Review

Genetic epidemiology Systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus is the prototype multisystem autoimmune disease. A strong genetic component of susceptibility to the disease is well established. Studies of murine models of systemic lupus erythematosus have shown complex genetic interactions that influence both susceptibility and phenotypic expression. These models strongly suggest that several defects in similar pathways, e.g. clearance of immune complexes and/or apoptotic cell debris, can all result in disease expression. Studies in humans have found linkage to several overlapping regions on chromosome 1q, although the precise susceptibility gene or genes in these regions have yet to be identified. Recent studies of candidate genes, including Fcγ receptors, IL-6, and tumour necrosis factor-α, suggest that in human disease, genetic factors do play a role in disease susceptibility and clinical phenotype. The precise gene or genes involved and the strength of their influence do, however, appear to differ considerably in different populations.

Keywords: candidate genes, disease susceptibility, linkage analysis, mouse models, SLE

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterised by a striking preponderance in females, multisystem involvement, and autoantibodies directed primarily against nuclear antigens. Pathogenic mechanisms have been partly elucidated and defects in immune complex clearance, B-cell tolerance, and T-cell function have all been described. Little, however, is known about predisposing factors and mechanisms leading to disease induction. Through a variety of study designs, a strong genetic predisposition has been shown. For example, studies of affected probands estimate the sibling recurrence risk (λs) to be approximately 20. Twin studies have demonstrated concordance rates among monozygotic twins of 24–65%, compared with 2–9% in dizygotic twins [1]. SLE is a complex, polygenic trait with contributions from MHC and non-MHC genes, and up to 100 genes may be involved in disease susceptibility [1]. The study of SLE genetics is at an exciting and rapidly advancing stage. This review aims to update our current understanding of this area.

Mouse models of systemic lupus erythematosus

Genetic analyses in the mouse have provided some important insights into the pathogenic processes mediating disease in experimental models of SLE. Linkage analysis and congenic dissection have provided insights into the genetic

Fc = crystallizable fragment [of antibody]; FcγR = Fc IgG receptor; IL = interleukin; SLE = systemic lupus erythematosus; TNF = tumour necrosis factor.

Table 1

Positions of the named susceptibility loci from murine genome studies involving NZB, NZW, NZM2410, BXSB, and MRL/lpr mice (Wakeland *et al*, 1999) [2].

Chromosome location	Susceptibility loci
1	*Bxs1, Bxs2, Sbw1, Gld, Sle1, Nba2, Lbw7, Bxs3*
3	*Sles3**
4	*Sle2, Sbw2, Lbm1, nba1, Lbw2, Lmb1, Sles2**
5	*Sle6, Lmb2, Lbw3*
6	*Lbw4*
7	*Lrdm1, Sle5, Sle3, Lbw5, Lmb3, Nba3*
9	*Sles4**
10	*Lmb4*
11	*Lbw8*
12	*Lrdm2*
17	*H2d/z, Sle4, Sles1**
18	*Lbw6*
19	*Fas*

* Suppressive modifiers, responsible for the suppression of fatal disease in the NZW genome.

basis for susceptibility in the classic lupus-prone mouse strains. These studies have delineated specific genetic pathways that are critical to the development of severe lupus nephritis and have identified allele-specific, suppressive modifiers capable of dramatically influencing disease progression. The 'synthesis' of mouse models of systemic autoimmunity via the production of targeted gene disruptions has also helped identify specific genes and gene combinations capable of causing and modifying disease.

The chromosomal locations of genes mediating susceptibility to lupus nephritis or systemic autoimmunity in the NZB/W, MRL, and BXSB mouse models have been determined through genome scans [2–5]. These studies show that lupus susceptibility is inherited in a complex fashion involving both genetic interactions and additive effects of individual genes. In all, 31 different gene designations have been defined thus far, distributed among 21 nonoverlapping 20-cM genome intervals (Table 1). Other investigators have mapped loci affecting a variety of component phenotypes associated with systemic autoimmunity [6]. The genomic segments on murine chromosomes 1, 4, and 7 are associated with disease susceptibility in multiple strain combinations, suggesting that these intervals contain genes or gene clusters that strongly influence autoimmunity. The *Sle1*, *Sle2*, and *Sle3* loci have been individually identified as the major SLE susceptibility loci in NZM2410 mice [2] and their immunophenotypes have been characterised. *Sle1* mediates loss of tolerance to nuclear antigens, *Sle2* lowers the activation threshold of B cells, and *Sle3* mediates dysregulation of $CD4^+$ T cells [2]. The combination of *Sle1* with any one of *Sle2*, *Sle3,* or *Yaa* (autoimmune accelerating gene) on the B6 genetic background results in the development of systemic autoimmunity with variably penetrant glomerulonephritis culminating in renal failure and death. In contrast, two-loci combinations of any of *Sle2*, *Sle3*, or *Yaa* did not mediate fatal disease. These results identify *Sle1* as a strategic locus in SLE pathogenesis [7]. The NZW genome also has four epistatic modifiers, SLE suppressors (*Sles1–Sles4*), which suppress autoimmunity. The most potent, *Sles1,* switches off the *Sle1* immunophenotype and can suppress the entire autoimmune pathological process [8]. Recent fine-mapping analysis of the *Sle1* locus has identified a cluster of functionally related loci (*Sle1a–d*). These loci share a common pathway leading to loss of tolerance to chromatin but differ by various other serological and cellular phenotypes [9]. This potent susceptibility locus is syntenic with the 1q23–42 segment of the human chromosome.

Other models of intense interest are those supporting an apoptosis-related autoantigen clearance defect, for example C1q knockout, DNase1-deficient, and serum-amyloid-P-deficient mice. These models have shown several important pathogenic abnormalities, including reduced macrophage clearance of apoptotic cells and increased concentrations of apoptotic bodies, in tissue samples associated with development of glomerulonephritis [10–13].

Human linkage studies in systemic lupus erythematosus

The traditional approach for locating a disease gene in humans is linkage analysis. Results from mouse models of SLE presented the first evidence for genetic linkage to an area of chromosome 1 in the mouse that is syntenic to human chromosome 1q23–42. In 1997, Tsao *et al* [14] published linkage evidence on the long arm of chromosome 1q41–42, using 43 families with 52 affected sibling pairs of mixed origin. Several additional linkage studies have been performed using sib-pairs and extended family pedigrees [15–19]. The parameters and test populations for each study as well as the genomic intervals detected in at least two mapping studies are summarised in Tables 2 and 3.

As Table 2 shows, there are many sources of variation between these studies, including ethnic mix, sample size, specific markers used, and analytic models used. Another source of variation may relate to clinical phenotypes of the affected individuals. Localisation of genes with modest effects by linkage analysis is difficult and such variations may further limit the power of such studies. Despite these important limitations, there is some agreement as regards regions providing evidence of linkage. Several areas on

Table 2

Summary of human linkage studies in systemic lupus erythematosus

Study parameter	Moser *et al* (1998) [15]	Gaffney *et al* (1998) [16]	Gaffney *et al* (2000) [17]	Shai *et al* (1999) [18]	Lindqvist *et al* (2000) [19]
Number of families	94	105	82	80	19
Type of study	Extended pedigrees	Sib-pair	Sib-pair	Extended pedigrees	Extended pedigrees
Number of affected individuals	220	220	179	188	44
Number of unaffected individuals	313	155	101	246	52
Number of ethnic groups	2	5	4	2	1
Ethnicity of families studied					
White	0	84	64	37	19
Mexican American	0	0	0	43	0
African American	31	6	12	0	0
Hispanic	0	8	5	0	0
European American	55	0	0	0	0
Asian	0	3	0	0	0
Mixed heritage	0	4	1	0	0
Number of loci analysed	312	341	366	350	336
Basis of linkage	LOD ≥1.5	LOD ≥1.0	LOD ≥1.0	NPLZ >1.5	LOD ≥1.0
Statistical methods	Model-based, then nonparametric	Nonparametric	Nonparametric	Nonparametric	Model-based

Information taken from from references [15–19]. LOD = logarithm of the odds; NPLZ = nonparametric linkage Zall statistic.

chromosome 1 have been detected (1p36, 1q21–23 and 1q41–42) [15–19] that contain genes of immunological importance, some of which may have direct relevance to pathogenic processes in SLE (Table 4). The importance of using well-defined populations is emphasised by recent studies of Nordic multi-case families in which a susceptibility locus at chromosome 2q37 (*SLEB2*) has been reported [19]. A study of single-case Swedish families confirmed association with further markers in this region but, in contrast, there was no linkage to this area in 13 Mexican families [20].

Study of individual genes in systemic lupus erythematosus

Many individual genes have been studied in SLE and a comprehensive analysis of these is beyond the scope of this review. Recent studies do, however, illustrate important points that are likely to apply to other genes in SLE.

Poly(ADP-ribose) polymerase

Poly(ADP-ribose) polymerase ('PARP') is involved in DNA repair and apoptosis, both of which may be of relevance in SLE pathogenesis. The gene for this protein is also within the area of linkage for SLE (1q41–42). Using a multiallelic approach using a transmission disequilibrium test, Tsao *et al* [21] found a significant association of an 85-bp allele of the gene for poly(ADP-ribose) polymerase in affected white patients with SLE. In contrast, Criswell *et al* [22] studied three separate cohorts of SLE patients and failed to confirm this association. Differences in statistical modelling may account for this difference and the original finding may be a false-positive result.

Mannose-binding protein

This protein has structural and functional similarities to C1q. Several polymorphisms of the protein have been described in association with SLE in different populations [23–24]. Recent evidence also suggests that polymorphisms of mannose-binding protein may increase susceptibility to infection in SLE [25].

IL-6

IL-6 is a pro-inflammatory cytokine that has a role in B-cell maturation and IgG production. High IL-6 production is associated with a G→C polymorphism at −174 in the promoter region. In a study of 211 German patients with SLE, Schotte *et al* [26] found no higher prevalence of the G allele than in the background population. This allele was, however, associated with discoid cutaneous lesions and anti-histone antibodies.

Table 3

Human systemic lupus erythematosus susceptibility loci identified in two or more mapping studies

Locus	Moser *et al* (1998) [15]	Gaffney *et al* (1998) [16]	Gaffney *et al* (2000) [17]	Shai *et al* (1999) [18]	Lindqvist *et al* (2000) [19]
1p36		D1S234	D1S468	D1S468	
1q23	FcγRIIA			D1S484	
1q41–44	D1S3462	D1S235		D1S2785	
2q32–37	D2S1391		D2S126		D2S125
3q11	D3S2406	D3S1271			
4p15	D4S403		D4S403		
4q28–31	D4S2431	D4S424	D4S413*		
6p11–22			D6S426*	D6S276	
14q11–23		D14S276		D14S258	
16q12–13		D16S415		D16S3136	
20p12–13		D20S186		D20S115	
20q11–13	D20S481	D20S3119		D20S195	

Information taken from from references [15–19]. *Based on a combined analysis of [16,17].

IL-10

IL-10 is a Th2 cytokine that downregulates antigen presentation and immune complex clearance. IL-10 is increased in SLE patients and their family members. Lazarus *et al* [27] found the IL-10-1082G, IL-10-819C, and IL-10–592C haplotype was associated with Ro autoantibodies and renal involvement in white patients with SLE. In Chinese patients, a different haplotype was associated with renal disease but not Ro autoantibodies [28]. These studies found no association with disease susceptibility. In contrast, Gibson *et al* [29] found single nucleotide polymorphisms in the IL-10 promoter region significantly associated with SLE susceptibility in African Americans.

Tumour necrosis factor-α

The tumor necrosis factor (TNF)-α gene lies within the MHC region on chromosome 6p. The HLA B8, DR3 haplotype has been associated with SLE in whites and confers a two- to threefold increased risk of SLE [1]. The TNF-α –308A polymorphism is located within the promoter region of the gene and is associated with increased production of TNF-α. This polymorphism is in strong linkage disequilibrium with the HLA B8, DR3 haplotype, but it also has an independent effect in SLE [1,30]. In addition, Werth *et al* [31] have demonstrated an enhanced susceptibility to photosensitive cutaneous lesions in SLE patients with this polymorphism. However the TNF-α –308A polymorphism is also in linkage disequilibrium with other polymorphisms across the TNF-α locus, and the functional association remains to be established.

Fc receptors

These receptors play a role in handling of immune complexes as well as in clearance of apoptotic cells. The Fc IgG receptor FcγRII and FcγRIII genes are both located at 1q23–24, and several polymorphisms have been described that affect the ability of receptors to bind. In a prospective study of Hispanic patients with SLE, Zuniga *et al* [32] observed that the low-affinity FcγR alleles (RIIa-R131 and RIIIa-F176) were inherited independently and were present at higher frequency in patients with SLE, especially as a haplotype. In SLE patients with nephritis, there was also a predominance of low-affinity alleles. Hatta *et al* [33], studying a Japanese population, also found an association between FcγRIIIB-NA2/NA2 genotype and development of SLE with an increased prevalence of nephritis. Selgiman *et al* [34] also recently reported that the FcγRIIIA-158F allele is a risk factor for nephritis in white patients with SLE. The exact role of these 'low-affinity' polymorphisms in disease susceptibility and expression remains controversial and further work is needed to fully elucidate their role.

These studies suggest that certain genetic defects (e.g. in complement, mannose-binding protein, and FcγR) associated with similar pathogenic mechanisms all can lead to susceptibility to SLE in different populations. The clinical expression of SLE, while diverse, may not be nearly as diverse as the range of genetic defects that may predispose to it. In addition, some genes not associated with susceptibility may nevertheless be important in phenotypic expression (e.g. those for IL-6, IL-10). In view of these observations, enriching populations with a particular

Table 4

Candidate genes for systemic lupus erythematosus at regions identified by linkage analysis

Region	Candidate genes
1q21–23	*FcγRIIA* (CD32) *FcγRIIIA* (CD16) *FcγRIA* (CD64) *IL-6R* *FasL* CD3Z chain H3 & 4 histone family 2 Serum amyloid protein C-reactive protein CD48
1q31–32	Complement-component-4-binding protein CR1 CR2 CD45 Small ribonuclear protein
1q41–42	*TGFβ2* *ADPRT* (ADP-ribosyltransferase factor-1)

phenotype might influence studies of susceptibility. Prospective studies will be important, both to accurately assess the association of certain markers with expression of disease and also to study the predictive value of genetic markers in defined populations.

Conclusion

The past decade has witnessed major advances in our understanding of the immunopathogenesis of SLE. Intensive study of several mouse models has allowed significant progress towards understanding the genetic contribution to the development and expression of the disease. The observed genetic synteny between human and murine loci provides valuable clues to the origins of human SLE, and future studies will make possible a clearer understanding of the role of genetic factors in disease susceptibility. The next challenge will be to focus on genetic and molecular pathways that determine an individual's particular phenotype as an aid to prognostication and early intervention to prevent complications.

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