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Associations between *TNFAIP3* gene polymorphisms and rheumatoid arthritis: a meta-analysis

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Abstract
Objective The aim of this study was to determine whether tumor necrosis factor alpha inducible protein 3 (*TNFAIP3*) polymorphisms confer susceptibility to rheumatoid arthritis (RA) in ethnically different populations.
Methods The authors conducted meta-analyses on associations between the *TNFAIP3* polymorphisms and RA susceptibility.
Result A total of ten comparative studies were included in this meta-analysis, which showed an association between the two allele of rs6920220 and RA in all study subjects [odds ratio (OR) 1.216, 95% confidence interval (CI) 1.166–1.269, $p < 1.0 \times 10^{-9}$]. The two allele of rs6920220 was also significantly associated with RA in Europeans only (OR 1.227, 95% CI 1.175–1.282, $p < 1.0 \times 10^{-9}$). Meta-analysis revealed no association between the two allele of the rs10499194 polymorphism and RA in Europeans, but a significant association was found in Asians (OR 1.254, 95% CI 1.101–1.429, $p = 6.7 \times 10^{-4}$). Furthermore, an association was found between the two allele of rs2230926 and RA in all study subjects (OR 1.390, 95% CI 1.214–2.331, $p = 1.9 \times 10^{-6}$).
Conclusions This meta-analysis confirms that the *TNFAIP3* polymorphisms are associated with RA susceptibility in different ethnic groups, namely, in Europeans for rs6920220 and in Asians for rs10499194.

Keywords
Tumor necrosis factor alpha inducible protein 3 · Polymorphism · Rheumatoid arthritis · Meta-analysis

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that predominantly involves synovial joints and affects up to 1% of adults worldwide. Although the etiology of RA remains unknown, a genetic component has been established by twin and family studies, in which it was estimated to contribute as much as 60% to RA liability. Human leukocyte antigen (HLA) class II molecules have been shown to be strongly associated with RA, but family studies suggest that this association accounts for only one-third of genetic susceptibility and that non-HLA genes are also involved [1].

The tumor necrosis factor alpha inducible protein 3 gene (*TNFAIP3*) also encodes ubiquitin-editing protein A20, which is an inhibitor of nuclear factor-κB (NF-κB) activation in several signaling pathways, including those of TNF and Toll-like receptors [2]. Furthermore, A20-deficient mice have been reported to exhibit systematic inflammation and damage to joints, and to develop autoimmunity [3]. TNFAIP3 protein participates in the negative regulation of inflammatory responses, and alterations in the activity or

expression of TNFAIP3-encoded A20 may influence the pathogenesis of RA [4]. *TNFAIP3* is located at 6q23, and is known to be associated with susceptibility to multiple autoimmune diseases [5]. In a genome-wide association study, it was shown that a strong association exists between the polymorphisms rs6920220 and rs10499194 and RA [6]. These polymorphisms lie between *OLG3* and *TNFAIP3*. Rs2230926 is located in the coding region of *TNFAIP3*, and an amino acid substitution of Phe to Cys at position 127 in the ovarian tumor domain of *TNPAIP3* has been suggested to play a role in the inhibitory function of A20 [7]. Furthermore, it has been reported that the Cys127 allele product is slightly less effective at inhibiting NF-κB activation than the Phe127 allele product [8].

Associations between *TNFAIP3* polymorphisms and RA have been reported in different ethnic groups, but reported results are contradictory [9–18]. Typically, the allelic frequencies of genes often differ substantially in different ethnic groups, and thus ethnicity specific association studies are required to determine genetic associations in different populations [19–21]. In the present study, using a meta-analysis approach we investigated whether the *TNFAIP3* polymorphisms, rs6920220, rs10499194, and rs2230926, contribute to RA susceptibility in different populations.

Materials and methods

Identification of eligible studies and data extraction

A literature search was conducted for studies that examined associations between the *TNFAIP3* polymorphisms and RA. The MEDLINE citation index was utilized to identify articles in which the *TNFAIP3* polymorphism was determined in RA patients and controls (until September 2011). In addition, all references mentioned in identified articles were reviewed to identify additional studies not indexed by MEDLINE. The following key words and subject terms were searched: "tumor necrosis factor alpha inducible protein 3," "*TNFAIP3*," "rheumatoid arthritis" and "RA". The following information was extracted from each study: author, year of publication, ethnicity of the study population, demographics, numbers of cases and controls, and the allele frequencies of the *TNFAIP3* polymorphisms.

Evaluation of publication bias

Funnel plots are used to detect publication bias, but require studies with different sizes that involve subjective judgments. Thus, we evaluated publication bias using Egger's linear regression test [22], which measures funnel plot asymmetry on a natural logarithm scale of odds ratios (ORs).

Evaluation of statistical associations

Allele frequencies of the *TNFAIP3* polymorphisms in each of the studies were determined using the allele counting method. Allelic effect contrast for the minor alleles (the two allele) versus the common alleles (the one allele) was examined, and point estimates of risk, ORs, and 95% confidence intervals (CIs) were determined for each study. Cochran's Q-statistic was used to assess within- and between-study variations and heterogeneities [23]. Heterogeneity testing was performed to assess the probability of the null hypothesis, namely, that all studies evaluated the same effect. When a significant Q-statistic ($p < 0.10$) indicated heterogeneity across studies, the random effects model was used for meta-analysis, and when heterogeneity was not indicated across studies, the fixed effects model was used. The fixed effects model assumes that genetic factors have similar effects on RA susceptibility across all studies, and that observed variations between studies are caused by chance alone [24]. On the other hand, the random effects model assumes that different studies show substantial diversity, and assesses both within-study sampling errors and between-study variances [25]. The random effects model is used in the presence of significant between-study heterogeneity. We quantified the effect of heterogeneity by using a recently developed measure, namely $I^2 = 100\% \times (Q - \mathrm{df})/Q$ [26]. I^2 ranges between 0 and 100% and represents the proportion of inter-study variability attributable to heterogeneity rather than chance. I^2 values of 25, 50, and 75% were defined as low, moderate, and high estimates, respectively. Statistical manipulations were undertaken using the 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 30 studies, and 11 were selected for full-text review based on their titles and abstracts [9–18, 27]. One study was excluded because it contained no extractable data [27]. Thus, ten studies were considered in this meta-analysis [9–18], and comprised six European, two Asian, one African–American, and one Tunisian population (Table 1). Meta-analyses were conducted separately on the rs6920220, rs10499194, and rs2230926 polymorphisms. The selected characteristics of the ten studies included are summarized in Table 1.

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

Study	Country (ethnicity)	Numbers, RA/control	*TNFAIP3* polymorphism (s)	Findings for association
Ben Hamad et al. [9]	Tunisia (T)	141/191	rs6920220	rs6920220 ($p = 0.35$)
Musone et al. [10]	USA (E)	148/1,513	rs2230926	rs2230926 ($p = 0.025$)
Hughes et al. [11]	USA (AA)	556/791	rs10499194, rs6920220	rs10499194 ($p = 0.164$), rs6920220 ($p = 0.321$)
Shimane et al. [12]	Japan (A)	3,415/2,326	rs2230926, rs10499194	rs2230926 ($p = 2.6 \times 10^{-5}$), rs10499194 ($p = 8.46 \times 10^{-4}$)
Han et al. [13]	Korea (A)	1,316/1,006	rs10499194, rs6920220	rs10499194 ($p =$ NS), rs6920220 ($p =$ NC)
Coenen et al. [14]	UK (E)	1,368/1,683	rs10499194	rs10499194 ($p = 0.987$)
Stark et al. [15]	Slovak (E)	431/2,155	rs10499194, rs6920220	rs10499194 ($p = 0.030$), rs6920220 ($p = 0.019$)
Dieguez-Gonzalez et al. [16]	Spain (E)	1,351/1,619	rs10499194, rs6920220	rs10499194 ($p =$ NS), rs6920220 ($p = 0.07$)
Raychaudhuri et al. [17]	USA (E)	3,393/12,460	rs10499194, rs6920220	rs10499194 ($p = 3.8 \times 10^{-5}$), rs6920220 ($p = 1.5 \times 10^{-9}$)
Thomson et al. [18]	UK (E)	431/2,155	rs6920220	rs6920220 ($p = 1.6 \times 10^{-8}$)

RA rheumatoid arthritis, *TNFAIP3* tumor necrosis factor alpha inducible protein 3 gene, *T* Tunisian, *E* European, *AA* African–American, *A* Asian, *NS* not significant, *NC* not calculated

Table 2 Prevalences of the two allele of the rs6920220 polymorphism of *TNFAIP3*

Population	No. of studies	Numbers		Two allele (%)	
		RA	Control	RA	Control
European	4	10,370	18,077	23.2	19.6
Asian	1	1,316	1,006	0.09	0.067
African–American	1	556	701	10.0	11.0
Tunisian	1	141	191	25.5	22.4
Overall	7	12,383	20,065	18.3	15.9

TNFAIP3 tumor necrosis factor alpha inducible protein 3 gene, *RA* rheumatoid arthritis

Frequency of the two allele of the *TNFAIP3* rs6920220 polymorphism in control groups

The mean frequency of the two allele was found to be 15.9% among all controls. Asian controls had the lowest two-allele prevalence (0.067%). Frequencies ranged from 0.067 to 22.4% in the other ethnic groups, and Tunisians had the highest two-allele frequency (22.4%) (Table 2).

Meta-analysis of the associations between the *TNFAIP3* polymorphisms and RA

Meta-analysis was performed on all RA patients and on RA patients in each ethnic group. A summary of the meta-analysis findings of the relations between the *TNFAIP3* polymorphisms and RA is provided in Table 3. Meta-analysis showed an association between the two allele of rs6920220 and RA in all study subjects (OR 1.216, 95% CI 1.166–1.269, $p < 1.0 \times 10^{-9}$) (Table 3; Fig. 1). Analysis after stratification by ethnicity indicated that the two allele of rs6920220 was significantly associated with RA in Europeans (OR 1.227, 95% CI 1.175–1.282, $p < 1.0 \times 10^{-9}$) (Table 3). The analyses performed in each Asian, African–American, and Tunisian study showed no significant association between the two allele of rs6920220 and RA (Table 3).

Meta-analysis revealed no association between the two allele of the rs10499194 polymorphism and the risk of developing RA in all study subjects, in Europeans, or African–Americans (Table 3; Fig. 2). However, meta-analysis showed a significant association between the two allele of rs10499194 and RA in Asians (OR 1.254, 95% CI 1.101–1.429, $p = 6.7 \times 10^{-4}$) (Table 3; Fig. 3).

Meta-analysis revealed an association between the two allele of rs2230926 and RA in all study subjects (OR 1.390, 95% CI 1.214–2.331, $p = 1.9 \times 10^{-6}$) (Table 3; Fig. 3). The analysis performed in a single Asian population showed a significant association between the two allele of rs2230926 and RA (OR 1.366, 95% CI 1.188–1.571, $p = 1.2 \times 10^{-5}$), and the analysis in the African–American study revealed a significant association between the two allele of rs2230926 and RA (OR 1.847, 95% CI 1.053–3.241, $p = 0.032$) (Table 3; Fig. 3).

Heterogeneity and publication bias

Some between-study heterogeneity was found during the meta-analyses, but no evidence of heterogeneity was found for rs6920220 in all study subjects or Europeans, for rs10499194 in Asians, or for rs2230926 in all study subjects (Table 3). Funnel plots, which are usually used to detect publication bias, were difficult to correlate,

Table 3 Meta-analysis of associations between *TNFAIP3* polymorphisms and RA

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95% CI	*p* value	Model	*p* value	I^2
rs6920220	Overall	7	1.216	1.166−1.269	$<1.0 \times 10^{-9}$	F	0.165	34.5
two versus one allele	European	4	1.227	1.175–1.282	$<1.0 \times 10^{-9}$	F	0.346	9.38
	Asian	1	1.529	0.139–16.87	0.729	NA	NA	NA
	African–American	1	0.897	0.698–1.154	0.398	NA	NA	NA
	Tunisian	1	1.180	0.824–1.691	0.367	NA	NA	NA
rs10499194	Overall	7	1.016	0.904–1.141	0.792	R	0.000	81.6
two versus one allele	European	4	0.921	0.845–1.005	0.065	R	0.055	60.4
	Asian	2	1.254	1.101–1.429	6.7×10^{-4}	F	0.518	0
	African–American	1	1.152	0.940–1.412	0.173	NA	NA	NA
rs2230926	Overall	2	1.390	1.214–1.593	1.9×10^{-6}	F	0.308	3.93
two versus one allele	Asian	1	1.366	1.188–1.571	1.2×10^{-5}	NA	NA	NA
	African–American	1	1.847	1.053–3.241	0.032	NA	NA	NA

TNFAIP3 tumor necrosis factor alpha inducible protein 3 gene, *RA* rheumatoid arthritis, *F* fixed effects model, *R* random effects model, *NA* not available

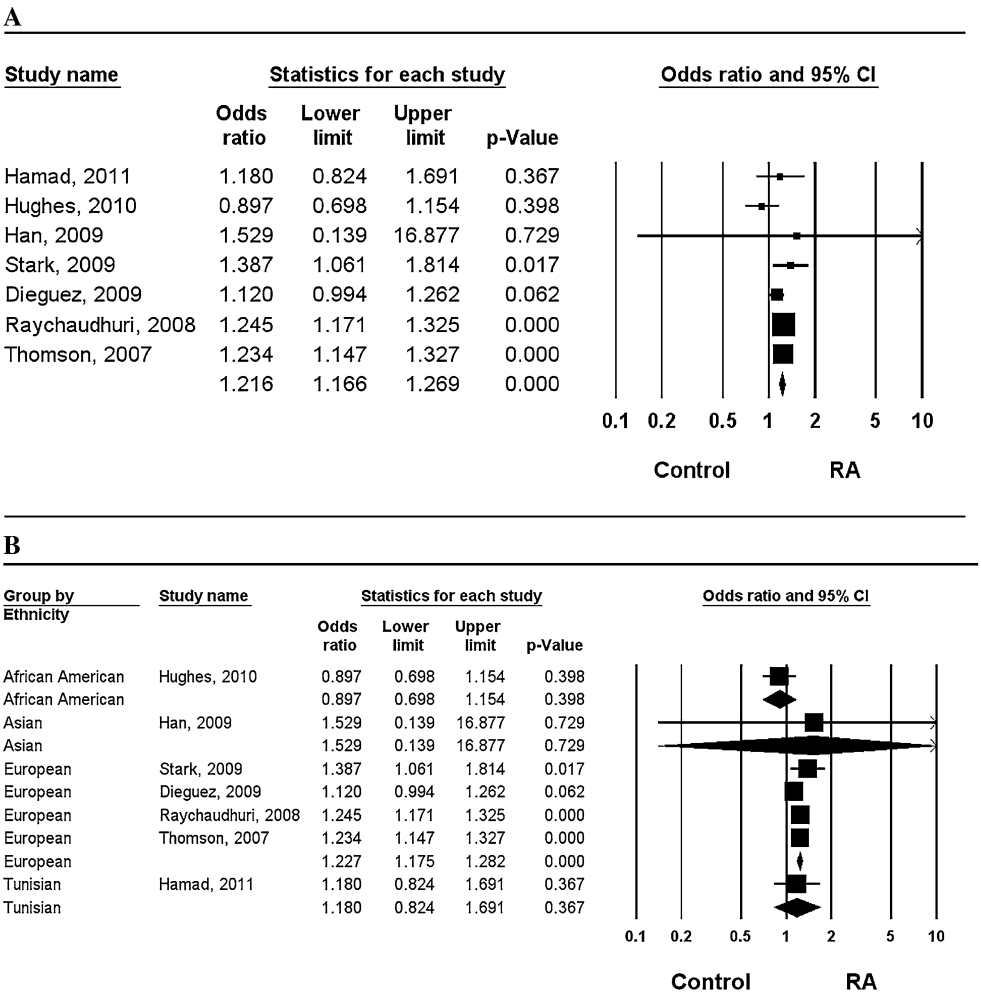

Fig. 1 ORs and 95% CIs of individual studies and pooled data for the two allele versus one allele of the *TNFAIP3* rs6920220 polymorphism with respect to susceptibility to RA in all study subjects (**a**) and in each ethnic group (**b**)

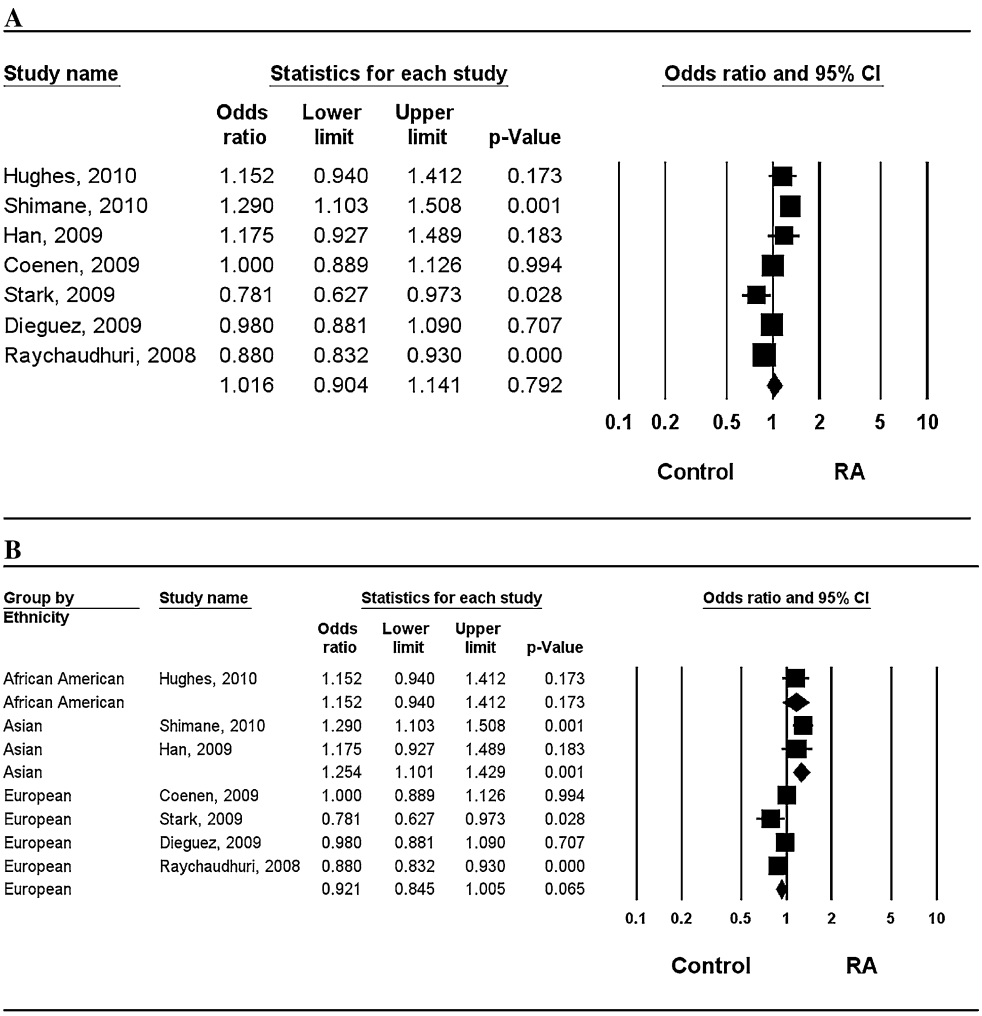

Fig. 2 ORs and 95% CIs of individual studies and of pooled data for the two allele versus one allele of the *TNFAIP3* rs10499194 polymorphism with respect to susceptibility to RA in all study subjects (**a**) and in each ethnic group (**b**)

presumably because of the small number of studies included. Egger's regression test showed no evidence of publication bias in this meta-analysis of *TNFAIP3* polymorphisms in any group analyzed (Egger's regression test $p > 0.1$).

Discussion

In this meta-analysis, we examined evidence of associations between the rs6920220, rs10499194, and rs2230926 polymorphisms of *TNFAIP3* and RA susceptibility. Our results provide evidence of strong associations between these polymorphisms and RA. Although our findings do not support associations between the *TNFAIP3* polymorphisms and RA susceptibility in all ethnic groups, our analysis does reveal a significant association between the rs6920220 polymorphism and the risk of developing RA in Europeans. Furthermore, our study shows an association between RA and rs10499194 in Asians and between rs2230926 and RA in all subjects. These findings suggest that the *TNFAIP3* polymorphisms are associated with the development of RA in Europeans and Asians.

The disease-associated variant of rs2230926 is a non-synonymous variant that results in a phenylalanine-to-cysteine change at residue 127 of A20, a key player in anti-inflammatory reactions. The risk allele (Cys127) leads to reduced inhibition of NF-κB activation or reduced *TNFAIP3* mRNA levels [8]. These findings suggest that reduced A20 negative regulatory activity leads to excessive immune activity, and thus enhanced autoreactivity, and that rs2230926 plays a functional role in the development of RA.

The prevalence of the two allele of the rs6920220 polymorphism was calculated in different populations, and was found to vary between 0.067 and 22.4%. Its mean frequency in all controls was 15.9%, and its frequency was lowest among Asian controls and highest among Tunisian controls. Furthermore, our ethnicity-specific meta-analysis showed that an association exists between the rs6920220 polymorphism and RA in Europeans. Unfortunately, meta-analysis of the rs6920220 polymorphism was not possible in Asians, African Americans, or Tunisians due to limited data.

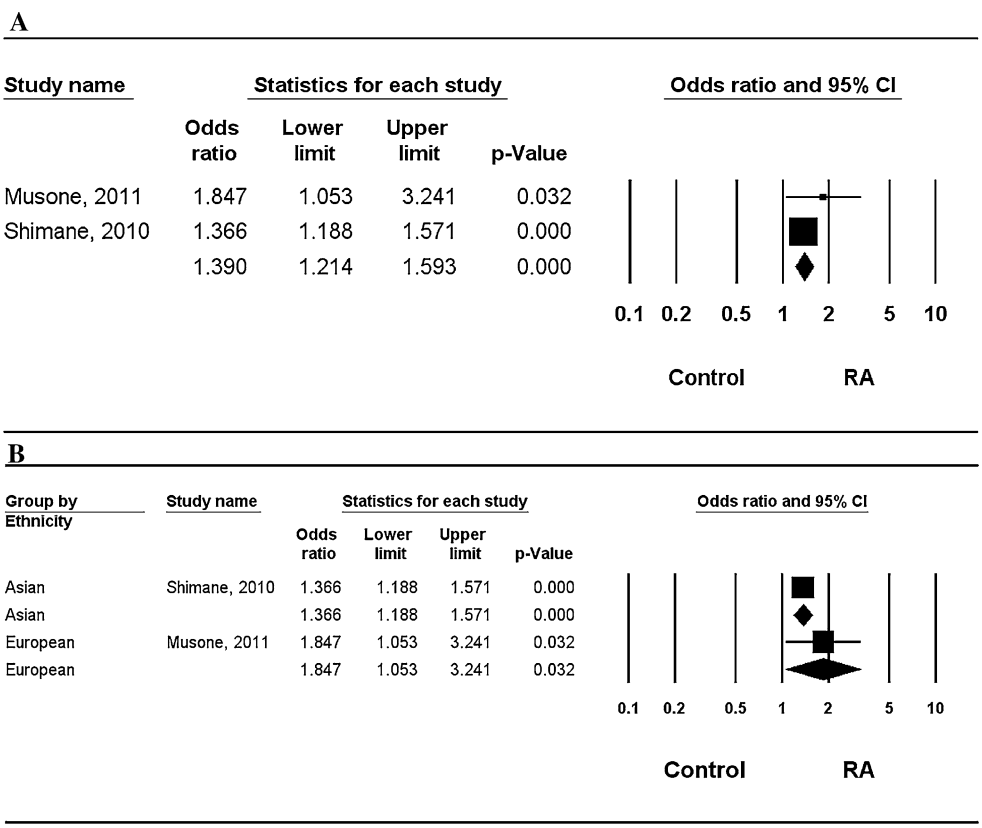

Fig. 3 ORs and 95% CIs of individual studies and pooled data for the two allele versus one allele of the *TNFAIP3* rs2230926 polymorphism with respect to susceptibility to RA in all study subjects (**a**) and in each ethnic group (**b**)

Several limitations of the present study require consideration. First, publication bias, heterogeneity, and confounding factors may have distorted the meta-analysis. However, most of the studies analyzed demonstrated the same directionality with respect to associations between the *TNFAIP3* polymorphisms and RA. Second, only data from European and Asian patients was included in the ethnicity-specific analysis, and thus our results are applicable to only these ethnic groups. Third, in the case of rs6920220, meta-analyses of minor populations like Asians, African–Americans and Tunisians were impossible because of lack of useful data concerning the minor populations. In the meta-analysis of rs2230926, we could include only two studies (African–Americans and Asians). Concerning the allele of rs10499194, it seems to be associated with RA in Asian populations and African–Americans but not so among Europeans. However, the current evidence is too limited to draw a definitive conclusion because the number of studies included in the meta-analysis was small. Thus, this meta-analysis may have not enough power to explore the association between the *TNFAIP3* polymorphisms in RA. Fourth, most of the studies included were performed in populations of European and Asian descent—African–Americans and Tunisians were the subjects of only one study apiece. Furthermore, the allelic frequencies of genes often differ substantially between populations, and thus further ethnicity-specific association studies are required to confirm genetic associations with RA susceptibility in different populations. In the present study, we performed meta-analyses on the rs6920220, rs10499194, and rs2230926 polymorphisms, and additional studies are needed to explore the roles of other *TNFAIP3* polymorphisms in RA. Fifth, the rs6920220, rs10499194, and rs2230926 polymorphisms have also been reported to be associated with the severity of autoimmune diseases [28], but limited data prevented our examining associations between these polymorphisms and the clinical manifestations of RA.

In conclusion, this meta-analysis of published data confirms that the rs6920220, rs10499194, and rs2230926 polymorphisms are associated with RA susceptibility in Europeans and Asians. Furthermore, it shows that the prevalence of the two allele of rs6920220 in the *TNFAIP3* gene is ethnicity-dependent. Further studies are required to determine whether *TNFAIP3* polymorphisms contribute to RA susceptibility in different ethnic groups.

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Conflict of interest We have no financial and non-financial conflicts of interest.

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