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Transforming Growth Factor-β Gene Polymorphisms and Their Association with Chronic Spontaneous Urticaria: A Comprehensive Review

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ABSTRACT

Background: Chronic spontaneous urticaria (CSU) is a common and distressing dermatological condition characterized by the spontaneous appearance of wheals, angioedema, or both, lasting for six weeks or longer without an identifiable external trigger. The global burden of CSU is considerable, with significant impacts on quality of life, productivity, and healthcare resources. Although the precise pathogenesis remains incompletely understood, accumulating evidence implicates immune dysregulation, autoimmunity, and genetic predispositions in disease onset and progression. Among the various genetic contributors, polymorphisms in cytokine genes such as transforming growth factor-beta (TGF-β) have gained attention for their potential role in immune modulation and susceptibility to CSU. TGF-β is a multifunctional cytokine involved in immune tolerance, tissue homeostasis, and inflammation. Variations in the TGF-β gene, especially functional single nucleotide polymorphisms (SNPs), have been associated with altered cytokine expression and activity, which may contribute to aberrant immune responses observed in CSU. This review aims to provide a comprehensive synthesis of current knowledge on the relationship between TGF-β gene polymorphisms and chronic spontaneous urticaria, exploring both the genetic and immunological underpinnings. We first summarize the clinical presentation, classification, and diagnostic criteria of CSU, followed by an in-depth analysis of its etiopathogenesis, including recent advances in our understanding of immune and genetic factors. The review then highlights the biology of TGF-β, its regulatory functions within the immune system, and the structural and functional relevance of key polymorphisms. Finally, we examine the evidence linking TGF-β genetic variants to CSU susceptibility, severity, and treatment response, drawing on published studies across diverse populations. In conclusion, while current data support a possible association between TGF-β gene polymorphisms and CSU, further research is required to elucidate precise mechanisms and to validate these findings in larger, multi-ethnic cohorts. Enhanced understanding of the genetic landscape may facilitate risk stratification and the development of personalized therapeutic approaches for CSU.

Keywords: *Transforming Growth Factor-β , Chronic Spontaneous Urticaria*

INTRODUCTION

Chronic spontaneous urticaria (CSU) is a persistent, often debilitating skin disorder characterized by the spontaneous occurrence of itchy wheals, angioedema, or both, persisting for at least six weeks

10.48047/jocaaa.2024.33.06.76

without an identifiable external trigger. CSU significantly impacts the quality of life, causing discomfort, sleep disturbances, and psychological stress for affected individuals. Despite advancements in understanding, the precise pathophysiological mechanisms underlying CSU remain incompletely defined, with current evidence highlighting a multifactorial etiology involving autoimmunity, immune dysregulation, and genetic predisposition. Among the cytokines implicated in immune regulation, transforming growth factor-beta (TGF-β) has emerged as a critical player due to its multifaceted roles in immune modulation and inflammation. Notably, functional polymorphisms in the TGF-β gene may influence cytokine expression and activity, thereby affecting susceptibility to immune-mediated diseases, including CSU. The aim of this review is to synthesize the current literature regarding the association between TGF-β gene polymorphisms and chronic spontaneous urticaria, address knowledge gaps, and highlight potential avenues for future research and personalized treatment strategies [1-3].

Chronic Spontaneous Urticaria

Chronic spontaneous urticaria (CSU) is defined by the recurrent presence of transient wheals, angioedema, or both, lasting for more than six weeks without a clear, identifiable cause. It affects approximately 0.5% to 1% of the general population at any given time and is more prevalent among adults, particularly women, than children. The unpredictable and often persistent nature of CSU leads to considerable morbidity, with significant impacts on daily functioning and psychological well-being. Studies indicate that CSU often follows a relapsing and remitting course, with symptoms lasting for several years in many cases[1]. The disease burden is not limited to physical discomfort but extends to economic consequences due to frequent healthcare visits and treatment expenses[2].

The etiology of CSU is complex, involving a combination of immune, environmental, and genetic factors. Although some cases may be linked to autoreactivity or autoimmunity, the majority remain idiopathic. Recent research suggests that genetic predisposition may play a crucial role in determining susceptibility and disease severity. Moreover, certain gene polymorphisms related to immune regulation have been associated with CSU, highlighting the importance of exploring genetic factors in this context[3].

Classification of Urticaria

Urticaria is broadly classified into acute and chronic forms based on symptom duration. Acute urticaria resolves within six weeks, whereas chronic urticaria, including CSU, persists beyond this period. Chronic urticaria is further categorized into chronic spontaneous urticaria and chronic inducible urticaria, the latter triggered by specific physical or environmental stimuli such as pressure,

10.48047/jocaaa.2024.33.06.76

temperature, or sunlight[4]. CSU represents the most common form of chronic urticaria and is characterized by the absence of identifiable external triggers.

Within chronic urticaria, further subclassification can be based on the presence of angioedema, a deeper form of swelling involving the dermis and subcutaneous tissues. The overlapping presentation of wheals and angioedema is frequently observed in CSU patients. Accurate classification is essential for guiding clinical management and informing research studies that investigate underlying mechanisms and therapeutic responses[5]. The distinction between spontaneous and inducible forms is particularly important for genetic and pathophysiological studies.

Etiopathogenesis of Chronic Spontaneous Urticaria

The etiopathogenesis of CSU is multifactorial and not yet fully elucidated. Current understanding highlights the role of immune dysregulation, with mast cells and basophils being central effector cells responsible for the release of histamine and other proinflammatory mediators. Autoreactivity is observed in a significant subset of patients, often linked to the presence of functional autoantibodies against either the high-affinity IgE receptor (FcεRI) or IgE itself, which can induce mast cell degranulation[6]. These autoantibodies are found in 30-50% of CSU patients and are associated with more severe disease.

Genetic susceptibility also appears to play a key role in CSU pathogenesis. Variations in genes encoding cytokines, such as TGF-β, interleukins, and tumor necrosis factor-alpha (TNF-α), have been explored in recent studies for their potential contribution to disease susceptibility and expression. Environmental factors, infections, and psychological stress may act as triggers in genetically predisposed individuals[7]. Despite the progress, the exact mechanisms by which genetic and environmental factors interact to produce the clinical phenotype of CSU remain unclear.

Clinical Features of Chronic Spontaneous Urticaria

CSU is characterized by the spontaneous appearance of wheals—raised, erythematous, and intensely pruritic lesions—often accompanied by angioedema, which involves swelling of deeper skin layers and mucous membranes. Wheals typically last less than 24 hours, resolving without residual pigmentation or scarring, while angioedema can persist for up to 72 hours. Pruritus is the predominant symptom, leading to significant sleep disturbance and impaired quality of life[8]. The distribution of wheals is variable, affecting any part of the body, but sparing the palms and soles is common.

Patients with CSU may experience varying frequencies and intensities of symptoms, often reporting daily or almost daily episodes. The disease course is unpredictable, with spontaneous remission occurring in some cases, but symptoms may persist for years in others. CSU has been associated with comorbid conditions such as autoimmune thyroid disease, atopy, and psychiatric disorders including

10.48047/jocaaa.2024.33.06.76

anxiety and depression, further complicating management[9]. Severity assessment tools such as the Urticaria Activity Score (UAS) are frequently used to monitor disease progression and treatment response.

Diagnosis of Chronic Spontaneous Urticaria

The diagnosis of CSU is primarily clinical, based on patient history and the characteristic presentation of wheals, angioedema, or both, occurring for more than six weeks without an identifiable external trigger. A thorough clinical assessment is necessary to exclude alternative diagnoses, such as urticarial vasculitis, hereditary angioedema, or physical urticarias. Laboratory investigations are generally reserved for atypical presentations or cases unresponsive to standard therapy and may include complete blood counts, inflammatory markers, thyroid function tests, and autoimmune screening[10].

The autologous serum skin test (ASST) may be performed to assess for the presence of autoreactivity, particularly in patients suspected of having autoimmune urticaria. However, the sensitivity and specificity of ASST are variable, and its use is primarily confined to research settings. Emerging diagnostic tools, including molecular and genetic testing, are under investigation to better stratify patients and identify underlying pathogenic mechanisms[11]. Early and accurate diagnosis is essential for optimizing management and improving patient outcomes.

Management of Chronic Spontaneous Urticaria

The management of CSU is challenging due to the heterogeneity of disease presentation and response to therapy. Current guidelines recommend a stepwise approach, beginning with second-generation non-sedating H1-antihistamines as first-line therapy. For patients with inadequate response, dose escalation or the addition of other agents such as leukotriene receptor antagonists, H2-antihistamines, or short courses of corticosteroids may be considered. Omalizumab, a monoclonal anti-IgE antibody, has emerged as an effective third-line therapy, particularly for antihistamine-refractory cases[12].

Immunosuppressants such as cyclosporine may be utilized in severe, treatment-resistant cases, although their use is limited by potential adverse effects. Non-pharmacological interventions, including patient education, trigger avoidance, and psychological support, are integral components of comprehensive care. Despite available therapies, a subset of patients remains refractory to treatment, underscoring the need for novel therapeutic targets and personalized medicine approaches based on underlying pathophysiological mechanisms, including genetic factors[13].

Transforming Growth Factor β

Background

Transforming growth factor-beta (TGF-β) is a multifunctional cytokine that regulates cell proliferation, differentiation, apoptosis, and immune responses. TGF-β is secreted in a latent form and requires

10.48047/jocaaa.2024.33.06.76

activation to exert its biological effects. Three isoforms—TGF-β1, TGF-β2, and TGF-β3—have been identified in humans, with TGF-β1 being the most abundantly expressed and widely studied. Dysregulation of TGF-β signaling is implicated in various pathological conditions, including fibrosis, cancer, autoimmune disorders, and allergic diseases[14].

TGF-β exerts profound effects on immune system homeostasis, functioning as both a pro-inflammatory and anti-inflammatory cytokine depending on the cellular context and microenvironment. In the skin, TGF-β modulates the activity of keratinocytes, fibroblasts, and immune cells, playing a critical role in wound healing, tissue remodeling, and immune tolerance. Aberrant TGF-β signaling has been associated with increased susceptibility to inflammatory and autoimmune diseases[15].

Gene Structure of TGF-β

The TGF-β1 gene is located on chromosome 19q13.1–13.3 and spans approximately 23 kilobases. It consists of seven exons and six introns, encoding a precursor protein that undergoes proteolytic cleavage to generate the mature cytokine. Several single nucleotide polymorphisms (SNPs) have been identified within the TGF-β1 gene, including promoter and coding regions, which may influence gene transcription, mRNA stability, and protein expression levels[15-18].

Key functional polymorphisms such as -509C>T (rs1800469) in the promoter region and +869T>C (rs1982073) in exon 1 have been associated with altered TGF-β1 production. The distribution of these SNPs varies among populations and has been linked to susceptibility and clinical outcomes in various immune-mediated and inflammatory disorders. Characterizing TGF-β1 gene structure and its functional polymorphisms is crucial for understanding individual differences in cytokine expression and disease risk[16-19].

10.48047/jocaaa.2024.33.06.76

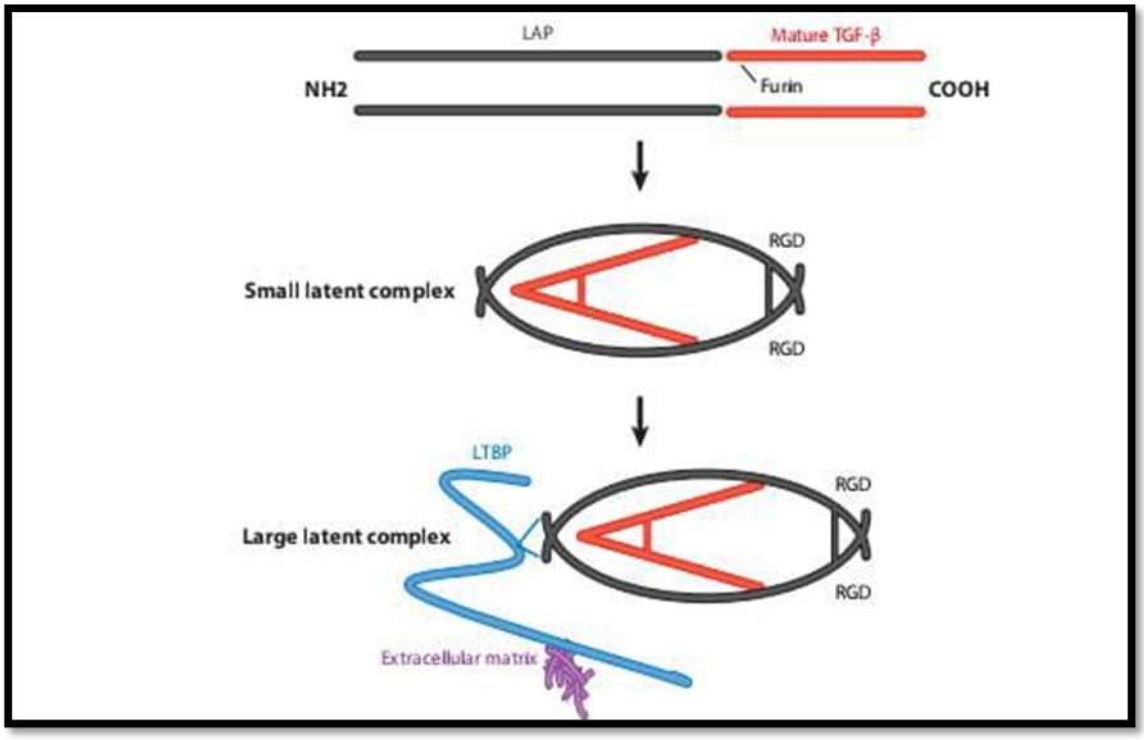

Figure 1 structure of Transforming growth factor-beta (TGF-β) [15].

Function of TGF-β in the Immune System

TGF-β plays a pivotal role in immune system regulation, balancing pro-inflammatory and anti-inflammatory responses. It suppresses the activation and proliferation of T lymphocytes, natural killer (NK) cells, and macrophages, thereby promoting immune tolerance and limiting tissue damage during inflammation. TGF-β is also essential for the differentiation of regulatory T cells (Tregs), which are critical for maintaining peripheral immune tolerance and preventing autoimmunity[16].

Moreover, TGF-β inhibits the production of pro-inflammatory cytokines such as interleukin-2 (IL-2) and interferon-gamma (IFN-γ), while promoting the secretion of anti-inflammatory cytokines like interleukin-10 (IL-10). In allergic and autoimmune diseases, impaired TGF-β signaling has been linked to loss of immune tolerance and excessive inflammatory responses. The dual roles of TGF-β in both promoting and resolving inflammation underscore its importance as a key regulator in immune-mediated diseases such as CSU[17].

10.48047/jocaaa.2024.33.06.76

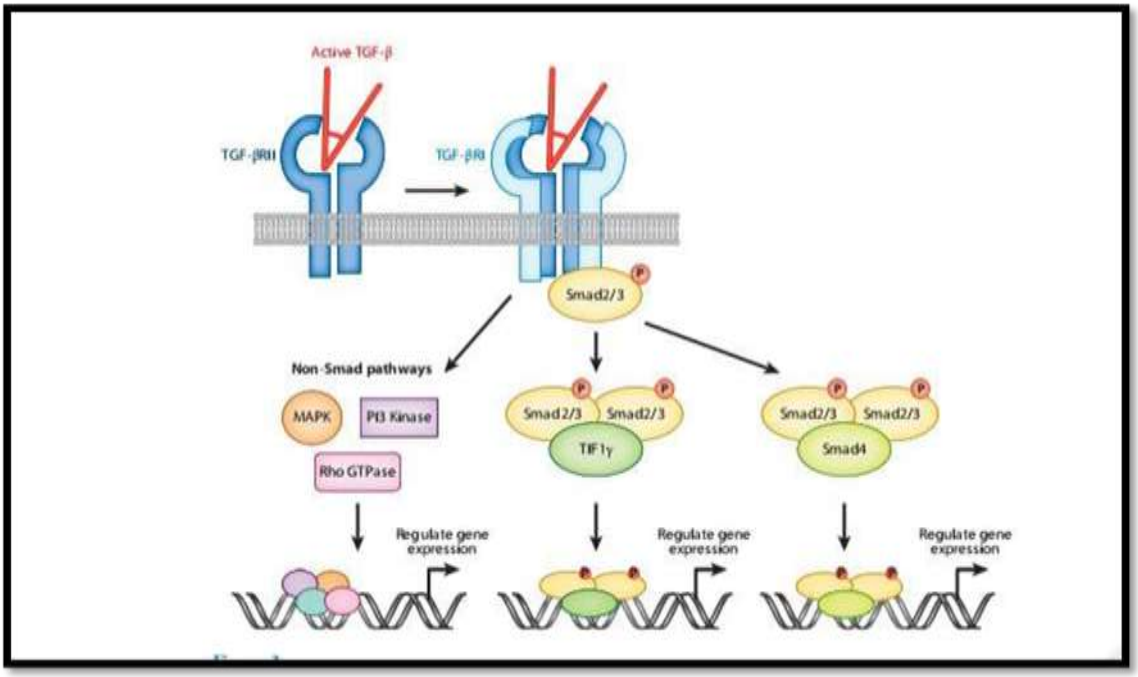

Figure 2: TGF-β signal transduction [17].

TGF-β1 Functional Polymorphisms

Functional polymorphisms in the TGF-β1 gene can lead to inter-individual variation in cytokine production and biological activity. For instance, the -509C>T polymorphism in the promoter region has been shown to increase transcriptional activity, resulting in higher TGF-β1 expression. Similarly, the +869T>C polymorphism in exon 1 is associated with increased protein secretion. These polymorphisms have been extensively studied in relation to various diseases, including asthma, systemic lupus erythematosus, and atopic dermatitis[20].

In the context of urticaria, emerging evidence suggests that TGF-β1 gene polymorphisms may modulate immune responses and influence susceptibility to CSU. Altered TGF-β1 expression could affect mast cell activity, histamine release, and inflammatory processes in the skin, thereby contributing to disease pathogenesis. Further research is needed to clarify the functional impact of specific TGF-β1 polymorphisms in CSU and their potential as biomarkers for disease risk and therapeutic response[21].

Transforming Growth Factor-β Gene Polymorphisms and Their Association with Chronic Spontaneous Urticaria

Several studies have investigated the association between TGF-β1 gene polymorphisms and susceptibility to CSU, with mixed results. Some studies have reported a higher frequency of certain TGF-β1 variants, such as the -509T allele, among CSU patients compared to healthy controls,

10.48047/jocaaa.2024.33.06.76

suggesting a potential genetic predisposition. These findings imply that individuals carrying risk alleles may have an altered immune response, increasing the likelihood of developing CSU[22].

The precise mechanisms by which TGF-β1 polymorphisms contribute to CSU pathogenesis remain under investigation. It is hypothesized that increased TGF-β1 expression in genetically predisposed individuals could enhance the suppressive function of Tregs, leading to impaired mast cell degranulation and histamine release. Conversely, reduced TGF-β1 activity due to certain polymorphisms might result in uncontrolled inflammation and autoimmunity, both of which are relevant to CSU pathophysiology[23].

Meta-analyses and population-based studies highlight the need for replication in diverse ethnic groups, as allele frequencies and linkage disequilibrium patterns may differ substantially across populations. Moreover, gene-gene and gene-environment interactions are likely to influence the observed associations, necessitating larger, well-designed studies to clarify the relationship between TGF-β1 gene variants and CSU risk[24].

The identification of TGF-β1 gene polymorphisms as potential biomarkers for CSU could have significant clinical implications, enabling risk stratification and personalized therapeutic strategies. For example, patients with specific genetic profiles may benefit from targeted immunomodulatory therapies or closer monitoring for disease progression and treatment response. Integrating genetic testing into routine clinical practice for CSU, however, requires further validation and consideration of ethical, legal, and social implications[25].

In conclusion, while current evidence supports a possible association between TGF-β1 gene polymorphisms and CSU, definitive causality has yet to be established. Future research should focus on elucidating the functional consequences of these variants, integrating multi-omics approaches, and evaluating their predictive value in clinical settings. Such efforts may pave the way for more effective, individualized management of chronic spontaneous urticaria[26].

A. Conclusion

Chronic spontaneous urticaria is a complex and heterogeneous disorder with significant personal and socioeconomic impacts. While the clinical management of CSU has advanced, considerable gaps remain in understanding its precise pathogenesis, particularly the interplay of genetic and immune factors. Accumulating evidence points to a multifactorial etiology in which cytokine gene polymorphisms, including those of transforming growth factor-β (TGF-β), play a potentially significant role in disease susceptibility, phenotype, and treatment response. Studies have highlighted the importance of TGF-β1 functional polymorphisms in modulating immune tolerance, mast cell activity, and inflammatory responses, which are all central to the pathophysiology of CSU. Despite

10.48047/jocaaa.2024.33.06.76

growing interest, the association between TGF-β gene polymorphisms and CSU remains an evolving field. Differences in study designs, ethnic backgrounds, and sample sizes have contributed to inconsistent findings across populations. The heterogeneity of CSU itself further complicates efforts to delineate clear genetic risk profiles. Nevertheless, understanding the genetic landscape of CSU—especially the role of TGF-β—may offer new opportunities for risk stratification, earlier diagnosis, and the development of targeted therapies

Future research should focus on multicenter, multi-ethnic studies with larger sample sizes to validate current findings and clarify the mechanistic pathways linking TGF-β polymorphisms to CSU. Advances in genomic and multi-omics technologies may help to unravel gene-gene and gene-environment interactions that underlie disease onset and progression. Ultimately, integrating genetic insights with clinical practice could pave the way for personalized medicine approaches, improving outcomes for patients suffering from chronic spontaneous urticaria.

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