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## **Gene Polymorphisms of TNF-238G/A, TNF-308G/A, IL10-1082G/A, TNFAIP3, and Comorbidity Occurrence: A Comprehensive Review**

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## ABSTRACT

Gene polymorphisms play a pivotal role in susceptibility to various diseases, including inflammatory and autoimmune disorders. Tumor Necrosis Factor-alpha (TNF- $\alpha$ ) gene polymorphisms (-238G/A and -308G/A), interleukin-10 (IL-10) gene polymorphism (-1082G/A), and TNFAIP3 (TNF- $\alpha$ -induced protein 3) polymorphisms are associated with inflammatory pathways and immune responses. These genetic variations are implicated in the occurrence and severity of comorbidities such as cardiovascular diseases, metabolic syndrome, autoimmune disorders, and infections. This review highlights the association of these polymorphisms with comorbid disease development, providing an analysis of the genetic contributions to disease pathophysiology and clinical implications.

## Introduction

Gene polymorphisms in cytokine-encoding genes like TNF- $\alpha$ , IL-10, and TNFAIP3 influence immune regulation, inflammation, and apoptosis pathways. Such genetic variations can modulate individual susceptibility to comorbid conditions, particularly in diseases like rheumatoid arthritis, diabetes, cardiovascular diseases, and infections. This review provides an overview of the key gene polymorphisms (TNF-238G/A, TNF-308G/A, IL10-1082G/A, and TNFAIP3) and their association with disease comorbidity occurrence.

### TNF- $\alpha$ Gene Polymorphisms: TNF-238G/A and TNF-308G/A

#### Role of TNF- $\alpha$ in Inflammation

Tumor necrosis factor-alpha (TNF- $\alpha$ ) is a pro-inflammatory cytokine that regulates immune responses and inflammation. It plays a central role in acute-phase reactions, apoptosis, and cell proliferation. Dysregulation of TNF- $\alpha$  is strongly associated with chronic inflammatory diseases and immune dysfunction.

#### TNF-308G/A Polymorphism

- The TNF-308G/A polymorphism involves a guanine (G) to adenine (A) substitution at position -308 in the promoter region of the TNF- $\alpha$  gene.
- Studies have shown that the A allele leads to increased TNF- $\alpha$  production, exacerbating inflammation and tissue damage.
- **Clinical Associations:**
  - In autoimmune disorders such as rheumatoid arthritis (RA), carriers of the -308A allele exhibit higher disease activity and (1) comorbidities like cardiovascular disease (CVD)(2).

- In type 2 diabetes mellitus (T2DM), the TNF-308G/A polymorphism contributes to insulin resistance and metabolic syndrome(3).

#### TNF-238G/A Polymorphism

The TNF-238G/A polymorphism similarly affects TNF- $\alpha$  transcription. However, the impact on TNF- $\alpha$  expression is less significant compared to the -308 polymorphism.

- **Clinical Associations:**

In liver diseases, such as chronic hepatitis B and C, the TNF-238A allele is linked to increased hepatic inflammation and fibrosis(4). It is also associated with susceptibility to sepsis and infections, which can complicate comorbid condition(5).

#### IL-10 Gene Polymorphism: IL10-1082G/A

##### Role of IL-10 in Immune Regulation

Interleukin-10 (IL-10) is an anti-inflammatory cytokine that suppresses excessive immune responses, preventing tissue damage and maintaining immune homeostasis.

##### IL10-1082G/A Polymorphism

- The IL10-1082G/A polymorphism in the promoter region affects IL-10 production. The G allele is associated with high IL-10 expression, while the A allele corresponds to lower expression levels.
- **Clinical Associations:**
  - ✓ **Autoimmune Diseases:** Low IL-10 production in A allele carriers leads to uncontrolled inflammation in diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis(6)
  - ✓ **Cardiovascular Disease:** IL-10 dysregulation contributes to atherosclerosis and endothelial dysfunction, increasing CVD risk in patients with inflammatory comorbidities(7).
  - ✓ **Infectious Diseases:** Lower IL-10 levels impair immune regulation, increasing susceptibility to infections like tuberculosis and sepsis(8).

#### TNFAIP3 Gene Polymorphisms

##### Role of TNFAIP3 in Inflammation

TNFAIP3 encodes the A20 protein, a negative regulator of NF- $\kappa$ B signaling, which is critical in inflammation, apoptosis, and immune responses. Mutations or polymorphisms in TNFAIP3 can result in chronic inflammation and immune dysregulation.

##### Clinical Associations:

###### 1. Autoimmune Diseases:

- TNFAIP3 polymorphisms are strongly associated with autoimmune diseases such as SLE, rheumatoid arthritis, and inflammatory bowel disease (IBD)(9).
- Polymorphisms lead to prolonged NF- $\kappa$ B activation, increasing inflammation and disease severity.

## 2. Comorbidities:

- **Cardiovascular Disease:** Chronic inflammation resulting from TNFAIP3 dysfunction predisposes individuals to endothelial damage and atherosclerosis(10).
- **Metabolic Syndrome:** Dysregulation of inflammatory pathways contributes to obesity, insulin resistance, and type 2 diabetes(11).

## 3. Infectious Diseases:

Impaired TNFAIP3 function reduces immune system control, increasing susceptibility to infections like sepsis(12).

### Comorbidity Occurrence and Genetic Polymorphisms

Genetic polymorphisms in TNF- $\alpha$ , IL-10, and TNFAIP3 influence the inflammatory and immune response, contributing to comorbid disease development:

**Autoimmune Diseases:** TNF-308A and IL10-1082A polymorphisms exacerbate inflammation, increasing the risk of CVD and infection(13)

- **Metabolic Syndrome:** TNF-308G/A is associated with insulin resistance, obesity, and diabetes(14).
- **Infections:** TNF-238A and IL10-1082A polymorphisms increase susceptibility to sepsis and chronic infections

### Future Perspectives

- **Personalized Medicine:** Genetic screening for TNF- $\alpha$ , IL-10, and TNFAIP3 polymorphisms can help identify at-risk individuals for early interventions.
- **Targeted Therapies:** Inhibitors of TNF- $\alpha$  and modulators of NF- $\kappa$ B signaling pathways hold promise in managing inflammatory comorbidities
- **Precision Nutrition:** Lifestyle and dietary interventions tailored to genetic susceptibility may mitigate disease progression.

### Conclusion

Gene polymorphisms in TNF- $\alpha$  (-238G/A, -308G/A), IL-10 (-1082G/A), and TNFAIP3 significantly influence inflammation and immune regulation, contributing to the occurrence of comorbidities such as autoimmune disorders, cardiovascular disease, and infections. A better understanding of these polymorphisms enables targeted management strategies and precision medicine approaches to reduce disease burden.

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