Associations between *TNFAIP3* Polymorphisms and Rheumatoid Arthritis: A Systematic Review and Meta-Analysis Update with Trial Sequential Analysis

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**Keywords**

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

**Abstract**

**Introduction:** The tumor necrosis factor alpha inducible protein 3 (*TNFAIP3*) gene produces ubiquitin-editing protein A20, which inhibits nuclear factor-κB (NF-κB) activation in a variety of signaling pathways. We examined the association between *TNFAIP3* polymorphisms and rheumatoid arthritis (RA) susceptibility.

**Methods:** MEDLINE, Embase, Scopus, and Web of Science were searched for available articles on *TNFAIP3* polymorphisms in RA patients from inception until July 11, 2022. We included case-control studies on the association between *TNFAIP3* polymorphisms and rheumatoid arthritis (RA) susceptibility. Seventeen studies were chosen for meta-analysis. Ten studies for rs2230926, and seven for rs5029937. An association was noted between *TNFAIP3* rs2230926 G allele and RA in all subjects (odds ratio [OR] = 1.389; 95% confidence interval [CI] = 1.161–1.662; *p* < 0.001). Ethnicity-specific analysis showed significant association of rs2230926 G allele with RA in Europeans and Asians (OR = 1.642; 95% CI = 1.099–2.452; *p* = 0.015; OR = 1.404; 95% CI = 1.262–1.562; *p* < 0.001). An association was also noted between *TNFAIP3* rs5029937 T allele and RA in all subjects (OR = 1.389; 95% CI = 1.207–1.785; *p* < 0.001). An ethnicity-specific meta-analysis revealed a significant association of the rs5029937 T allele with RA in Europeans and Asians. Dominant model analysis showed the same pattern for *TNFAIP3* rs2230926 G and rs5029937 T alleles in Europeans and Asians, suggesting an association between *TNFAIP3* rs2230926 G and rs5029937 T alleles. TSA indicated a robust association between the *TNFAIP3* polymorphisms and the risk of RA.

**Conclusion:** *TNFAIP3* rs2230926 and rs5029937 polymorphisms are associated with RA susceptibility in European and Asian populations. However, the data were not stratified by parameters such as rheumatoid factor status, disease activity, or environmental variables.

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes persistent synovial joint inflammation, resulting in disability and a diminished quality of life. Although the cause of RA is unknown, vulnerability to it can be inherited [1, 2]. Only one-third of the genetic susceptibility is accounted for by human leukocyte antigen (HLA) class II molecules, and non-HLA genes have also been implicated [3, 4].

The tumor necrosis factor alpha inducible protein 3 (TNFAIP3) gene produces ubiquitin-editing protein A20, which inhibits nuclear factor-κB (NF-κB) activation in a variety of signaling pathways, including those involving TNF and Toll-like receptors [5]. Furthermore, A20-deficient animals have been shown to exhibit systemic inflammation, joint injury, and autoimmunity [5]. TNFAIP3 protein is involved in the negative control of inflammatory responses, and changes in the activity or expression of TNFAIP3-encoded A20 protein may affect the pathophysiology of RA [6]. TNFAIP3 is found on chromosome 6q23 and has been linked to susceptibility to a variety of autoimmune disorders [7]. The rs2230926 is found in the TNFAIP3 coding region, and an amino acid change from phenylalanine (Phe) to cysteine (Cys) at position 127 in the TNFAIP3 ovarian tumor domain has been proposed to play a role in the inhibitory activity of A20 [8]. The Cys127 allele product was found to be less efficient than the Phe127 allele product at inhibiting NF-κB activation [9]. The intronic variation of rs5029937 may have a high degree of linkage disequilibrium [10].

Several studies have examined the impact of TNFAIP3 polymorphisms on RA susceptibility [11–26]. However, these investigations have shown conflicting results in various ethnicities. Typically, the allelic frequencies of genes vary dramatically between ethnic groups, necessitating ethnicity-specific association studies to discover genetic relationships in distinct populations [27–29]. Previous meta-analyses have assessed the relationship between TNFAIP3 polymorphisms and RA susceptibility [14, 30]. However, several further papers regarding this relationship between TNFAIP3 polymorphisms and the risk of RA have been published recently. We performed an updated meta-analysis to determine whether TNFAIP3 polymorphisms rs2230926 and rs5029937 are associated with RA susceptibility in various ethnic populations.

Materials and Methods

Identification of Eligible Studies and Data Extraction

We searched for studies that examined the association between TNFAIP3 polymorphisms and RA. MEDLINE, Embase, Scopus, and Web of Science were searched for available articles on TNFAIP3 polymorphisms in RA patients from inception until July 11, 2022. Combinations of keywords, such as “tumor necrosis factor alpha inducible protein 3,” “TNFAIP3,” and “rheumatoid arthritis” were entered as medical subject headings and text words. References in the cited studies were also examined to identify additional studies that were not indexed by electronic databases. No restrictions were placed on language, race, ethnicity, or geographical location, nor were language or country restrictions applied. Studies were included if (1) they were case-control studies on the association between rs2230926 and rs5029937 polymorphisms of TNFAIP3 and RA, (2) the data were original (to ensure independence among studies), and (3) they provided sufficient data to calculate odd ratios (OR). We excluded studies that contained overlapping data, those in which the number of alleles could not be ascertained, and studies involving family members, as such analyses are based on linkage considerations. The following information was extracted from each study: author, year of publication, region/ethnicity of the study population, demographics of the subjects, and number of cases and controls. Allele frequencies were calculated from the genotype distributions. We scored the quality of each study included based on the Newcastle-Ottawa Scale [31]. The highest score was 9. Scores ranging from 6 to 9 were considered to indicate high methodological quality. This meta-analysis was registered in the PROSPERO register (number: CRD42022345160). There was no funding source.

Evaluation of Statistical Associations

A χ² test was used to determine whether the observed genotype frequencies conformed to Hardy-Weinberg equilibrium (HWE). Point estimates of the 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, and the heterogeneity test assessed the null hypothesis that all studies evaluated the same effect. F values were used to quantify the effect of heterogeneity, with values ranging between 0% and 100%, representing the proportion of between-study variability attributable to heterogeneity rather than to chance [32]. F values of 25%, 50%, and 75% were defined as low, moderate, and high, respectively. The fixed-effects model assumes that a genetic factor has the same effect on disease susceptibility across all studies investigated and that observed variations between studies are caused by chance alone. The random-effects model assumes that different studies show substantial diversity and assesses both within-study sampling error and between-study variance. When study groups are homogeneous, the two models are similar, but if this is not the case, the random-effects model usually provides wider CIs than the fixed-effects model. Furthermore, the random-effects model was used in the presence of significant between-study heterogeneity [33]. Statistical manipulations were performed using comprehensive meta-analysis software (Biostat, Englewood, NJ, USA). We performed a meta-analysis in compliance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16].

The TNFAIP3 Polymorphism and RA

Public Health Genomics 2022;25:174–184
DOI: 10.1159/000526212

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Trial Sequential Analysis

Due to random errors or systematic bias, cumulative meta-analysis may result in type I errors (false positives). Random errors may sometimes lead to spuriously significant findings when data accumulates, and an increased frequency of statistical testing by meta-analyses increases the potential of such being reported; thus, intervention effects are often exaggerated (type I errors). As a result, trial sequential analysis (TSA) was created to adjust for the increase in type I error.

TSA is conceptually comparable to sequential interim analyses of randomized controlled trials, in which trial results are checked periodically to see if a particular difference attributed to the intervention—or its absence—has been amply demonstrated by the available data, allowing the trial to be ended [34]. TSA reduces the likelihood of type I and type II errors by calculating the required sample size and trial sequential monitoring boundaries [34]. The predicted intervention effect was confirmed if the measured Z-curve passed the trial sequential monitoring border or the futility boundary [35]. However, the present data were insufficient to make a firm judgment if the Z-curve does not transcend the aforementioned borders or achieve the requisite information size. We calculated the required information size using a two-sided 5% risk for type I error (α) and a 20% risk for type II error (β), with a relative risk (RR) reduction of 20%. The TSA version 0.9.5.10 beta software (http://www.ctu.dk/tsa) was used.

Evaluation of Heterogeneity, Publication Bias, and Sensitivity Test

Funnel plots were used to detect publication bias but required a range of studies of varying sizes and subjective judgments. We evaluated publication bias using Egger’s linear regression test [36], which measures funnel plot asymmetry on a natural logarithm.
## Table 1. Characteristics of the studies included in the meta-analysis

| Polymorphism                  | Author (reference) | Ethnicity | Numbers | RA TT | RA TG | RA GG | Control TT | Control TG | Control GG | Association p value<sup>a</sup> | Study quality |
|-------------------------------|--------------------|-----------|---------|-------|-------|-------|------------|------------|------------|---------------------------------|---------------|
| **TNFAIP3 rs2230926 T/G polymorphism** |                    |           |         |       |       |       |            |            |            |                                 |               |
| TNFAIP3 rs2230926 T/G polymorphism | Zeng et al. [26], 2021 | Asian     | 552     | 492   | 60    | 0     | 543       | 46         | 0          | 0.084                           | 8             |
| TNFAIP3 rs2230926 T/G polymorphism | Ciccacci et al. [24], 2019 | European | 256     | 229   | 26    | 1     | 217       | 18         | 1          | 0.372                           | 7             |
| TNFAIP3 rs2230926 T/G polymorphism | Moaaz et al. [22], 2016 | Arab      | 105     | 75    | 78    | 24    | 65        | 10         | 0          | 0.027                           | 7             |
| TNFAIP3 rs2230926 T/G polymorphism | Zhu et al. [21], 2015 | Asian     | 50      | 47    | 3     | 0     | 28        | 2          | 0          | 0.907                           | 6             |
| TNFAIP3 rs2230926 T/G polymorphism | Hao et al. [18], 2014 | Asian     | 207     | 170   | 34    | 3     | 184       | 13         | 2          | 0.003                           | 7             |
| TNFAIP3 rs2230926 T/G polymorphism | Zhang et al. [20], 2014 | Asian     | 1,280   | 1,072 | 200   | 8     | 1,133     | 143        | 4          | <0.001                          | 8             |
| TNFAIP3 rs2230926 T/G polymorphism | Kim et al. [19], 2014 | Asian     | 416     | 364   | 52    | 0     | 367       | 45         | 0          | 0.495                           | 7             |
| TNFAIP3 rs2230926 T/G polymorphism | Perkins et al. [16], 2012 | African American | 446   | 177   | 208   | 61    | 282       | 345        | 106        | 0.627                           | 7             |
| TNFAIP3 rs2230926 T/G polymorphism | Musone et al. [13], 2011 | European | 148     | 133   | 14    | 1     | 8,847     | 82         | 1          | 0.013                           | 7             |
| TNFAIP3 rs2230926 T/G polymorphism | Shimane et al. [12], 2010 | Asian     | 3,415   | 2,815 | 571   | 29    | 2,876     | 299        | 11         | <0.001                          | 8             |

| **TNFAIP3 rs5029931 G/T polymorphism** |                    |           |         |       |       |       |            |            |            |                                 |               |
| TNFAIP3 rs5029931 G/T polymorphism | Pakzad et al. [25], 2021 | Arab      | 50      | 16    | 30    | 4     | 31        | 19         | 0          | 0.003                           | 6             |
| TNFAIP3 rs5029931 G/T polymorphism | Vernerova et al. [23], 2016 | European | 499     | 477   | 21    | 1     | 850       | 43         | 1          | 0.728                           | 7             |
| TNFAIP3 rs5029931 G/T polymorphism | Zhu et al. [21], 2015 | Asian     | 50      | 48    | 2     | 0     | 28        | 2          | 0          | 0.605                           | 6             |
| TNFAIP3 rs5029931 G/T polymorphism | Kim et al. [19], 2014 | Asian     | 419     | 364   | 54    | 1     | 379       | 43         | 0          | 0.168                           | 77            |
| TNFAIP3 rs5029931 G/T polymorphism | Maxwell et al. [15], 2013 | European | 256     | 227   | 29    | 0     | 236       | 18         | 0          | 0.109                           | 7             |
| TNFAIP3 rs5029931 G/T polymorphism | Plant et al. [17], 2012 | European | 7,731   | 6,977 | 735   | 19    | 8,847     | 547        | 9          | <0.001                          | 8             |
| TNFAIP3 rs5029931 G/T polymorphism | Orozco et al. [11], 2009 | European | 3,613   | 3,291 | 309   | 13    | 2,876     | 207        | 5          | 0.001                           | 8             |

TNFAIP3, tumor necrosis factor alpha inducible protein 3; RA, rheumatoid arthritis. <sup>a</sup>Minor versus major allele.
of ORs. A “leave-one-out” analysis was also performed to investigate the possibility of a causal association being driven by a single study. To examine potential sources of heterogeneity observed in the meta-analysis, a meta-regression analysis was performed using the following variables: ethnicity, publication year, sample size, and study quality.

### Results

#### Studies Included in the Meta-Analysis

Seven hundred and fourteen studies on the association between TNFAIP3 polymorphisms and RA were identified using an electronic search (online suppl. Data; see www.karger.com/doi/10.1159/000526212 for all online suppl. material). Twenty-two relevant studies were identified that examined the association between polymorphisms of TNFAIP3 and RA. Five studies were excluded because they did not include data on TNFAIP3 polymorphisms or review articles. A total of 15 studies met the inclusion criteria [11–13, 15–26] (Fig. 1). Two of these studies contained data on two different groups [19, 21]. Therefore, 17 separate studies were included in the meta-analysis (Table 1). Ten studies included 5,962 patients with RA and 6,493 controls for rs2230926, and seven studies included 12,019 patients with RA and 13,167 controls for rs5029937. The quality assessment score of each study ranged from 6 to 9, indicating high study quality. Select details of the individual studies are summarized in Table 1.

#### Meta-Analysis of the Associations between TNFAIP3 rs2230926 Polymorphism and RA

The meta-analysis showed an association between TNFAIP3 rs2230926 G allele and RA in all study subjects (OR = 1.389; 95% CI = 1.161–1.662; p < 0.001) (Table 2; Fig. 2). Ethnicity-specific meta-analysis indicated that the rs2230926 G allele was significantly associated with RA in Europeans and Asians (OR = 1.642; 95% CI = 1.099–2.452; p = 0.015; OR = 1.404, 95% CI = 1.262–1.562; p < 0.001) (Table 2; Fig. 2). Furthermore, analysis using the dominant model showed the same pattern for the TNFAIP3 rs2230926 polymorphism and RA in Europeans and Asians (Table 2).

### Table 2. Meta-analysis of associations between TNFAIP3 rs2230926 polymorphisms and RA

| Polymorphism       | Population        | Studies, n | Test of association | Test of heterogeneity |
|--------------------|-------------------|------------|---------------------|-----------------------|
|                    |                   |            | OR                  | 95% CI                | p value | model | p value | I² |
| rs2230926          | Overall           | 10         | 1.389               | 1.161–1.662           | <0.001  | R      | 0.005   | 61.5 |
|                    | European          | 2          | 1.642               | 1.099–2.452           | 0.015   | F      | 0.299   | 7.15 |
|                    | Asian             | 6          | 1.404               | 1.262–1.562           | <0.001  | F      | 0.464   | 0    |
|                    | Arab              | 1          | 2.333               | 1.103–4.935           | 0.027   | NA     | NA      | NA   |
|                    | African American  | 1          | 0.958               | 0.807–1.138           | 0.627   | NA     | NA      | NA   |
|                    |                   |            |                     |                       |         |        |         |      |
| GG + GT versus TT  | Overall           | 10         | 1.397               | 1.179–1.654           | <0.001  | F      | 0.004   | 48.0 |
| (Dominant)         | European          | 2          | 1.636               | 1.074–2.494           | 0.022   | F      | 0.395   | 0    |
|                    | Asian             | 6          | 1.426               | 1.274–1.595           | <0.001  | F      | 0.395   | 3.31 |
|                    | Arab              | 1          | 2.250               | 1.014–4.991           | 0.046   | NA     | NA      | NA   |
|                    | African American  | 1          | 0.950               | 0.747–1.209           | 0.678   | NA     | NA      | NA   |
|                    |                   |            |                     |                       |         |        |         |      |
| GG versus GT + TT  | Overall           | 7          | 1.153               | 0.865–1.537           | 0.331   | F      | 0.296   | 17.4 |
| (Recessive)        | European          | 2          | 3.079               | 0.432–21.95           | 0.262   | F      | 0.229   | 31.0 |
|                    | Asian             | 3          | 1.806               | 1.020–3.198           | 0.042   | F      | 0.957   | 0    |
|                    | Arab              | 1          | 5.156               | 0.262–101.3           | 0.280   | NA     | NA      | NA   |
|                    | African American  | 1          | 0.937               | 0.667–1.316           | 0.708   | NA     | NA      | NA   |
|                    |                   |            |                     |                       |         |        |         |      |
| GG versus TT       | Overall           | 7          | 1.184               | 0.874–1.603           | 0.276   | R      | 0.227   | 26.3 |
|                    | European          | 2          | 3.193               | 0.448–22.80           | 0.247   | F      | 0.226   | 31.9 |
|                    | Asian             | 3          | 1.908               | 1.077–3.378           | 0.027   | F      | 0.971   | 0    |
|                    | Arab              | 1          | 5.841               | 0.296–115.1           | 0.246   | NA     | NA      | NA   |
|                    | African American  | 1          | 0.917               | 0.635–1.323           | 0.643   | NA     | NA      | NA   |

TNFAIP3, tumor necrosis factor alpha inducible protein 3; RA, rheumatoid arthritis; OR, odds ratio; CI, confidence interval; F, fixed-effects model; R, random-effects model; NA, not available.
**Meta-Analysis of the Associations between TNFAIP3 rs5029937 Polymorphism and RA**

Meta-analysis revealed an association between TNFAIP3 rs5029937 T allele and RA in all study subjects, as well (OR = 1.389, 95% CI = 1.207–1.785, p < 0.001; Table 3; Fig. 3). Ethnicity-specific meta-analysis revealed that the rs5029937 T allele is significantly associated with RA in Europeans and Asians (Table 3; Fig. 3). Analysis
using the dominant model showed the same pattern for the \textit{TNFAIP3} rs5029937 T allele in Europeans and Asians, suggesting an association between the \textit{TNFAIP3} rs5029937 polymorphism and RA (Table 3).

\textit{Trial Sequential Analysis}

The z-score curve (blue line) crossed the trial sequential monitoring boundary and the conventional statistical significance boundary corresponding to 2-sided \( P \) value of 0.05, but it did not cross the required information size (vertical red line; Fig. 4). This indicates that the observed association between the rs2230926 polymorphism and the risk of RA could be considered conclusive with existing evidence (Fig. 4). TSA demonstrated that the meta-analysis results were robust; however, further research is needed. The Z-curve exceeded the trial sequential monitoring border for the rs5029937 polymorphism but failed to reach the required information size, suggesting that the meta-analysis result for the rs5029937 polymorphism was robust, but additional research is needed (Fig. 4).

\textit{Heterogeneity, Publication Bias, and Sensitivity Test}

The distribution of \textit{TNFAIP3} polymorphisms in the control groups was consistent with HWE, except for one study on the rs2230926 polymorphism \cite{18}. However, the exclusion of this study did not affect the meta-analysis results. Between-study heterogeneity was observed in the meta-analysis of RA for the rs2230926 polymorphism in the overall group. However, heterogeneity was resolved or reduced in ethnic-specific meta-analyses. Between-study heterogeneity was observed in the meta-analyses of RA for the rs5029937 polymorphism in the overall and European groups for allelic and dominant models. No evidence of publication bias was found in the meta-analyses of \textit{TNFAIP3} polymorphisms (Egger’s regression test \( p \) value >0.1).

Results from the “leave-one-out” analysis demonstrated that no single study was driving the meta-analysis results of the \textit{TNFAIP3} polymorphisms. Meta-regression analysis showed that ethnicity, study quality, publication year, and sample size had no significant impact on the heterogeneity in the meta-analysis of \textit{TNFAIP3} polymorphisms.

\textbf{Discussion}

In this meta-analysis, we utilized data from previously published studies to assess the genetic correlations between \textit{TNFAIP3} rs2230926 and rs5029937 polymorphism.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
\textbf{Polymorphism} & \textbf{Population} & \textbf{Studies, \( n \)} & \textbf{Test of association} & \textbf{Test of heterogeneity} & \\ & & & \textbf{OR} & \textbf{95\% CI} & \textbf{\( p \) value} & \textbf{model} & \textbf{\( p \) value} & \textbf{\( \rho \)²} \\
\hline
rs5029931 & Overall & 7 & 1.468 & 1.207–1.785 & <0.001 & \textit{R} & 0.035 & 55.8 \\
& European & 4 & 1.427 & 1.137–1.791 & 0.002 & \textit{R} & 0.022 & 68.8 \\
& Asian & 2 & 1.291 & 0.864–1.927 & 0.213 & \textit{F} & 0.432 & 0 \\
& Arab & 1 & 2.613 & 1.374–4.967 & 0.003 & NA & NA & NA \\
\hline
TT + TG versus GG (Dominant) & Overall & 7 & 1.469 & 1.179–1.830 & <0.001 & \textit{R} & 0.018 & 60.9 \\
& European & 4 & 1.426 & 1.118–1.817 & 0.004 & \textit{R} & 0.016 & 70.9 \\
& Asian & 2 & 1.286 & 0.849–1.947 & 0.235 & \textit{F} & 0.432 & 0 \\
& Arab & 1 & 3.467 & 1.521–7.905 & 0.003 & NA & NA & NA \\
\hline
TT versus TG + GG (Recessive) & Overall & 5 & 2.560 & 1.419–4.621 & 0.002 & \textit{F} & 0.919 & 0 \\
& European & 3 & 2.401 & 1.300–4.436 & 0.005 & \textit{F} & 0.955 & 0 \\
& Asian & 1 & 3.029 & 0.123–74.60 & 0.498 & NA & NA & NA \\
& Arab & 1 & 9.774 & 0.512–186.5 & 0.130 & NA & NA & NA \\
\hline
TT versus GG & Overall & 5 & 2.693 & 1.492–4.863 & 0.001 & \textit{F} & 0.794 & 0 \\
& European & 3 & 2.476 & 1.341–4.575 & 0.004 & \textit{F} & 0.943 & 0 \\
& Asian & 1 & 3.123 & 0.127–76.92 & 0.486 & NA & NA & NA \\
& Arab & 1 & 17.18 & 0.871–338.9 & 0.062 & NA & NA & NA \\
\hline
\end{tabular}
\caption{Meta-analysis of associations between \textit{TNFAIP3} rs5029931 polymorphisms and RA}
\end{table}

\textit{TNFAIP3}, tumor necrosis factor alpha inducible protein 3; RA, rheumatoid arthritis; OR, odds ratio; CI, confidence interval; \( F \), fixed-effects model; \( R \), random-effects model; NA, not available.
phisms and RA susceptibility. Our findings revealed a link between these polymorphisms and RA risk. We show a substantial relationship between TNFAIP3 rs2230926 and rs5029937 polymorphisms and the possibility of RA in Europeans and Asians. These data imply that TNFAIP3 polymorphisms are associated with the onset of RA in Europeans and Asians. Our previous meta-analysis of the relationship between TNFAIP3 polymorphisms and RA risk was updated in this research as well [30]. Furthermore, TSA demonstrated that the cumulative Z-curve for the rs2230926 and rs5029937 polymorphisms crossed traditional monitoring boundaries despite not meeting the required information size, indicating that the evidence obtained for this meta-analysis on the genetic as-

![Fig. 3. ORs and 95% CIs of individual studies and pooled data for the two alleles versus one allele of the TNFAIP3 rs5029937 polymorphism with respect to susceptibility to RA in all subjects (a) and in each ethnic group (b).](image)

![Fig. 4. TSA of TNFAIP3 rs2230926 and rs5029937 polymorphisms and risk of RA in allelic model. The blue line represents the cumulative Z-score of the meta-analysis. The red straight line represents the conventional $p = 0.05$ statistical boundaries. RIS: Required information size.](image)

(For figure see next page.)
sociation between the TNFAIP3 polymorphisms and the risk of RA was robust.

We proposed possible explanations for the association between RA incidence and TNFAIP3 polymorphisms. First, our findings were consistent with the functional impact of the rs2230926 polymorphism. The disease-associated variation in rs2230926 is a non-synonymous mutation that leads to a phenylalanine-to-cysteine alteration at A20 residue 127, which is important for anti-inflammatory effects. The risk allele (Cys127) results in reduced suppression of NF-κB activation or lower TNFAIP3 mRNA levels [9]. These data imply that decreased A20 negative regulatory activity leads to increased immunological activity, thereby increasing autoreactivity, and that rs2230926 plays a functional role in the development of RA. Second, the rs5029937 polymorphism may be linked to a neighboring causative variant.

This meta-analysis differs from earlier studies that examined the relationship between TNFAIP3 polymorphisms and RA risk [30]. The present investigation included five more studies as well as a more complete stratified analysis. TSA was also used to ensure the consistency and reliability of our findings. Our revised meta-analysis agreed with findings from previous research that was based on Europeans; however, unlike the previous meta-analysis, our updated meta-analysis found a significant relationship between the rs5029937 polymorphism and RA among Asians [30].

However, this study has a few limitations that are detailed as follows. First, publication bias, heterogeneity, and confounding factors may have skewed the meta-analysis results. Second, because our ethnic-specific meta-analysis included data from European and Asian patients, our results are restricted to these ethnic groups. There was only one study each based on the Arab and African American groups. Additional studies on other ethnic populations are required. Third, since there was inadequate data in the trials, the data were not stratified by parameters such as rheumatoid factor status, anti-cyclic citrullinated peptide antibody status, clinical characteristics, or environmental variables.

In conclusion, our meta-analysis of published data revealed that TNFAIP3 polymorphisms rs2230926 and rs5029937 are related to RA susceptibility in Europeans and Asians. Further research is needed to understand whether TNFAIP3 polymorphisms influence RA susceptibility in other ethnic groups. A thorough explanation of TNFAIP3’s involvement in RA and knowledge of its modulation would undoubtedly be helpful in the treatment of RA, according to the results of this updated meta-analysis. TNFAIP3’s clinical potential as a biomarker for RA diagnosis and prognosis is impressive antecedent to its potential as a therapeutic target.

Statement of Ethics

An ethical statement was not required for this study type, as no human or animal subjects or materials were used.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no funding for this work.

Author Contributions

Young Ho Lee was involved in conception and design of study, acquisition of data, analysis and/or interpretation of data, drafting the manuscript, and revising the manuscript critically for important intellectual content. Gwan Gyu Song was involved in conception and design of study, analysis and interpretation of data, and drafting the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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DOI: 10.1159/000526212