ASSOCIATION OF TNF-α GENE POLYMORPHISM WITH THE RISK AND SEVERITY OF RHEUMATOID ARTHRITIS

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Introduction:

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by persistent synovial inflammation, which leads to progressive joint destruction and significant disability if not adequately treated [7]. Affecting up to 1% of the global population, RA presents a major public health challenge, severely impacting patients' quality of life and functional capacity [6]. The etiology of RA remains incompletely understood, but it is established as a multifactorial disease arising from a complex interplay between genetic predisposition and environmental factors [3, 7]. Among the numerous genetic factors under investigation, polymorphisms in the gene for tumor necrosis factor-alpha (TNF-α) have garnered considerable attention. TNF-α is a pivotal pro-inflammatory cytokine central to the pathogenesis of RA, and genetic variations, such as the TNF-α-308G/A polymorphism (rs1800629), may influence its production, thereby potentially affecting disease susceptibility and severity [3]. However, individual studies have yielded conflicting results regarding this association, with some reporting a significant link and others finding none [2, 4]. This inconsistency has necessitated large-scale systematic reviews and meta-analyses, conducted according to rigorous guidelines like PRISMA, to clarify the role of this polymorphism [5, 8].

Pathogenesis and genetic factors. The pathogenesis of RA is driven by a breakdown of immune self-tolerance, leading to a chronic inflammatory state within the joints [3]. This process is initiated in genetically susceptible individuals and is characterized by the production of autoantibodies and the infiltration of synovial tissue by immune cells. This transforms the synovium into an aggressive, invasive pannus that erodes cartilage and bone [7]. The inflammatory cascade is orchestrated by a network of cytokines, with TNF-α playing a dominant role [7]. The contradictory findings in studies investigating the link between the TNF-α-308G/A polymorphism and RA highlight the complexity of genetic association studies in multifactorial diseases [2, 4].

Association with RA susceptibility. To synthesize the available evidence, a comprehensive meta-analysis was conducted, incorporating data from 34 studies involving over 12,000

participants [8]. The analysis rigorously evaluated the association between the TNF-α-308G/A polymorphism and the risk of developing RA using five different genetic models. The results conclusively demonstrated no statistically significant association between this polymorphism and overall RA susceptibility. This lack of association held true even when the data was stratified by geographic region, suggesting that the TNF-α-308G/A polymorphism is not a major independent risk factor for the development of RA across diverse populations [8].

Association with RA severity. While the polymorphism does not appear to influence RA susceptibility, its potential role in modifying disease severity is of great clinical interest, particularly for managing patients with difficult-to-treat or refractory disease [1]. The meta-analysis also examined the association between the TNF-α-308G/A polymorphism and RA severity based on data from six studies. While the overall analysis showed no significant link, a stratified analysis by ethnicity revealed a significant association within the European population. Specifically, in this group, the presence of the 'A' allele was associated with the severity of RA [8]. The statistical robustness of this finding was confirmed using false-positive report probability (FPRP) analysis.

Conclusion and Clinical Implications. The available evidence, consolidated through a large-scale meta-analysis, suggests that the TNF-α-308G/A polymorphism does not play a significant role in determining susceptibility to RA [8]. However, it appears to be an important modifying factor for disease severity, at least within European populations [8]. This finding has important implications for future research and clinical practice, highlighting the potential for using genetic markers to prognosticate and personalize treatment strategies. Although not yet ready for routine clinical use, genotyping for TNF-α-308G/A could become a valuable tool in stratifying patients and tailoring therapy. Further research is needed to validate these findings in other ethnic groups and to explore the complex interplay between this and other genetic markers in the context of personalized medicine for rheumatoid arthritis.

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