyses on the *TNF-α G/A + A/A* versus *TNF-α G/G* genotypes and investigated the risk. Point estimates of risk, ORs, and their 95% confidence intervals (CIs) were estimated for each study. We assessed within- and between-study variations or heterogeneity using Cochran's Q-statistic [42]. This heterogeneity test assesses the null hypothesis that all the studies are evaluating the same effect. We also quantified the effect of heterogeneity by using $I2 = 100\% \times (Q - df)/Q$ [43]. I^2 ranges between 0 and 100% and represents the proportion of between-study variability that can be attributed to heterogeneity rather than chance. I^2 values of 25, 50, and 75% were defined as low, moderate, and high estimates, respectively. Fixed effects assumes that genetic factors have similar effects on RA susceptibility across all investigated studies, and that observed variations between studies are caused by chance alone [44]. The random effects model assumes that different studies show substantial diversity and assesses both within-study sampling errors and between-study variances [45]. If study groups show no heterogeneity, the fixed and random effects models produce similar results, and if not the random effects model usually produces wider CIs than the fixed effects model. The random effects model is used when between-study heterogeneity is evident [44]. Statistical manipulations were undertaken using a comprehensive meta-analysis computer program (Biosta, Englewood, NJ, USA).

Results:

Studies included in the meta-analysis:

Electronic and manual searches resulted in the identification of 18 studies that met the study inclusion criteria [22-39]. Five polymorphic studies were excluded because they were not case control studies. Three polymorphic studies were with respect to radiographic progression [46-48] while one study was with respect to drug response [49]. One of the eligible study contained information on two different ethnic groups [27] and nine of the eligible studies contained data on both *TNFα-308G/A* and *-238 G/A* polymorphisms [22,23,26-28,30,32,36,39] .These groups were treated independently, and hence a total of 29 separate comparisons were available for analysis. The study was in compliance with the MOOSE checklist (Provided as Annexure 1). The meta-analysis included 3131 RA cases and 3490 healthy controls.

Meta-analysis of the *TNFα–308G/A* polymorphism and rheumatoid arthritis susceptibility:

Meta-analysis identified a significant association between RA and *TNFα–308G/A* polymorphism in the overall population (OR =0.845, 95%CI =0.752-0.949, P = 0.005 **(Table 2, Fig. 1)**. However, on stratification by ethnicity a significant association was found between *TNFα–308G/A* polymorphism and the risk of developing RA in Latin American (OR=1.578, 95%CI=1.073 - 2.320, P=0.020) and Asian (OR=0.644, 95%CI=0.501-0.828) populations but not in European populations.

Meta-analysis of the *TNFα –238 G/A* polymorphism and rheumatoid arthritis susceptibility:

A significant association was also found between RA susceptibility and *TNFα –238 G/A* polymorphism by meta-analysis (OR = 0.744, 95% CI = 0.602-0.920, P = 0.006). Furthermore, stratification by ethnicity revealed a significant association between this polymorphism and RA in Europeans (OR=0.595, 95%CI=0.435-0.815, P=0.001) and Latin Americans (OR=0.493, 95%CI=0.245-0.992, P=0.047), but not in Asian populations **(Table 2, Fig. 2)**.

Heterogeneity and publication bias:

Some between-study heterogeneity was found during the meta-analyses, but no evidence of heterogeneity was found for analyses of *TNFα-308* polymorphism in European populations and *TNFα – 238* polymorphism in the Asian population **(Table 2).** It was difficult to correlate the funnel plot, which is usually used to detect publication bias, as the number of studies included in the analysis was small. Egger's regression test showed no evidence of publication bias in this meta-analysis of TNFα polymorphisms in all groups (Egger's regression test P-values > 0.1).

Discussion:

Several studies suggest that variability in the promoter of TNFα gene region caused by a single nucleotide polymorphism at positions *-308* and *-238* may result in increased transcription of the gene and high TNFα levels [16-20]. The difference in the levels of TNFα caused by these SNPs among different individuals can be a possible explanation for differences in susceptibility and severity to RA.

Many studies investigating the relationship between the *TNFα -308G/A* and *-238G/A* promoter polymorphism and risk of RA report varying results. Therefore, a meta-analysis offers a good alternative for evaluating the presence or absence of an association in situations where individual studies are inconclusive. Meta-analysis allows us to maximize the sample size, increase statistical power and provide more robust findings. The meta-analysis presented here is the largest to have investigated the effects of *TNFα -308G/A* and *-238G/A* promoter polymorphism on the overall risk of developing RA. Although the result of the meta-analysis is inconsistent with the results of our primary study [38], it is important to mention that there was significant heterogeneity in the studies included in the meta-analysis ($I2 = 87.3\%$ & 61.1% for *TNFα -308G/A* and *-238G/A* respectively). This could be caused by the differences in study design, mean duration of RA, sample size or ethnicity.

In our meta-analysis that includes 3131 RA cases and 3490 healthy controls, a significant association was found between *TNFα -308G/A* and *-238G/A* promoter polymorphism and the risk of developing RA in the overall populations worldwide. However, study stratification by ethnicity revealed a significant association between *TNFα–308G/A* polymorphism and the risk of developing RA only in Latin Americans and Asians but not in Europeans. The *TNFα -238G/A* polymorphism was found to be significantly associated with the risk of developing RA in Latin Americans and Europeans but not in Asians. In this context, we considered that the genetic background is important in interpopulation genetic variability of the *TNFα*-308 and *TNFα*-238 polymorphisms. Moreover, the lack of significant correlation of the polymorphism with the risk of disease in some populations cannot be regarded as an absence of TNFα associations with RA but it may reflect heterogeneity in the genetic susceptibility to this disorder. Also, the lack of association of polymorphism cannot annul the role of the SNP on the transcription regulation and its subsequent effect on the various clinical and laboratory parameters and the treatment response to the biologics in individual patients. In a meta-analysis by Young Ho Lee *et al*, an association between treatment responses to infliximab, a TNF-α blocker and the *TNF-α –238 A/G* polymorphism has been revealed [50]. Another meta-analysis by Erik JM Toonen *et al* has indicated an association of *TNFA -308G/A* promoter polymorphism with joint damage in patients with RA [49]. These results suggest that even though the polymorphisms in the TNF promoter region may not confer risk of developing RA in all the populations but the presence of the risk alleles in a particular patient may contribute to the disease severity and altered response to the biological agents.

The present study has some limitations that require consideration. First, our study could suffer from publication bias because of the small number of studies, especially in the subgroup analysis. Second, heterogeneity and confounding factors may have affected the meta-analysis. Third, analysis of data stratified by gender, shared epitope (SE), radiographic erosions and disease severity (as measured by DAS 28 score), would have provided more information, but this information was not available from all the studies examined. Fourth, it is unclear whether the *TNF-α -308G/A* and *-238 G/A* polymorphisms alone or in combination with other polymorphisms or genes are responsible for susceptibility to RA. Fifth, regarding *TNFα -238G/A* polymorphism most of the studies were performed in populations of Asian descent, and only a handful of studies were conducted in European and Latin American populations. Thus, further studies are needed in other ethnic populations. Sixth, the possibility that TNFα haplotypes contributing to the development of RA also needs to be examined by meta-analysis. In the present study, we could not conduct meta-analysis on TNFα susceptibility haplotypes due to limited data available**Conclusion:** In conclusion, this meta-analysis of published data finds that the *TNFα-308G/A* polymorphisms is a susceptibility factor for developing RA in Latin Americans and Asians but not in Europeans. Also, our meta-analysis shows that and *TNFα-238* polymorphism is susceptibility factor for RA in Latin Americans and Europeans but not in Asians.

Disclosure of interest

All the authors declare no conflict of interest regarding this article.

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Table 1. Characteristics of individual studies included in the meta-analysis.

Study[Ref]	Country(Ethnicity)	No of Cases	No of Controls
Brinkman *et al* 1997 [22]	Netherland(E)	144	116
Yen JH *et al* 2001 [23]	Taiwan(A)	97	97
Cvetkovic TJ *et al* 2002[24]	Swedish(E)	154	324
J Cuenca *et al* 2003 [25]	Chilean(LA)	92	42
Rodriguez C *et al* 2005 [26]	Mexican(LA)	133	162
Leyla Kazkaz-1 *et al* 2007 [27]	Syria(A)	156	120
Leyla Kazkaz-2 *et al* 2007[27]	France(E)	512	471
Ruiwen Chen *et al* 2007 [28]	Chinese(A)	367	271
Rezaieyazdi Z *et al* 2007[29]	Iran(A)	34	30
Ates O *et al* 2008 [30]	Turkish(A)	98	122
Nemec P *et al* 2008 [31]	Czech(E)	130	150
Oregon Romero *et al* 2008 [32]	Mexico(LA)	50	100
Fakhfakh Karray *et al* 2011 [33]	Tunisia(M)	108	226
Mosaad YM *et al* 2011 [34]	Egypt(M)	122	120
Al-Rayes H *et al* 2011[35]	Saudi(A)	106	126
Mariek Emonths et al 2011[36]	Netherland(E)	375	461
Hussein YM *et al* 2011[37]	Egyptian(M)	172	160
Antonio Luiz *et al* 2013[38]	Brazilian(LA)	131	192
Syed Shafia *et al* 2013[39]	Kashmiri(A)	150	200
	Total	**3131**	**3490**
M=Mixed , A=Asian, LA=Latin American, E=European			

Table2: Results of meta-analysis on the associations between TNFα polymorphisms and Rheumatoid arthritis.

SNP	Population	No of Studies	Number		Test of association			Test of Heterogeneity		
			Patients	Controls	OR	95%CI	PValue	Model	PValue	I2
TNFα	Overall	19	3131	3490	0.845	0.752-0.949	0.005	R	0.000	87.3%
-	European	5	1315	1522	1.001	0.851-1.177	0.990	F	0.438	0.0%
308G/	LA	4	406	496	1.578	1.073-2.320	0.020	R	0.167	40.8%
A	Asian	7	1008	966	0.644	0.501-0.828	0.001	R	0.001	73.1%
	Mixed	3	402	506	0.505	0.380-0.672	0.000	R	0.000	97.7%
TNFα	Overall	10	2079	2081	0.744	0.602-0.920	0.006	R	0.006	61.1%
-	European	3	1031	1002	0.595	0.435-0.815	0.001	R	0.009	78.7%
238G/	LA	2	180	269	0.493	0.245-0.992	0.047	R	0.015	83.0%
A	Asian	5	868	810	1.049	0.758-1.453	0.772	F	0.824	0.0%
F: fixed effects model; R: random effects model: LA: Latin Americans										

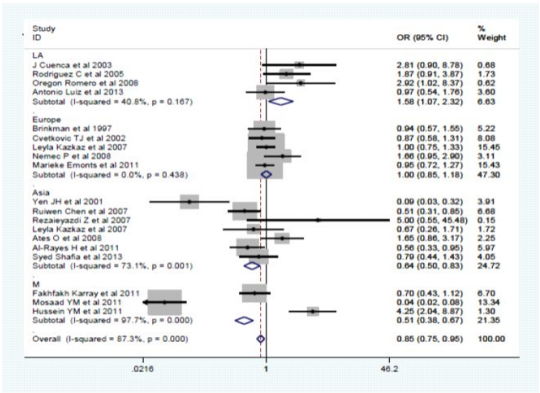

Figure 1. Odds ratios and 95% CIs of individual studies and pooled data for the *G/A+A/A* vs *GG* genotypes of the *TNFα -308* polymorphism for susceptibility to RA(LA=Latin American, M= Mixed ethnicity)

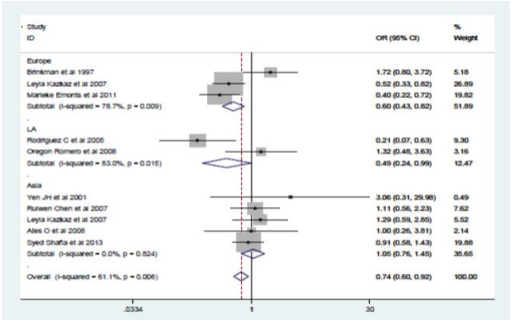

Fig.2. Odds ratios and 95% CIs of individual studies and pooled data for the *G/A+A/A* vs *GG* genotypes of the *TNFα -238* polymorphism for susceptibility to RA(LA=Latin American).

Annexure I

Moose Checklist:
The associations between TNFα polymorphisms and susceptibility to Rheumatoid arthritis: A meta-analysis

Criteria	Brief description of how the criteria were handled in the meta-analysis	
Reporting of background:		
	Problem definition	Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic inflammation of the synovial joints. *TNFα* has a pivotal role to play in the pathophysiology of RA. Polymorphisms in the *TNFα* gene promoter have an association with susceptibility to RA
	Hypothesis statement	*TNFα* gene promoter, including *-308* and *-238* positions have an association with susceptibility to RA.
	Description of study outcomes	Increased risk for Rheumatoid arthritis
×	Type of exposure or intervention used	None
	Type of study designs used	We included case-control studies and cohort studies, comparisons of study populations with age and ethnic origin matched.
	Study population	We placed no restriction.
Reporting of search strategy		
should include		
	Qualifications of searchers	The credentials of the two investigators *Dr Syed Shafia* and *Dr Zafar Amin Shah* are indicated in the author list.

	Search strategy, including time period included in the synthesis and keywords	PubMed and Google Scholar upto May 2017. The keywords used were "Rheumatoid arthritis" and "*TNFα–308G/A* and *–238 G/A* polymorphism"
	Databases and registries Searched	PubMed and Google Scholar
	Search software used, name and version, including special features	We did not employ a search software. EndNote was used to merge retrieved citations and eliminate duplications
	Use of hand searching	We hand-searched bibliographies of retrieved papers for additional references,
	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the references. The citation list is available upon request
	Method of addressing articles published in languages other than English	We placed no restrictions on language; local scientists fluent in the original language of the article were contacted for translation
	Method of handling abstracts and unpublished studies	There were no unpublished studies available.
	Description of any contact with Authors	We contacted some of the authors. It was not possible to contact all the authors.
Reporting of methods:		
	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria were described in the methods section.
	Rationale for the selection and coding of data	They selection criteria was that the studies were case- control and cohort studies, (2) they contained original data, (3) they provided enough data to calculate odds ratios (ORs).
	Assessment of confounding	Restricted the analysis to age and ethnic origin adjusted estimates only. Conducted sensitivity analyses by eliminating studies that had not adjusted for possible confounders such as studies not matched for matched age and ethnic origin.
	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Sensitivity analyses by several quality such as method of Rheumatoid arthritis diagnosis, control selection, adjustment factors, potential duplicate data.
	Assessment of heterogeneity	Heterogeneity of the studies were explored within two types of study designs using Cochrane's Q test of heterogeneity and I^2 statistic that provides the relative amount of variance of the summary effect due to the between-study heterogeneity.
	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analyses, sensitivity analyses, and assessment of publication bias are detailed in the methods.
	Provision of appropriate tables and graphics	We included Table 1 for giving details of all the studies included in our metanalysis, Table 2 for the sensitivity analyses, Figure 1 for Forest plot of TNFα -308 SNP and Figure 2 for TNFα -238 SNP.
Reporting of results:		
	Graph summarizing individual study estimates and overall estimate	Figure 1 & 2
	Table giving descriptive information for each study included	Table 1
	Results of sensitivity testing	Table 2
	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates, I^2 values and results of sensitivity analyses
Reporting of discussion:		
	Quantitative assessment of bias	Sensitivity analyses indicate heterogeneity in strengths of the association due to most common biases in observational studies.
	Justification for exclusion	We excluded studies that had not adjusted for or were standardized by age and ethnic origin matched. Those studies that did not provide the sufficient information to calculate the OR were also excluded.
	Assessment of quality of included studies	We discussed the results of the sensitivity analyses, and potential reasons for the observed heterogeneity.
Reporting of conclusions:		
	Consideration of alternative explanations for observed results	The lack of significant correlation of the *TNFα-308G/A and TNFα-238* polymorphism with the risk of disease in some populations cannot be regarded as an absence of TNFα associations with RA but it may reflect heterogeneity in the genetic susceptibility to this disorder. Also, the we cannot annul the role of these polymorphisms on the transcription regulation and its subsequent effect on the various clinical and laboratory parameters and the treatment response to the biologics in individual patients
	Generalization of the Conclusions	The meta-analysis indicated that *TNFα-308G/A* polymorphisms is a susceptibility factor for developing RA in Latin Americans and Asians but not in Europeans. Also, our meta-analysis shows that and *TNFα-238* polymorphism is susceptibility factor for RA in Latin Americans and Europeans but not in Asians.
	Guidelines for future research	We recommend future studies on the effect of *TNFα- 308G/A* and *TNFα-238 on Rheumatoid arthritis* risk.
	Disclosure of funding source	No separate funding was necessary for the undertaking of this systematic review.

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