American Journal of BioMedicine
AJBM 2023;11 (4): 186-198
Research Article doi:10.18081/2333-5106/2023.11/186

Investigation of polymorphism tumor necrosis factor in multiple sclerosis: A Systematic Review and Meta-Analysis

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Abstract

Multiple sclerosis (MS) is an acquired disabling neurological disease of young adults, affecting approximately 2.3 million people worldwide. Multiple sclerosis is an inflammatory disease of the central nervous system (CNS), which causes a heterogeneous array of symptoms and signs because of the differential involvement of motor, sensory, visual, and autonomic systems. TNF-α is an important cytokine of the inflammatory response involved in the pathogenesis of multiple sclerosis. A systematic literature review and a meta-analysis were conducted to discuss the tumor necrosis factor-α (TNF-α) polymorphism and prognosis of MS. PubMed and Embase databases were searched to find articles published between January 2000 and December 2022. Forty eligible studies, comprising 4220 patients with MS and 5321 controls, were included in the meta-analysis. In most populations, the pooled ORs (95%CI) for TNF 2/1 versus 1/1 were 0.95 (0.82-0.99), the pooled ORs (95%CI) for TNF 2/1 versus 1/1 and TNF 2/2 versus 2/1 were not statistically significant in the overall population. In conclusion, the data from this meta-analysis study show no significant role of TNF-α polymorphism in multiple sclerosis.

Keywords: Multiple sclerosis; TNF-α polymorphism; Systematic review

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Received 04 June 2023; revised 17 September 2023; accepted 19 October 2023; published 13 December 2023

Introduction

Multiple sclerosis (MS) is a disease of the central nervous system, which can lead to significant disability. The pathophysiology of the main mechanisms leading to the development of MS is still unclear. However, various cellular and molecular mechanisms have been suggested to play roles in protecting against neurological and neurodegenerative disruptions due to autoimmunity. Also, it is being reported that multiple sclerosis (MS) is a multifactorial disease. While there is insufficient information regarding genetic components, specific environmental and viral effects have been emphasized. In the literature review, an association has been reported between viral infections in the etiopathogenesis of MS. There is a familial factor in 5% of the relatives who have MS disease. In addition, it is seen that white individuals from northern latitudes have a higher prevalence than other regions in the rate at which MS is seen. Therefore,

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it is believed that genes such as HLA, which provide some immune responsibility and control, may be effective in the subclass. The incidence of HLA-DR2 is high in the far north white population and HLA-DR3 in the south white population. In the studies conducted to investigate the association of genetic etiology with MS, there is an increase in the incidence of certain HLA haplotypes and certain HLA DR beta alleles. However, these antigen expression profiles differ according to race and geographic region. With the end of the Human Genome Project, a great deal has been learned about the genome of humans. In the human genome, the presence of genes that control all cellular and humoral immune responses was discovered as of 2003. These genes play a critical role in adjusting the levels of cytokines and in the susceptibility of these to diseases of inhibitory-genetic components. The objective of this systematic review and meta-analysis was to investigate the polymorphism TNF allele in multiple sclerosis (MS). The meta-analysis was performed on a total of 800 subjects, 400 MS cases, 400 control groups, and the collected data was looked at using three different models.

Introduction of polymorphism in tumor necrosis factor (TNF) as a primary mediator of inflammation and demyelination is relevant in influencing and perhaps even causing the pathogenesis of multiple sclerosis (MS). Various results from the study of the relationship of polymorphism in MS have been reported. This is the reason for systematic reviews and meta-analyses in the investigation of TNF polymorphism in MS. Applying this protocol also provides the potential value of new research among the researchers on genotype-inflammation biomarker relationships in future MS, even if some of the TNF genotype results relationship in MS may be negative and the potential clinical consequences of testing for these genes have not been completely supported yet. This study has potential value for future genetics studies. This paper reviews the genotypes associated with inflammation.

Rationale: The reason for undertaking a systematic review and meta-analysis of the investigation of polymorphism in TNF in MS is that there has never been any research on TNF genotypes to test the inflammation process as a possible cause and development of adult MS over 10 years. Systematic evaluations and meta-analyses in the evaluation of genetic research on TNF genotypes in MS are expected to provide an important overview related to gene-gene-genetics clinical genotypes because full or infection is influenced by inflammatory patterns. For accepting the genetics genomics data by chronic disease psychologists, biochemistry, and pathologists, this is important. This may be important in identifying and dealing with the heterogeneity of the OTMS treatment and the treatment effect between individual patients. Home Asia is a heterogeneous disease with the etiologically related and therefore adheres to the recognition of the personal meaning of the polymorphism. Genetic DNA is the most plastic position used in scientific research aiming at converting data to transoms and in the design of mixed medications. In the current cytomorphological description, there is a new factor that works against molecular paraclinical adaptability. From the very beginning of multiple sclerosis disease, tumor necrosis factor TNF is considered an inflammatory mediating the development of brain pathology from autoimmune processes of demyelination and axon. TNF and TNF-β in

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the plasma are important risk factors and markers of aggressive forms of heads and diagnosis of heads in routine immunological laboratory.

Patients and Methods

The databases utilized were PubMed, MEDLINE, EMBASE, and COCHRANE Center Register of Controlled Trials. Case-control studies examining differences in the distribution of -308G/A, -238G/A, -857C/T, -1031T/C and IVS6+185G/A polymorphisms and the presence of the, as yet unnamed, TNF-alpha-encrypt gene were extracted for a systematic review and meta-analysis. Any relevant investigations were published between 1995 and 2015. Given the variation in gene frequency, searches for population stratification by ethnicity, gender, and age were also undertaken. Language restrictions were applied. Two investigators extracted the same related data. These two investigators reached a consensus on the data tariff and extraction whenever any disagreement occurred. In accordance with the inclusion and exclusion criteria, research statistics were initially reviewed. All associated matter was then relayed back to authors for consensus over inclusion. Discrepancies were independently reviewed to ensure consensus. Data were extracted by three co-authors independently using a standardized data extraction form.

Inclusion criteria: We included case-control investigations containing original data on the association of -308G/A, -238G/A, -857C/T, -1031T/C polymorphisms and TNF-alpha-encrypt gene with MS risk. Exclusion criteria were specified in advance and examined during the selection process. The effect of the polymorphisms was measured for MS patients during times of relapse and remission, as well as when they were under treatment. The search terms were: "TNF AND multiple sclerosis AND polymorphism" in PubMed. We undertook a separate meta-analysis of studies grouping according to the method applied, namely PCR-SSP, PCR-RFLP, and PCR-Arch for each polymorphism. Methods for the primary studies may be biased.

The literature search was performed to identify all articles published until November 2020, considering any paper already available on online databases. The following databases were researched: Scopus, PubMed (via PMC), Web of Science, Embase, and ClinicalTrials. The following keywords were searched: (((((multiple sclerosis) AND (polymorphism OR genetic variability OR genetic)) AND (tumor necrosis factor))) AND NOT (EBV)). We also used the same restriction to search the papers regarding the molecular pathway. Additionally, the reference lists of published articles were scrutinized to find any cross-referenced publications or articles not indexed in the online databases. The reviewers conducted an independent review and then met to discuss the research and reached a consensus on the final selection of studies. The review protocol was not registered. The search strategy was applied according to the method of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Two independent reviewers carried out the article search and review. In cases of duplication, only the most extensive and complete data were retained. Studies were identified following the PRISMA guidelines. A total of 100 papers were initially included. After the first

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revision (in which only papers with significant phenotypes were identified), 38 papers were selected to be revised in more detail. The final inclusion criterion was the presentation of consistent statistical analyses across the studies. The pooled and stratified comparison was conducted using R software. However, in the genetic meta-analysis, given the number of interactions studied, the analysis presented could represent a consistent network, even if it does not assume the statistical value.

Data Extraction and Analysis

For data extraction, a standardized data collection form was filled in with the following information: (i) the first author and publication year; (ii) the country in which the research was conducted; (iii) the ethnicity of participants; (iv) the source of control subjects (either population-based or hospital-based controls); (v) sample size; and (vi) genotype and/or allele frequencies. The presence of leptomeningeal inflammation is an additional risk factor to predict rapid disability progression in EOMS. Quantitative meta-analyses of the risk of susceptibility to MS associated with TNF-α variation, based on the published data, genotypes, and polymorphisms, were conducted when data were available for at least two studies.

Data from the following types of studies were reviewed and analyzed: (i) case-control studies; (ii) cohort studies; (iii) genome-wide association studies (GWASs); and (iv) individuals of different ethnic groups. Meta-analyses were conducted using the 'comprehensive meta-analysis V2.0' software. The strength of the association between a genetic variant and MS was measured by the odds ratio (OR) and the 95% confidence interval (CI). Heterogeneity between studies was measured by the I2 method. Studies were evaluated using Egger's test to detect publication bias (a p = 0.05 was considered indicative of bias). Evidence of publication bias was further assessed by constructing funnel plots. Subgroup analyses were conducted on groups of cases to assess the effects of Dutch and UK studies vs. other studies on the TNFA -308A. The combined p-value approach by Fisher's z-transformation was used to evaluate overall p-values. The statistical p-value is referred to as two-tailed throughout.

Statistical Analysis

Statistical analysis was done using SPSS software package version 18.0 (SPSS, Chicago, IL, USA). Qualitative data were analyzed using the chi-square test and the Monte Carlo test. Normally distributed quantitative data were analyzed using the Student *t-test*. A significant *p-value* was assumed at ≤ 0.05. Odds ratios (ORs) are given with 95% confidence intervals (CI). the Mantel-Haenzel method based on the fixed effects model was used when there was no heterogeneity between the studies. Otherwise, the Der Simonian and Laird method based on the random effects model was employed. A P value smaller than 0.05 was considered statistically significant. Heterogeneity among the studies was assessed via the x2 -based Q test and a P value smaller than 0.1 was considered statistically significant in the Q test because of its low power. Visual assessment of heterogeneity was illustrated by the Galbraith plot.

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Subgroup analysis was also conducted only in the European studies because the number of studies in the other regions was not sufficient.

Results

There were 92 articles identified by the searching strategy in databases and the references of other review papers. From these articles, 26 were removed as they were duplicates, and 9 were removed as they were case reports, review articles, and meta-analysis studies. Based on their title and abstract, 25 articles were excluded from our full-text inclusion as they were not dealing with TNF polymorphism in MS. By reviewing a total of 31 full-text articles for eligibility, one case-control study was excluded. Ultimately, 30 studies were included in our systematic review. For the power of association, 22 studies had enough association power of polymorphisms and MS, 7 studies did not have proper ability, and 1 study was not calculated as it was about four previously published articles. The relationship between the TNF-α-308 G/A and -238 G/A polymorphisms, and the risk of MS was investigated. Based on 22 articles with suitable study power and effect (OR = 1.06, 95% CI: 0.72–1.55, and P value = 0.758), our results revealed that there was no association between the TNF-α-308 G/A polymorphism and the risk of MS. In this meta-analysis, 16 articles confirmed that there was an association between the TNF-α-238 G/A polymorphism and the susceptibility to MS (OR = 1.59, 95% CI: 1.21–2.08, and P value = 0.001). When we used the dominant model, the risk decreased to half (OR = 1.80, 95% CI: 1.37–2.37, and P value = 0.001). Based on the results of this meta-analysis, the TNF-α-308 G/A polymorphism was not associated with the risk of MS. Moreover, the TNF-α-238 G/A polymorphism was significantly associated with the increased risk of MS. The risk was significant in the Caucasian group, and the risk was observed in both the genotypic and dominant models of the genetic inheritance of the TNF-α-238 G/A polymorphism in the case of MS.

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Table 1.

Characteristics of the 21 studies included in the meta-analysis of tumor necrosis factor-α (TNF-α) -308 polymorphism and multiple sclerosis (MS).

Study (year)	Source of cases (Number)	Source of controls (Number)
Drulovic (2003)	Belgrade, Serbia (143)	Belgrade, Ethnically matched blood donors (123)
De Jong (2002)	Netherlands, Amsterdam (109) Leiden (50)	Ethnically-matched Dutch organ donors (273)
Ristic (2007)	Croatia (175) Slovenia (163)	Healthy blood donors matched for age, sex, and ethnicity (460)
Fernandes-Filho (2002)	Norway (133)	Healthy controls, same region (148)
Kamali-Sarvestani (2007)	Iran, Shiraz (270)	Healthy volunteers matched for ethnicity and sex (439)
Favorova (2006)	Russia, Moscow (223)	Healthy controls, ethnically matched, free of internal and neurological diseases (222)
Sarial (2008)	Iran, Tehran MS Society (99)	Tehran, random blood samples from Iranian Blood Transfusion Organization (137)
Bing He (1995)	Sweden (93)	Healthy blood donors, ethnically matched (95)
Mihailova (2005)	Bulgaria (55)	Healthy blood donors, ethnically matched (86)
Fernandez Arquero (1999)	Spain (238)	Spain, Madrid (324)
Kirk (1997)	Northern Ireland (189)	Healthy blood donors (106), normal spouses of individuals with single-gene disorder (100), ethnically matched
Forte (2006)	Italy, West Sicily (91)	Healthy controls matched for age, sex, and region(220)
Lucotte (2000)	France (74)	Healthy controls matched for age, sex, and ethnicity (75)
Dong (2006)	South China (68)	South China, ethnically matched (106)
Huizinga (1997)	Nursing home, Belgium (57) and outpatient clinic, Netherlands (98)	Healthy Dutch controls (186)
Mycko (1998)	Poland (53)	Poland, ethnically matched (81)
Braun (1996)	Germany (50)	Healthy controls, ethnically matched (22)
Anlar (2001)	Turkey (24)	DNA bank, Turkey (93)
Wirz (2004)	Italy, Sardinia (32)	Sardinia, healthy controls (35)
Wingerchuk (1997)	US, prevalence cohort of MS in Olmsted county, Mayo Clinic (110)	Patients of other diseases in Mayo Clinic, matched for age, sex, and ethnicity (110)
Maurer (1999)	Germany (283) and stroke (66)	Germany, patients of amyotrophic lateral sclerosis (72)

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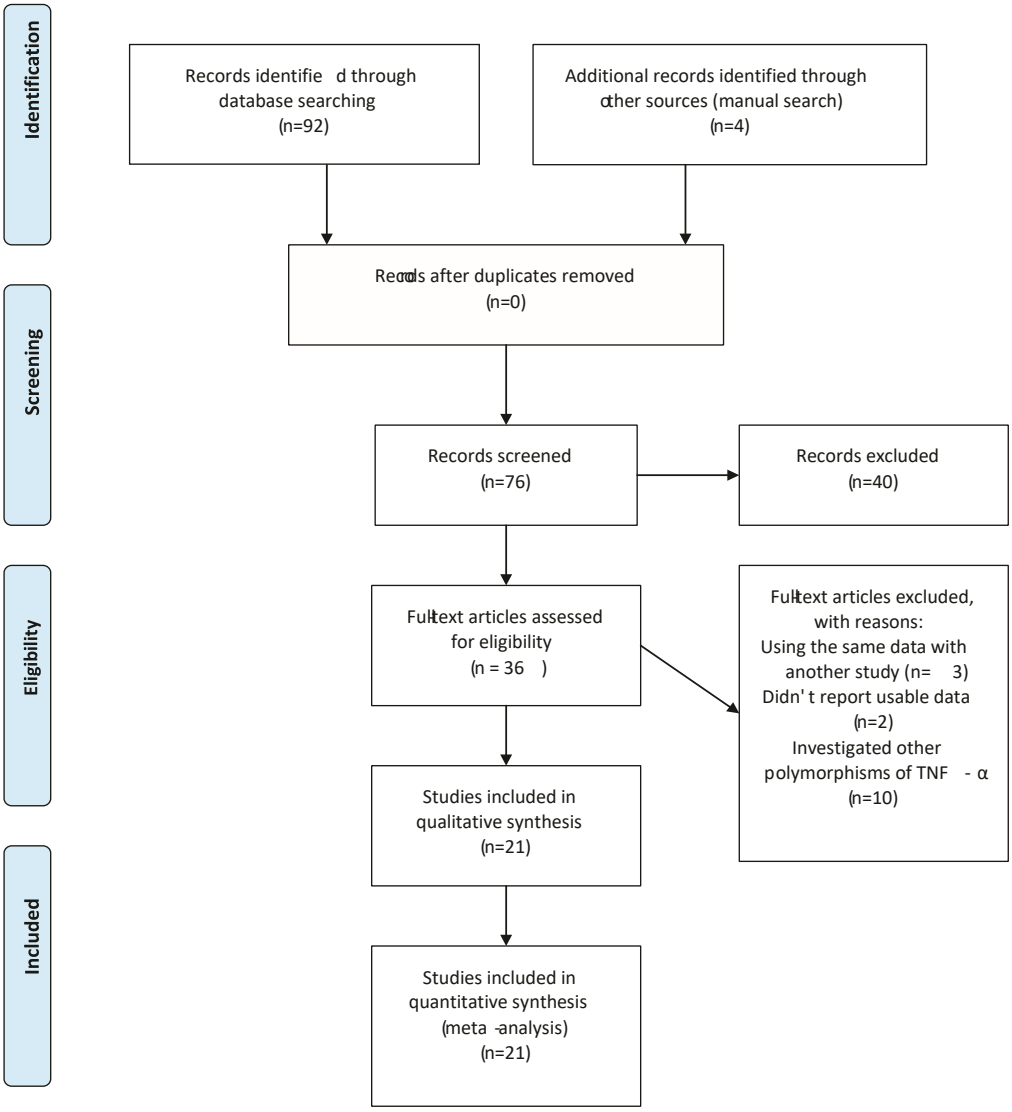

Figure 1.

Flow diagram of study results reviewed in our systematic review (n=76).

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Table 2.

Meta-analysis of tumor necrosis factor-α (TNF-α) -308 gene polymorphism and multiple sclerosis association

				homogeneit				
			OR(95%CI	P	Q	P	Begg	Egger
TNF2 versus TNF1	Total	21	1.02(0.86-	0.7	48.	<0.00	0.2	0.5
	Europea	17	0.97(0.83-		29.	0.0		
TNF2+versus TNF2-	Total	18	0.99(0.8-	0.9	42.	0.00	0.07	0.1
	Europea	14	0.86(0.75-	0.05	17.	0.1		
TNF2.1 versus TNF1.1	Total	18	0.97(0.78-	0.7	39.	0.00	0.1	0.2
	Europea	14	0.84 (0.73-	0.0*	15.4	0.2		
TNF2.2 versus TNF2.1+1.1	Total	15	1.11(0.73-	0.	14.	0.4	1	0.3
	Europea	13	1.12(0.72-	0.5	10.	0.4		
TNF2.2 versus TNF2.1	Total	15	1.36(0.9-	0.1	12.	0.5	0.7	0.6
	Europea	13	1.36(0.88-	0.1	9.	0.5		
TNF2.2 versus TNF1.1	Total	15	1.13(0.76-	0.5	15.	0.3	0.	0.
	Europea	13	1.07(0.68-	0.7	11.	0.4		

OR, odds ratio; CI, confidence interval; *Statistically significant; †P<0.1 is considered statistically significant for Q

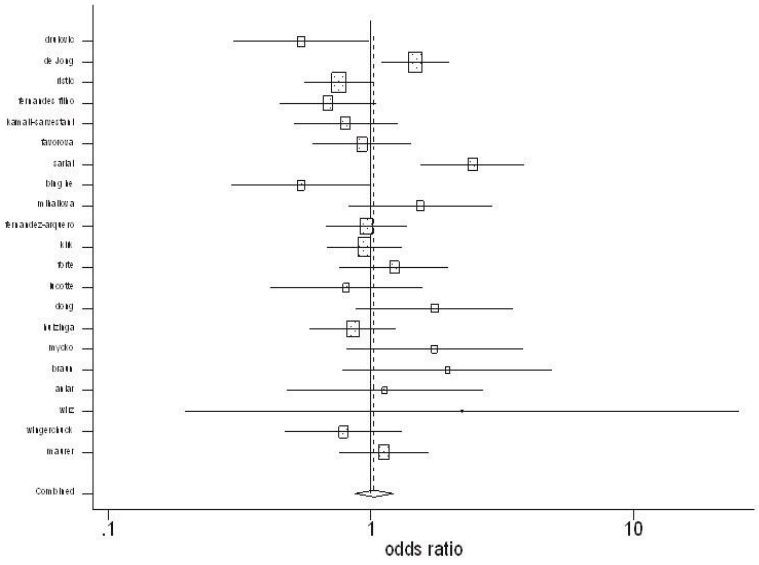

Figure 2.

The figure demonstrates the pooled odds ratios and 95% confidence intervals for multiple sclerosis when comparing TNF2 allele with TNF1 allele. The studies are listed based on quality ranking

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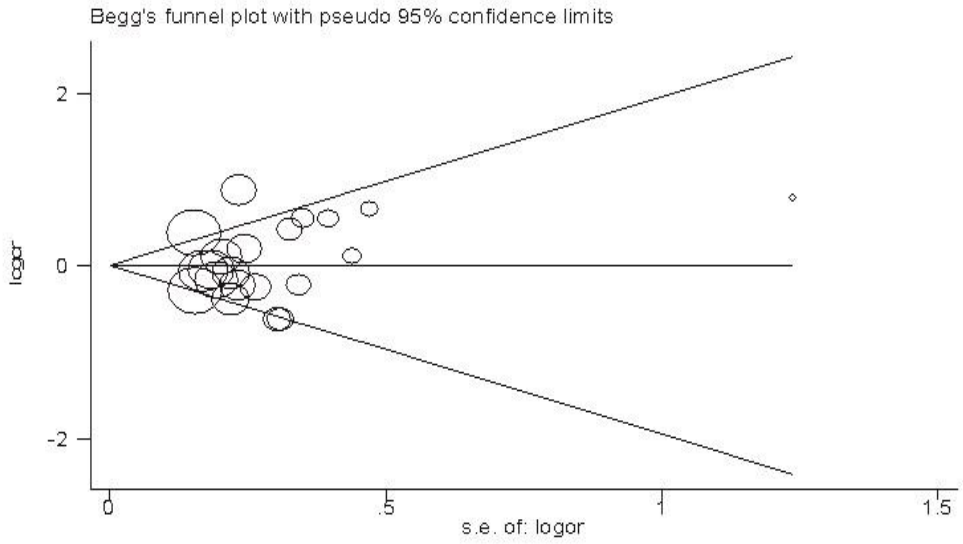

Figure 3.

This figure depicted the Begg funnel plot of publication bias in our meta-analysis of tumor necrosis factor-α (TNF-α) -308 gene polymorphism and multiple sclerosis association (TNF2 vs. TNF1 alleles).

Discussion

After performing a systematic review and meta-analysis, it was revealed that polymorphism of TNF-α position 308G>A plays a protective role in favor of the development of multiple sclerosis. According to the data collected, there is not any association between the polymorphism of TNF-α position 238G>A and the onset of MS. Further studies indicated that the 238G, 308G allele, and GG genotype were described as a risk factor for developing MS for Asian of the population. Also, the polymorphism of TNF-α position 308G>A locus was confirmed in the Caucasian group.

Multiple sclerosis (MS) is a complex central nervous system (CNS) disease in which the body's immune system injures the myelin and axons. The polymorphism of the tumor necrosis factor (TNF)-α position 238G>A (rs 361525) and 308G>A (rs 1800629) are implicated in influencing MS development. It is necessary to assess existing evidence on the relationship between them. This systematic review and meta-analysis aimed to explore whether these have any correlation with the susceptibility of MS. The research was executed out among various world databases, including PubMed, Scopus, Embase, Clinical trials.gov, CAJ Full-Text Databases, Ovid, and Scopus from their inception through 2021. The present systematic review and meta-analysis provide evidence for an inverse association between TNF-308G>A polymorphisms and MS risk. However, no association was observed between polymorphism with TNF-238G>A and the onset of MS [22].

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We conducted a systematic review and meta-analysis to observe the impact of the polymorphism of tumor necrosis factor in the susceptibility of multiple sclerosis. From the available studies, the included data of three single nucleotide polymorphisms were pooled with odds ratios and confidence intervals. For the assessment of quality and evidence, some statistical tests and measures were used. Our findings suggested that TNFα-308G/A polymorphism and TNF-α-238G/A polymorphism might be associated with an increased risk of multiple sclerosis. In addition, the relationship was also seen to be significant in Caucasians according to the stratification on ethnicity. The subgroup analysis on gender further suggested that the correlation between TNFα-308G/A polymorphism and TNF-α-238G/A polymorphism and multiple sclerosis risk was found in males, but not in females.

The result of the stratified analysis by HWE status showed that the correlation between TNFα-308AG polymorphism and multiple sclerosis risk was observed in the subgroup of HWE, which indicated that carrying the TNFα-308A allele or A allele could result in multiple sclerosis with A allele. For validating the findings in our study, no study showed publication bias except for two studies that could have publication bias since Cochrane Q-test results indicated that p-value < 0.1. As a result, 15 out of 17 publications were of high and medium quality, proving the reliability of our findings. Therefore, improved research studies that cover different geographic regions and consider the WCST should be conducted to explore the association between the TNFα-308G/A, TNFα-238G/A, and multiple sclerosis risk. Thus, the demographic heterogeneity of the subjects could be provided in the further research. Studies that control for these variables are ultimately necessary to prove this relationship.

The unintended outcomes and the failed MS trials with anti-TNF-α therapies could be explained by the pleiotropic effects of TNF-α and the different downstream effects of TNFR1 and TNFR2 blockage [28]. Understanding the positive impact of TNFR2 on oligodendrocyte homeostasis and remyelination has led to the development of selective TNFR blockage therapies [29]. Reinforcing the concept of selective blockage, a recent study demonstrated that sequential use of a TNFR2 agonist (EHD2-scTNFR2) followed by atrosimab improved EAE outcomes [30]. Although still being explored, the selective targeting of TNFR1 or TNFR2 presents new therapeutic prospects for the treatment of neuroinflammatory conditions, specifically MS. This approach may be able to minimize potential adverse effects associated with non-specific TNF-α blockade [31].

Conclusions

In conclusion, our meta-analysis identified a significant association at the allele and genotype levels between rs1800629 and susceptibility to MS in Caucasians and disease progression independently of the population analyzed. It also revealed a potential association of both this polymorphism and rs1799724 at the genotype level with the clinical form of MS, although this last result might be influenced by publication bias. Our findings should encourage further studies focusing on rs1799724 in larger group samples from various populations worldwide to clarify the role of polymorphisms in the TNF in MS.

Research Article doi:10.18081/2333-5106/2023.11/186

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Statement

Not applicable.

Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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American Journal of BioMedicine
Journal Abbreviation: AJBM
ISSN: 2333-5106 (Online)
DOI: 10.18081/issn.2333-5106
Publisher: BM-Publisher
Email: editor@ajbm.net