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ASSOCIATION OF POLYMORPHISMS INTERLEUKIN-10 GENE 819C/T ON SUSCEPTIBILITY SYSTEMIC LUPUSERYTHEMATOSUS: A LITERATURE REVIEW

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Abstract

Interleukin-10 (IL-10) gene polymorphisms play an important role in influencing individual susceptibility to Systemic Lupus Erythematosus (SLE). Genetic variations in the IL-10 gene can alter mRNA transcription levels and IL-10 protein expression, thereby affecting the balance of immune responses. Increased IL-10 levels are known to enhance B-cell activity and autoantibody production, contributing to immune complex formation and tissue damage characteristic of SLE. Although several studies have shown an association between IL-10 polymorphisms and increased SLE risk, findings vary across populations due to factors such as ethnicity, environmental conditions, and research design. Therefore, this review aims to summarize the existing literature on the association between IL-10 gene polymorphisms and susceptibility to SLE..

Keywords: *IL-10 Polymorphism, Systemic Lupus Erythematosus, Genetics, Disease Susceptibility.*

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic, complex autoimmune disease involving multiple organ systems with varying severity.[1] It is characterized by the formation of autoantibodies against self-antigens, resulting in immune complexes that deposit in tissues, triggering inflammation and organ damage. SLE is more common in women, with a ratio ranging from 4:1 to 9:1 compared to men, and its estimated prevalence in Indonesia is about 0,5% of the population. [2,3,5]

Several factors such as genetic, hormonal, and environmental factors play major roles in SLE pathogenesis. Genetically, individuals with a family history of SLE have higher risk than normal. Hormonal factors, such as estrogene and progesterone hormone will increase B-cell activity and antibody production. Ultraviolet exposure, viral infection, smoking, chemicals, and drugs is an environmental factor that can trigger SLE disease.[9,10]

Advances in molecular genetics have improved understanding of how genetic variations contribute to autoimmune diseases. One such variation is genetic polymorphism—DNA variation that does not alter protein structure but affects its expression or biological activity. Polymorphisms in cytokine-regulating genes can influence autoimmune susceptibility, including SLE.[12,15]

Interleukin-10 (IL-10) is an essential anti-inflammatory cytokine that inhibits pro-inflammatory cytokines (IL-1, IL-6, TNF-α) and regulates immune cell activity. The IL-10 gene, located on chromosome 1q31–q32, has promoter regions that determine its expression level. Variations in these promoters can alter IL-10 production, affecting the balance between protective and pathological immune responses. Excess IL-10 may increase B-cell proliferation and autoantibody formation, contributing to SLE pathogenesis.[17,21,22]

The researchers aimed to compile comprehensive information regarding IL-10 gene polymorphisms at the –819 C/T locus and their relationship on susceptibility Systemic Lupus Erythematosus diseases across diverse global populations. By integrating data from various ethnic and geographical groups, the study seeks to identify potential genetic patterns that may contribute to differential disease risk. The insights obtained from this cross-population synthesis are expected to serve as a valuable reference for future investigations involving Indonesian cohorts.

METHODS

This review was conducted with PRISMA guidelines. Inclusion criteria the articles is published on 2018 till 2025, identifying and analyzing IL-10 gene polymorphisms on -819C/T sites. The study design is case control only without intervention. English articles only are eligible.

Searching the literature or journal by Google website, Medline/PUBMED, Sagepub and Wiley Online Library in Oktober – November 2025. The term use referred to "*Polymorphisms - 819T/C*" AND OR "*SLE*" AND OR "*Interleukin-10*". The articles then identified and selected establish the eligibility criteria. Data were taken from the articles include: authors(s), years of publication, country, total sample and main findings.

LITERATURE REVIEW

Systemic Lupus Erythematosus (SLE)

Systemic Lupus Erythematosus (SLE) is a chronic, multisystem autoimmune disorder characterized by the involvement of multiple organs and a wide spectrum of clinical severity.[1] Epidemiological data consistently indicate that SLE predominantly affects women, with a female-to-male ratio ranging from 4:1 to 9:1.[2,3] The incidence among women has been estimated at
8.82 cases per 100,000 individuals per year (ranging from 2.4 to 25.99), corresponding to approximately 0.34 million newly diagnosed cases annually. In contrast, men exhibit a much lower incidence rate, approximately 1.53 cases per 100,000 individuals per year (ranging from 0.41 to 4.46), with an estimated 0.06 million new diagnoses annually.[4] In Indonesia, the exact national prevalence of SLE remains uncertain; however, a survey conducted by Prof. Handono Kalim and colleagues suggested that approximately 0.5% of the general population may be affected by this condition.[5]

Pathophysiologically, SLE represents a complex autoimmune reaction arising from the generation of autoantibodies directed against self-antigens. These autoantibodies form immune complexes that deposit in tissues, initiating

chronic inflammation and leading to progressive organ damage.[6] The formation of autoantibodies is regarded as a central immunopathological hallmark of SLE.[6,7] More than 75% of affected individuals exhibit circulating anti-DNA antibodies, whose titers fluctuate in accordance with disease activity and duration.[7]

Clinically, SLE manifests with nonspecific but persistent symptoms such as fatigue, weight loss, and arthralgia, while approximately 25–50% of patients experience serious organ involvement, including lupus nephritis, pleural disease, and myocarditis.[8] Moreover, SLE poses significant reproductive challenges; it has been closely associated with adverse pregnancy and peripartum outcomes, including a heightened risk of preeclampsia, spontaneous abortion, preterm delivery, stillbirth, and low birth weight.[8] These complications underscore the systemic and multifactorial nature of the disease and its substantial impact on women of reproductive age.

Several factors are known to contribute to the development and progression of Systemic Lupus Erythematosus (SLE). These include genetic predisposition, hormonal influences, and environmental exposures, each playing a distinct yet interrelated role in disease susceptibility and immune dysregulation.[9, 10]:

a. Genetic Factors

Individuals with a familial history of SLE demonstrate a markedly elevated risk—approximately 17 times higher—compared with those lacking such a background. This observation underscores the strong heritable component of SLE, suggesting that specific genetic loci, particularly those involved in immune regulation and autoantibody production, contribute substantially to disease pathogenesis.

b. Hormonal Factors

SLE disproportionately affects females, with a reported female-to-male ratio of roughly 9:1. This gender disparity is believed to arise from the modulatory effects of sex hormones and the presence of the X chromosome, both of which enhance B-cell autoreactivity and autoantibody production.

- Estrogen: In autoimmune responses, estrogen promotes the proliferation of B-cell progenitors in the bone marrow and enhances the survival of splenic B cells, leading to the expansion of autoreactive B-cell populations.
- Progesterone: Prolonged exposure to progesterone has been shown to increase splenic B-cell survival but may also result in a reduction of IgG levels, thereby aggravating inflammatory processes and tissue damage.
- Testosterone: Conversely, testosterone exerts a protective immunomodulatory role by suppressing B-cell proliferation within the bone marrow. Consequently, males, who generally possess higher testosterone levels, exhibit a lower prevalence of autoimmune diseases such as SLE.

c. Environmental Factors[9, 10]

Environmental triggers are widely recognized as pivotal contributors to the onset of SLE in genetically predisposed individuals. Commonly implicated factors include ultraviolet (UV) radiation, particularly UV-A1 and UV-B, endogenous viral infections or viral-like elements, cigarette smoke, chemical agents, and certain vaccinations. These stimuli may induce apoptosis, oxidative stress, or aberrant immune activation, which collectively promote the loss of self- tolerance and the development of autoimmunity.

At present, the diagnosis of SLE is most frequently established using the EULAR/ACR 2019 classification criteria, which provide standardized parameters for identifying and categorizing the disease. These criteria are comprehensively summarized in Table 1, which outlines the major diagnostic components employed in the clinical evaluation of patients with Systemic Lupus Erythematosus.[11]

Table 1. Establishing the Diagnosis of Systemic Lupus Erythematosus (SLE) Patients

Initial criterion: The Antinuclear Antibody (ANA) test shows a titer of ≥1:80 on Hep-2 cells or a positive test
If not present, do not classify as an SLE case. If present, proceed to evaluate the additional criteria.

Additional Criteria:
Do not count additional criteria if there is a more likely explanation than SLE. These manifestations must have occurred at least once.
SLE classification requires at least one clinical symptom and a total score of ≥10 points.
The criteria do not need to occur simultaneously.
Within each category, only the criterion with the highest weight is counted.

Clinical Categories and Criteria	**Weight**	**Immunology Categories and Criteria**	**Weight**
Constitutional		Antiphospholipid Antibodies	
Fever	2	Anti-cardiolipin antibodies or Anti-β2GP1 antibodies or Lupus anticoagulant	2
Hematology		Complement Proteins	
Leukopenia	3	Low C3 or C4	3
Thrombocytopenia	4	Low C3 and C4	4
Autoimmune hemolysis	4		
Neuropsychiatry		SLE-specific Antibodies	
Delirium	2	Anti-dsDNA antibodies or Anti-Smith antibodies	6
Psychosis	3		
Seizures	5		
Mucocutaneous			
Alopecia without scarring	2		
Oral ulcers	2		
Subacute cutaneous or discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria > 0.5 g/24 hours	4		
Renal biopsy class II or V lupus nephritis	8		
Renal biopsy class III or IV lupus nephritis	10		

Didiagnosis sebagai LES apabila skor ≥ 10 dengan minimal 1 kriteria imunologi dan 1 kriteria klinis.

Polymorphisms Gene

Genetic polymorphism is defined as a variation or mutation within a gene that results in functional differences in the corresponding protein without altering its overall structural integrity. Such genetic variations can influence an individual's susceptibility to diseases even in the absence of overt clinical manifestations, thereby contributing to population-level differences in disease prevalence. The frequency of these polymorphisms varies among ethnic groups, reflecting the hereditary transmission of allelic diversity across generations.[12]

A genetic variant is considered a polymorphism when an alternative allele occurs in more than 1% of a given population. These variations may arise over the course of evolution through several molecular events such as gene conversion, insertions, point mutations (including frameshift, nonsense, or missense changes), and deletions, which collectively represent adaptive genetic responses to environmental influences.[13]

In humans, polymorphisms occur frequently—approximately once every 1,000

nucleotides—and typically lack any direct pathological significance.

Observable manifestations of such polymorphisms include differences in blood group systems, hair color, and other phenotypic traits, which are considered normal genetic variations rather than disease- causing alterations.[14]

Genetic variations are broadly classified into small insertions and deletions (indels), structural variations, and single-nucleotide polymorphisms (SNPs), the latter being the most prevalent form. A polymorphism, defined as a DNA sequence change present in more than 1% of the general population, can occur as repetitive sequence variations such as microsatellites or minisatellites (known as length polymorphisms), or as single-nucleotide substitutions, commonly referred to as SNPs. SNPs are regarded as predisposing genetic factors that do not directly cause disease but may influence susceptibility under certain environmental or biological contexts.[15]

Conversely, mutations represent permanent alterations in the DNA sequence of a gene and are often pathogenic in nature. Mutations can occur as somatic or germline events: somatic mutations are confined to tumor cells, whereas germline mutations are present in all cells of the body and can be inherited by offspring.[15]

The identification of polymorphisms employs a variety of molecular techniques, including Polymerase Chain Reaction (PCR), DNA microarray analysis, DNA sequencing (such as Next Generation Sequencing [NGS]), comparative genomic hybridization (CGH), and fluorescence in situ hybridization (FISH), alongside other conventional molecular diagnostic methods.[15]

In recent years, a growing number of studies have focused on examining gene polymorphisms in relation to disease severity, environmental susceptibility factors (such as toxin exposure), pharmacogenomic responses, and immune system variability—including differences in cytokine production that play central roles in chronic inflammation and autoimmune pathogenesis.[15]

***Interleukin-10* (IL-10)**

Interleukin-10 (IL-10) is an anti-inflammatory cytokine that functions primarily by inhibiting the production of proinflammatory cytokines secreted by monocytes and lymphocytes. The IL-10 gene is located on chromosome 1q31–q32, and its signaling is mediated through two receptor complexes, namely IL-10 receptor 1 (IL-10R1) and IL-10 receptor 2 (IL-10R2). Together, these receptor subunits initiate intracellular signaling cascades that regulate immune activation and inflammation.[17, 18]

Functionally, IL-10 acts as a critical inhibitory cytokine that suppresses phagosome maturation and the process of apoptosis, thereby exerting a regulatory effect on immune cell homeostasis. When activated, IL-10 enhances the proliferation, differentiation, and maturation of B lymphocytes, leading to increased antibody production and the amplification of its immunosuppressive properties in response to infection or inflammatory stimuli.[20]

Structurally, IL-10 belongs to the class II cytokine family, which includes IL-19, IL-20, IL-22, IL-24 (Mda- 7), IL-26, and interferons (IFN-α, -β, and -γ). It is characterized as a helical cytokine, with each IL-10 monomer composed of six α-helices (A–F).[19] The principal role of IL-10 as an anti-inflammatory mediator is to suppress excessive immune responses and prevent uncontrolled inflammation. This cytokine is synthesized by a wide variety of immune cells, including T lymphocytes, B lymphocytes, macrophages, and dendritic cells, reflecting its broad regulatory function in maintaining immune equilibrium by modulating cellular activity across different immune compartments.[20]

IL-10 specifically downregulates the expression of proinflammatory mediators such as interleukin-1 (IL-1), interleukin-6 (IL-6), and Tumor Necrosis Factor (TNF). Despite its well-established anti-inflammatory profile, IL- 10 exhibits pleiotropic effects, acting in some contexts as a proinflammatory cytokine, depending on the cellular environment and the nature of the immune challenge.[20]

Dysregulation of IL-10 production or receptor responsiveness has been associated with a range of pathological conditions, including inflammatory bowel disease (IBD), Systemic Lupus Erythematosus (SLE), and rheumatoid arthritis (RA). Given its poten anti- inflammatory properties, IL-10 has been extensively investigated as a therapeutic target in the treatment of chronic inflammatory and autoimmune disorders.[20] Mechanisms of IL-10 Action[21, 22]:

1. Inhibition of Proinflammatory Cytokines. IL-10 suppresses the synthesis of IL-1, IL-6, TNF-α, and IFN-γ, thereby mitigating excessive inflammatory responses and preventing unintended tissue damage.
2. Modulation of Immune Cell Activity. IL-10 inhibits T-cell activation and proliferation, suppresses dendritic cell and macrophage activity, and downregulates antibody production by B cells. Through these mechanisms, IL-10 maintains the delicate balance between immune protection and tissue preservation
3. Role in Wound Healing. IL-10 contributes to tissue repair by stimulating epithelial cell proliferation and migration, facilitating the regeneration of damaged tissue and the resolution of inflammation.
4. Regulation of Gut Immunity. Within the gastrointestinal tract, IL-10 modulates immune responses by inhibiting excessive inflammation, thus protecting against the development of inflammatory bowel conditions such as colitis.
5. Influence on the Nervous System. IL-10 also exerts regulatory effects on the nervous system, modulating the function of neuronal and glial cells and contributing to neuroprotective and neuroinflammatory processes.
6. Role in Systemic Lupus Erythematosus (SLE). IL-10 promotes B-cell proliferation and differentiation into plasma cells, leading to increased antibody synthesis. According to Richter et al., IL-10 exerts a paradoxical influence in SLE: while it enhances B-cell activation and autoantibody production—potentially exacerbating disease activity—it also possesses immunoregulatory properties that can protect against severe disease manifestations. This dual function highlights IL-10's complex role in autoimmune pathophysiology.

Polymorphisms of IL-10 gene

Genetic polymorphisms of the IL-10 gene represent normal interindividual variations within the DNA sequence of the IL-10 locus, which encodes Interleukin-10, a cytokine with potent anti-inflammatory functions. Previous studies have demonstrated that promoter polymorphisms within the IL-10 gene can influence mRNA transcription and overall gene expression levels. These variations most commonly occur in the promoter region, a cis-acting transcriptional regulatory element located in the 5′-flanking segment upstream of the transcription start site.[24] Alterations within this region can modify transcription factor binding affinity, leading to differential gene activation. Consequently, IL-10 promoter polymorphisms have been linked to varying degrees of susceptibility to multiple diseases, including cancers, autoimmune disorders, and infectious diseases.[25-27]

Such polymorphisms may alter the quantity of IL-10 produced, resulting in either an increased or decreased predisposition to specific pathologies such as autoimmune or neoplastic conditions.[23,25,29] The observed variations in IL-10 expression are closely tied to molecular processes described by the central dogma of molecular biology.

The central dogma outlines the sequential flow of genetic information through three fundamental biological processes: DNA replication, transcription, and translation. All genetic information is encoded within a four-nucleotide alphabet (A, T, G, and C in DNA; A, U, G, and C in RNA), which forms triplet nucleotide sequences known as codons. These codons determine the amino acid composition of the synthesized proteins, thereby dictating functional expression.[30]

The central dogma proceeds through three principal stages[31] :

1. Replication, in which DNA molecules duplicate themselves (DNA → DNA);
2. Transcription, where DNA is transcribed into messenger RNA (mRNA) through the catalytic action of RNA polymerase; and
3. Translation, occurring in ribosomes, where the mRNA sequence is decoded to synthesize the corresponding protein (RNA → protein).

Polymorphisms within the IL-10 gene can disrupt this molecular sequence by modifying the transcriptional output or translational efficiency, ultimately affecting cytokine expression and immune regulation. Several investigations have identified that promoter variants of IL- 10—specifically rs1800896, rs1800871, and rs1800872— are associated with altered IL-10 mRNA transcription and protein expression levels, leading to dysregulated cytokine production and increased susceptibility to Systemic Lupus Erythematosus (SLE).[23,25,29]

RESULTS AND DISCUSSION

Total 54 articles are collected and screening from the databases, but only 5 articles included to this study. Articles from various country and population. There are 4 articles from Asia and 1 article from Europe. Findings of polymorphisms IL-10 gene on -819T/C sites are collected. The results of this study shown in Table 2.

Table 2. Result of data extraction

Study (years)	Coun-try	Ca-se	Cont-rols	Findings	p value
Umare V et al (2020)[30]	India	200	201	Associated with genotype TC+CC	0.0051*
Wang GH et al (2020)[31]	China	391	785	Associated with T alleles in SLE patients than normal	p < 0.05*
Zak-Golab et al (2024)[23]	Poland	67	67	No clinical significance	p > 0.05
Mohammadi et al (2018)[32]	Iran	116	131	Associated with genotype CC	0.034*
Nahar N et al (2024)[33]	Bangladesh	75	75	Associated with genotype TC/CC	0.041*

*****_Significant statistically_

Discussion

The results of data extraction shown in Table 2. There are total 849 SLE cases and 1.259 healthy controls had been included, and all study design are case control study. The studies show various sites polymorphisms, but we are only take the results on -819T/C sites.

This review only have a few results, but 80% all of them statistically significant. In our study, 80% of the significant findings were derived from research conducted in Asian populations, whereas the remaining 20% originated from European cohorts. This distribution aligns with the observations reported by Liu et al., who identified that the –819 polymorphic site represents the most frequent mutation point among Asian individuals affected by Systemic Lupus Erythematosus (SLE).[25]

Association of polymorphisms gene I-10 on susceptibility SLE diseases

Autoimmune diseases arise from a complex interplay between genetic and environmental factors.[32,33,34] The genetic component may involve either gene polymorphisms or gene mutations, whereas environmental influences include ultraviolet (UV) radiation, ionizing radiation, viral infections, lifestyle factors, and other external stimuli.[9,10] Gene polymorphism is a normal variation occurring in approximately 1% of the general population. Such polymorphisms typically take place within the promoter regions of genes, either at distal or proximal sites along the DNA strand. Transcription factors such as RNA polymerase and TFIIF bind to the promoter sequences; therefore, any nucleotide base substitutions within this region can alter the resulting mRNA transcription and subsequently affect the translation process in the ribosome.[34,35,39] Even minor alterations in transcriptional output can modify the quantity of synthesized proteins, including Interleukin-10 (IL-10).[23,25,29]

Promoter polymorphisms do not directly alter the structural conformation or functional domains of the IL-10 protein; however, they may influence cytokine production levels, thereby modulating immune activity and shifting the equilibrium between proinflammatory and anti-inflammatory responses.[40]

In autoimmune conditions, a fundamental failure of self-tolerance occurs, in which the immune system erroneously recognizes self-antigens as foreign. When tissue damage or physiological processes such as apoptosis lead to cell necrosis, the immune system may misinterpret the resulting cellular debris as exogenous antigenic material. Cells undergoing necrosis lose their membrane integrity, display nuclear fragmentation and chromatin condensation, and release inflammatory signals such as ICAM-3, CXCL, ATP, and UTP, as well as damage-associated molecular patterns (DAMPs). These molecular cues attract macrophages for phagocytic clearance of damaged cells.

As antigen-presenting cells (APCs), macrophages process these fragments and present them to T lymphocytes and B lymphocytes. However, when T and B cells fail to recognize these fragments as self-antigens, naïve T cells differentiate into effector T cells, initiating

inflammation, while B cells undergo proliferation and differentiate into plasma cells with the assistance of IL-10.

Interleukin-10, a key anti-inflammatory cytokine, plays a vital role in suppressing the expression of proinflammatory mediators such as IL-1, IL-6, and TNF-α. Despite its inhibitory nature, IL-10 exhibits pleiotropic effects—it can stimulate antibody production by facilitating B-cell activation, yet paradoxically, its strong anti-inflammatory action may also impair efficient clearance of apoptotic cells, leaving residual tissue fragments.

Previous studies have demonstrated that IL-10 gene polymorphisms can alter mRNA transcription efficiency and increase IL-10 cytokine levels.[23,41,42] Elevated IL-10 production correlates with enhanced autoantibody synthesis, leading to the formation of immune complexes composed of autoantigens (necrotic cell remnants) and autoantibodies (produced by autoreactive B cells). These immune complexes deposit in various tissues, provoking inflammation and organ damage characteristic of Systemic Lupus Erythematosus (SLE).

Research conducted by Rezotarska et al. revealed a positive association between IL-10 gene polymorphisms and increased IL-10 cytokine concentration among Polish SLE patients.[29] Conversely, findings from Golab et al., conducted within the same population, did not identify a significant relationship between IL-10 polymorphisms and disease susceptibility.[23] This divergence in outcomes has generated considerable debate within the scientific community. Excessive IL-10 production may inhibit macrophage-mediated clearance of apoptotic cells, leading to secondary necrosis and accumulation of cellular debris, which subsequently act as autoantigens that trigger B-cell activation and autoantibody production. The resulting autoantigen–autoantibody complexes accumulate within tissues, inducing immune complex deposition and organ damage that typify Systemic Lupus Erythematosus.

CONCLUSION

IL-10 gene polymorphisms influence susceptibility to Systemic Lupus Erythematosus by altering mRNA transcription and IL-10 protein expression. Increased IL-10 enhances B-cell activity and autoantibody production, contributing to immune-complex formation and tissue damage typical of SLE. Findings remain inconsistent across populations; thus, further large-scale, population-specific studies are needed, especially in Indonesia.

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