

The Genetics of Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a disease characterised by diverse clinical manifestations and the presence of multiple autoantibodies. There are multiple aetiological factors involved in its pathogenesis. Genetic factors do play an important role and the major histocompatibility complex has been studied extensively and many human leukocyte antigen (HLA) associations have been reported. Twin and familial lupus studies confirm the importance of genetic factors in the development of SLE. Reported HLA associations range from that of HLA-DR3 in Caucasians to HLA-DR2 in Chinese, Japanese and American Blacks. These associations however may only represent linkage disequilibrium and not the actual susceptibility genes. Other non-major histocompatibility complex genes have also been reported to play important roles in the pathogenesis of lupus. The advent of molecular biological techniques has advanced the understanding of susceptibility genes in many diseases. The use of microsatellite genome scanning to study multiplex lupus families has yielded a wealth of information on clusters of susceptibility genes. The identification of these genes will be an important advance in the understanding of this complex disease.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic rheumatic disease characterised by protean clinical manifestations as well as the presence of multiple autoantibodies.¹ Tissue deposition of autoantibodies and immune complexes can lead to tissue injury.² Hormonal, environmental and genetic factors are known to be involved in the pathogenesis of this complex disease. Across population groups, the ratio of female to male sufferers is about 10:1.^{3,4} This points strongly to hormonal factors playing an important part in the pathogenesis of this disease. Oestrogens,⁵ androgens^{6,7} and prolactin^{8,9} have been implicated and the interaction of cytokine factors with the neuro-endocrine system¹⁰ may also contribute to the disease process. The detection of retroviral particles in lupus patients,¹¹ development of drug-induced lupus, aggravation with exposure to ultraviolet light (especially Ultra-Violet B) as well as observations in animal experiments¹² suggest that environmental agents may play key roles in the pathogenesis. Disease onset generally occurs in the presence of a genetically susceptible background. The role that genetic factors play is not yet fully understood but is certainly very complex. Rapid advances in molecular biological techniques as well as the enormous amount

of information gathered through the World Genome Project have resulted in genetic information increasing by leaps and bounds. These have also led to a deeper understanding of the genetics of lupus. Studies to date have indicated that SLE is a complex polygenic disease¹³ with many possible susceptibility genes that may act singly, but more likely as a group, leading to the development of the disease. The multifactorial model of common disease aetiology,¹⁴ which proposes a threshold for development of disease that may be exceeded by a number of different combinations or interactions of multiple genetic and environmental factors, may best describe this complexity. In addition, genetic factors have been reported to be associated with specific clinical features and autoantibodies¹⁵ in lupus and subsets of patients have been identified. The potential of gene therapy¹⁶ intensified the search for contributory factors e.g. ethnic diversity, reduced penetrance, clinical heterogeneity and environment factors.¹⁷ A clear understanding of genetic mechanisms will ultimately influence clinical management and the availability of more accurate prognostic markers for lupus patients. This review will look at the current understanding of the genetics of this complex disease and its potential clinical usefulness.

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Observations from Twin Studies and Multiplex Lupus Families

Studies of twins with lupus indisputably support the importance of genetic factors. It is noted that monozygotic twins have a much higher concordance for the disease when compared to dizygotic twins. It has been reported that 60% of monozygotic twins have the disease compared to only about 5% of dizygotic twins.^{18,19} The 5% concordance rate for dizygotic twins is quite similar to that expected of siblings of lupus patients. This indicates that genetic factors, as exemplified by monozygotic twins with lupus, play a major role in the susceptibility to this disease. The calculated heritability value for lupus based on twin studies was 0.95,²⁰ indicating a very strong genetic basis. In a separate analysis of disease occurrence in the first-degree relatives and spouses of systemic lupus erythematosus and discoid lupus patients, Lawrence et al²¹ suggested a polygenic inheritance with a heritability value of 0.66 and 0.44, respectively. They concluded that genetic factors are less important in SLE than in ankylosing spondylitis (heritability = 0.72)²² or generalised osteoarthritis (heritability = 0.90).²³ The absence of complete concordance in monozygotic twins and the lower heritability value shown in Lawrence's study, point to the presence of environmental factors that may modify or retard the development of clinical disease. Monozygotic twins living in the same environment have been known to develop lupus at different times²⁴ and Afro-Americans from central and west Africa (reported to have no lupus) develop lupus when they live in the USA.²⁵ These provide strong circumstantial evidence for environmental influence. Attempts to quantify the influence of the environment have not been easy and requires gene-environment interaction models,²⁶ and the assistance of a good biostatistician. Among lupus populations, about 10% of patients come from multiplex lupus families, mainly with parent-child or sib-pairs involvement. This suggests that certain heritable genetic factor(s) is the cause of the familial lupus. Kindred analysis showed a non-Mendelian mode of transmission of the disease.²⁷ The complex nature of the genetic influence, with reported genetic associations in one lupus population study which is not replicable in other lupus population groups, indicates a need for a systematic search for the susceptibility genes. The spin-offs from the World Genome Project make microsatellite genome scans an important tool in the laboratory. Complete genome scans, using a set of 390 markers with a mean 10 cM spacing are currently used to study extended families with multiple cases in Sweden.²⁸ Regions of linkage have been identified and will yield very useful genetic information in the near future. The ultimate aim of these research efforts is to identify useful genetic factors that may be amenable to therapeutic intervention, and aid in the

genetic counselling of patients in the reproductive age group.

Observations from Animal Studies

Animal models of lupus disease offer an easier way to unravel the location of susceptibility genes. Susceptibility loci have been identified by murine experiments^{29,32} and the distal end of the mouse chromosome 1 is one such region. It was demonstrated that this region predisposes to specific features e.g. splenomegaly, glomerulonephritis, IgG antibodies to chromatin, DNA and histone in murine lupus. This finding led to the study of the homologous region in human chromosome 1 (1q41-q42) in various ethnic groups and how it confers risk for SLE patients.³³ MRL-lpr/lpr mice which developed glomerulonephritis, lymphadenopathy and auto-antibodies have a defective Fas gene that leads to a low expression of Fas mRNA. This was however corrected in mice born after the insertion of a normal Fas gene at the embryonic stage.³⁴ Thus the potential for gene therapy exist, at least at the murine level. In humans however, apoptosis has not been shown to play significant roles in the pathogenesis of lupus. Ohsako et al³⁵ studied the Fas antigen and bcl-2 expression in lymphocytes from human SLE patients. Fas antigen and bcl-2 expression are increased in active lupus when compared to inactive SLE and normal controls but how this relate to lymphocyte survival is still unclear. Mysler et al³⁶ also made similar conclusions after studying the apoptosis/Fas receptor.

Major Histocompatibility Complex (MHC) Genes in Lupus

The major histocompatibility complex is one of the most polymorphic and well studied regions in the genome. Genes in class I, II and III regions have been reported to be associated with lupus. Many associations have been reported with SLE but none have been shown to be the definitive susceptibility gene(s). However, homozygous complement component deficiencies resulting from gene deletion or non-functioning genes^{37,38} can lead to SLE. C1q and C2 complement deficiencies, and C4 deficiencies, result in the development of lupus disease.^{39,40} Studies in different ethnic groups have also yielded different HLA associations (Table I), suggesting that they may be in linkage disequilibrium with the susceptibility gene(s)⁴¹ or may play roles in the modulation of function of the actual susceptibility genes. HLA-DR2 and DR3 have been noted to be associated with SLE.^{42,43} The HLA-DR3 association is part of the extended haplotype B8 / DR3 / C4Adel in Caucasians with predisposition to lupus. Decreased TNF α production has resulted from the presence of specific polymorphic allele of the TNF α gene, located in the class III region. In Caucasian lupus patients,⁴⁴ but not in Chinese lupus patients,⁴⁵ TNF α polymorphic alleles are associated with

TABLE I: MHC ASSOCIATIONS IN LUPUS

Ethnic Group	HLA Marker
American Blacks	DR2, C4A, CYP21A deletion
Caucasians	DR2, DR3, C4A0, C4B0, TNF2
Chinese	DR2, C4A0
Indians	DR4
Japanese	DR2, C4A0
Koreans	DR2, DR9, C4A deletion
Malay	DR2

MHC: major histocompatibility complex

SLE. The resulting increased risk for SLE may be due to its linkage disequilibrium to the extended haplotype B8/DR3/C4Adel. Specific manifestations or autoantibody production in lupus patients have also been linked with different genetic associations (Table II). HLA-DR2 has been found to be associated with nephritis, while HLA-DR4 seems to be protective in several racial groups studied in California.⁴⁶ Lupus patients with anti-Ro(SSA) but without anti-La(SSB) antibodies are associated with HLA-DR2 while those with anti-Ro(SSA) and anti-La(SSB) antibodies are associated with HLA-DR3.⁴⁷ The anti-Ro(SSA) and anti-La(SSB) responses are probably restricted to a certain number of HLA-DQA1 and DQB1 alleles represented on the HLA-DR2 and HLA-DR3 molecules. All the DQA alleles associated with the anti-Ro(SSA) response have a glutamine residue in position 34 and all the DQB alleles have leucine in position 26. Other MHC region genes studied include the TAP genes but this has not been shown to confer risk for SLE.⁴⁸

Non-MHC Genes in Lupus

The MHC genes probably interact with non-MHC genes in the induction of susceptibility and severity of lupus disease. Non-MHC genes conferring risk include the Gm and Km genes that encode for some immunoglobulin molecules,⁴⁹ complement receptors (CR1 and CR2) genes,⁵⁰ specific TCR polymorphisms in patients with anti-Ro(SSA),⁵¹ mannose-binding protein gene polymorphisms,⁵² and IL-6 flanking region genetic polymorphisms.⁵³ Recently, reports on the association of

African-American and Caucasians lupus patients with FcγRIIa⁵⁴ have added to the non-MHC genetic influence on disease susceptibility. Fc receptors are receptors for IgG2a and IgG3. Diminished capacity of monocytes to phagocytize has been noted in such patients.⁵⁵ Polymorphisms of IL-1 receptor antagonist gene have been reported to be associated with disease severity,⁵⁶ although this have not been reported elsewhere.⁵⁷

Clinical Applications

Genetic counselling, the process by which patients or relatives at risk of a disorder that may be hereditary are advised of the consequences of the disorder, the probability of developing and transmitting it and of the ways in which this may be prevented or ameliorated, is difficult for a complex disease like SLE. The observation-derived empiric risk for relatives of lupus patients is at best an educated estimate and varies from study to study. The complexity of the disease resulting from interaction between the genes and environment makes genetic counselling difficult and imprecise. Nevertheless, the risk of approximately 5% in first-degree relatives is a reasonable estimate,⁵⁸⁻⁶¹ with the risk increasing *pari passu* with the number of first-degree relatives affected. If the relatives share similar HLA haplotypes with the probands, a higher risk will be present, though the actual quantum of increase is unknown. The question of “whether my child will have the same disease” is a commonly asked question in young female lupus patients in the reproductive age group. The estimated risk is 5%. Lockshin et al⁶² studied 91 infants born to mothers with SLE and found only 4 with definite neonatal lupus. What genetic factors determine the occurrence of the disease in the child are unknown. Apart from genetic counselling, the knowledge of genetic associations and the roles that various genetic factors play can help us in subsetting lupus patients into more homogenous groups. This has an added advantage of allowing clinical trials to be conducted on homogenous groups of patients which may lead to precise targeted therapy for lupus subsets. The understanding of the effect of gene dosage or polymorphic alleles will be helpful for prognostication in lupus patients. If accurate and early prediction of severe disease in lupus patients can be based on the presence of certain genetic factors, it will then aid in the overall management of the lupus patients. Early therapeutic interventions or more potent immunosuppressive combinations can be used to retard or reverse progression of the disease before major organ damage occurs.

Conclusion

The future of genetic research in lupus is bright. Better and more elegant molecular biology techniques will yield a more comprehensive understanding of the genetic influence on SLE. Genome scans of nearly 200 lupus families with multiple cases have been performed

TABLE II: MHC ASSOCIATIONS WITH LUPUS FEATURES

Features	HLA marker
Nephritis	
American Blacks	DR2, DQβ1.2, DQβ1.AZH
Asians/Polynesians	DR2, DQβ1.2, DQβ1.AZH
Caucasians	DR2, DQβ1.2, DQβ1.AZH
Autoantibodies	
Anti-Ro without anti-La	DR2, DQw1
Anti-Ro with anti-La	DR3
Anti-cardiolipin	DR4, DR7, DQ7, C4 null

MHC: major histocompatibility complex

by researchers in the United States and Sweden. Eventually this will clarify the regions containing susceptible genes for lupus and allow a more in-depth study of these regions. These are but early steps in the full understanding of the genetics of lupus. The actual susceptibility genes, function of these genes and their interaction with environmental factors will have to be fully understood before the actual pathogenetic processes can be unravelled. Gene therapy or stem-cell transplantation therapy in those with severe disease, will probably be feasible in the new millennium. In the near future, the expanded genetic information will allow rheumatologists to give more accurate genetic counselling; classify patients into homogenous subsets and, hopefully offer better and more varied and effective therapeutic options.

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