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Review Article

Genetic Role in Autoimmune Disease, Systemic Lupus Erythematsous : A Review Article

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Abstract

Introduction: The concept of the relationship between genome and SLE is important to discuss because it has various benefits. The first is to predict high-risk patients who carry one or more genetic susceptibility factors among the general population or in the family. Second, it can identify individuals with high-risk genetic backgrounds who can prevent or delay disease progression, so that genetic counseling of high-risk family members can be carried out and control of environmental factors. In addition to better improving our understanding of the pathogenesis of the disease, because clinical manifestations, treatment response, and prognosis may be heterogeneous, genetic research may help reduce the prevalence and clinical setting of outpatients more precisely and may provide alternative treatments. The article aims to review genetic role in autoimmune disease, especially systemic lupus erythematosus.

Discussion: SLE due to autoantibodies is also associated because it is influenced by genomic variation by several components. Replicated linkages with SLE have been investigated as 1q23-q25, 7p22, 16p12-q13, 19q13, and 20q12. The relationship with SLE has also been demonstrated on HLA9, FCGR3A10, FCGR2A11, PDCD1, IRF5 and PTPN22. The rare monogenic form of lupus also occurs with mutations in TREX1, which encodes exonuclease DNA16, or with complete deficiency of complement components C1q, C2 or C4. A recent study reported an association between SLE and variants in STAT4.

Conclusion: the results of research between genome and SLE involve several chromosomes. The involvement of SLE susceptibility loci on chromosome 4p16-15,2 and chromosome 20. These results reach a level of significance for SLE association to date. The results support the epistatic relationship between the susceptibility locus and the potential susceptibility locus on the chromosome.

Key Words: Autoimmune; Genetic; chromosome; SLE

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by the development of autoantibodies and immune complexes associated with a variety of clinical manifestations and tissue damage. SLE is the production of reactive antibodies against the body's own cells. SLE is multifactorial and most likely involves complex interactions between genetic, environmental and hormonal factors. Some specimens of autoantibodies that contribute to disease either by binding directly to self-antigens or by induction of inflammation after deposition of a network of antigen antibody immune complexes [1].

Immunological components that undergo functional changes play a role in the pathogenesis of SLE resulting in pathogenic autoantibodies, deficient T- and B-lymphocyte regulation and imperfect immune complexes. Autoantibody is a condition where the antibody attacks itself.

Autoantibodies found in lupus are directed at intracellular nucleoprotein particles, with 98% of patients presenting with antinuclear antibodies, while anti-double-stranded DNA antibodies are found in 50-80% of patients [2].

The concept of the relationship between genome and SLE is important to discuss because it has various benefits. The first is to predict high-risk patients who carry one or more genetic susceptibility factors among the general population or in the family. Second, it can identify individuals with high-risk genetic backgrounds who can prevent or delay disease progression, so that genetic counseling of high-risk family members can be carried out and control of environmental factors [1,3].

In addition to better improving our understanding of the pathogenesis of the disease, because clinical manifestations, treatment response, and prognosis may be heterogeneous, genetic research may help reduce the prevalence and clinical setting of outpatients more precisely and may provide alternative treatments [3]. The article aims to review genetic role in autoimmune disease, especially systemic lupus erythematosus.

Discussion

Etiology of Sytemic Lupus Erythematosus

The etiology of SLE remains unclear, but it should be noted that genetic predisposition, environmental and hormonal factors play an important role. These factors interact to transform the complex relationships between host, pathogen and environment. It is along with the development of recent research that there is a newly discovered gene associated with SLE. Various studies have shown a strong genetic predisposition has been demonstrated [5].

Several studies on the probability of being affected estimate the risk of sibling recurrence in monozygous twins to be 24-65%, compared with 2-9% in zygote-differentiated twins. Whereas in another study the concordance rate increased among monozygotic twins (25% -69%), compared with dizygotic twins and other siblings (2% -3%). SLE with complex polygenic traits contributes to both MHC and non-MHC genes, and up to 100 genes are involved in disease susceptibility. This paper will review current concepts regarding the mechanism, genomics, and pathogenesis of SLE and the potential for this management [1].

Clinical Manifestations and Prevalence of SLE

The clinical manifestation of SLE patients is inflammation of various organ systems, including skin and mucous membranes, joints, kidneys, brain, serous membranes, lungs, heart, and sometimes the gastrointestinal tract. Organ systems can be affected either alone or in combination. The main features of SLE are the overproduction of autoantibodies and a rash of induration. The SLE classification requires that patients meet four of the 11 criteria established by the American College of Rheumatology (ACR). Clinical manifestations that appear are identified by clinical examination, laboratory tests, and patient records [6].

The prevalence of SLE is nine times more common in women, but the main cause of the sex differences remains unclear. The prevalence of SLE is 31 per 100,000 women in a population of European descent, which is 50-75% lower than in other populations. SLE predominantly affects women in a 9: 1 ratio. The prevalence of women is 90% in African Americans, compared with men [2].

Pathophysiology of SLE

SLE is characterized by chronic inflammation with various clinical manifestations. Several important factors are known in the pathogenesis of SLE: endocrine-metabolic, environmental, and genetic. The dominance of lupus in women suggests that it is also influenced by hormones. Environmental factors that cause or aggravate SLE include viruses (eg Epstein Barr virus) and chemicals. However, the mechanism of SLE itself is due to the presence of antibodies that attack the body's SL. Here are some of the mechanisms of SLE [6,7]:

1. Changes in T lymphocytes.

There was a continuous decrease in the number of CD8 T cells, and the number of T, B, and NK cells also decreased in general. Meanwhile, IgG production increased in lupus patients due to a decrease in the production of transformed beta growth factor (TGF-β). There is hypersensitivity to the production of cytokines by lymphocytes.

2. Lymphocytes B

Anti-dsDNA autoantibodies bind to nucleosomes, laminin, collagen type IV, and heparan sulfate. In addition, antiplatelet antibodies also participate directly so that they both cause tissue damage.

3. Cytokines

There was a reduction in IL2 production and a reduction in TGF-β production. Lymphocyte-derived TGF-β production, both in its latent and active form, is decreased in SLE patients. The expression of increase in IFN Y, IFN-Y can exacerbate or even trigger SLE. The increase in IL10 production by B lymphocytes leads to an increase in the proliferation of B lymphocytes. In addition, there is also an increase in IL4 production. IL-4 also increases the proliferation of B lymphocytes, resulting in autoantibodies. There was an increase in IL-6, a pro-inflammatory cytokine that plays a role in B cell maturation and IgG production. There is also an increase in IL-10, which functions to lower the number of antigens and cleanse the immune complex. Tumor necrosis factor-α (TNF) -α located within the MHC region on chromosome 6p also has a significant increase [6,8].

Role of Genetic in SLE

SLE due to autoantibodies is also associated because it is influenced by genomic variation by several components. Replicated linkages with SLE have been investigated at 1q23-q25, 1q41-q42, 2q35-q37, 4p16-p15, 4q31-q33, 6p21.3, 6p22-p11, 7p22, 16p12-q13, 19q13, 20p13-p12 and 20q12. The relationship with SLE has also been demonstrated on HLA9, FCGR3A10, FCGR2A11, PDCD1, IRF5 and PTPN22. Existing genom-wide association (GWA) technology allows genome-wide search of the genome for variants predisposing to disease. This method allows

the exploitation of not only identical relationships with offspring but information of affected families - siblings and other relatives. This method also excludes an identification boundary analysis of the often unrelated relationships. This method of analysis also results in identification and confirmation of linkages in independent pedigrees. The rare monogenic form of lupus also occurs with mutations in TREX1, which encodes exonuclease DNA16, or with complete deficiency of complement components C1q, C2 or C4. A recent study reported an association between SLE and variants in STAT4 [8].

HLA at 6p21.3 has been shown to be involved in B cell and T cell signaling. HLA DR2 in several studies has been shown to be associated with early onset of SLE. HLA DR3 is also associated with later onsets and dermatitis (less nephritis). The MECP2 gene involved in DNA methylation suggests that impaired CD4 T cell DNA methylation, induced by environmental influences, contributes to the pathogenesis of SLE by altering gene expression in people with a genetic predisposition. It also suggests that preventing or correcting the pattern can be therapeutic in SLE. However, the existing epigenetic changes for SLE must be more certain before therapy can be carried out in patients with SLE [8,9].

Apart from HLA, that other component related to SLE is ITGAM in 16p11.2. ITGAM (also called CD11b) combines with the b2 chain (ITGB2) to form leukocyte integrins (commonly referred to as MAC-1 or complement receptor 3 (CR3)) which are important on neutrophils and monocytes to stimulate the endothelium. ITGAM is also a receptor for the complement component of the C3 degradation product, iC3b19. Another study also found an association between SLE and ITGAM20 by studying genes in the 16p12-q13 linkage interval [10].

Previous studies have also established an association between SLE and IRF5 and TNPO3 at 7q32. IRF5 and TNPO3 in this study were also triggered by the rs752637 and rs729302 haplotypes. The genome at rs4963128 in KIAA1542 and 11p15.5, a regional genome homologous to genes encoding cell elongation factors. The rs4963128 gene is 23 kb telomeric to IRF7, a gene that is important in interferon production and has rs709266 in IRF7. Both encode the Phox homology domain containing serine-threonine kinase which has five known human variants, three of which are expressed in a wide variety of tissues. Third, rs10798269, which lies outside the recognized gene, was also associated with SLE as a marker in the 1q23-q25 SLE relationship interval [11,12].

Conclusion

In conclusion, the results of research between genome and SLE involve several chromosomes. The involvement of SLE susceptibility loci on chromosome 4p16-15,2 and chromosome 20. These results reach a level of significance for SLE association to date. The results support the epistatic relationship between the susceptibility locus and the potential susceptibility locus on the chromosome. We hope that further research is carried out to corroborate this evidence. Further research is also needed to support other applications and new techniques to identify gene therapy as a treatment for SLE patients.

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