An Update on the Genetics of Systemic Lupus Erythematosus

Bo Johanneson BSc and Marta E. Alarcón-Riquelme MD PhD

Department of Genetics and Pathology, Section for Medical Genetics, Rudbeck Laboratories, Uppsala University, Uppsala, Sweden

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Abstract

The development of systemic lupus erythematosus has a strong genetic basis. The techniques to study the genetics of SLE have improved, and family-based studies have been gaining importance due to advances in the human genome project. Recently, complete genome scans with microsatellite markers and linkage analysis have been performed in human systemic lupus erythematosus in various populations. These studies represent the first step of a process towards the identification of susceptibility genes in SLE. We review here the results of the human genome scans performed until now and provide an update of the latest advances on the genetics of SLE in linkage studies and association analyses of candidate genes.

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Systemic lupus erythematosus is the prototype of systemic autoimmune diseases, characterized by multi-organ pathology and autoantibodies against a variety of autoantigens such as double-stranded DNA, intracellular ribonuclear proteins and membrane phospholipids. SLE has a clear female predominance (>90%), and the onset of the disease usually occurs during the childbearing years. Populations of African origin in the United States appear to have earlier onset and a more severe disease [1] than European populations.

SLE is regarded as a complex disease with an etiology that appears to be the result of the interplay between genes and environment [2,3]. In complex diseases multiple genes with unknown modes of inheritance determine a risk, and no particular gene is necessary or sufficient for disease expression. The disease is therefore the result of epistatic interactions or additive effects of such genes and the presence of environmental triggers. How these interactions take place is at present unknown.

During the past several years, the development of densely mapped genetic markers covering the entire human genome has dramatically changed the study of genetic predisposition to disease. Chromosomal regions containing possible susceptibility loci can be identified by linkage analysis based on their genetic location, without a prior hypothesis on the function of the genes. In this review we summarize the recent advances in identifying susceptibility genes for human SLE by linkage analysis, and provide an update of the results. We do not review the work performed in animal models of SLE.

SLE = systemic lupus erythematosus

Association studies of candidate genes

Most of the genetic factors proposed to date as involved in SLE have been analyzed by association studies in unrelated patients and healthy controls. The interpretation of associations may be complicated by the presence of linkage disequilibrium between the investigated marker or gene alleles and the actual etiologic allele. The many studies of association of major histocompatibility complex alleles or haplotypes and SLE exemplify this difficulty. In addition, the high rate of type I errors or false positive results is characteristic of association studies, where the control population must be carefully ascertained. A large body of literature has described the involvement of HLA genes in SLE, which has been reviewed thoroughly [4–6].

Complete deficiencies of the early components *C1q*, *C2* and *C4* in the classical pathway of complement are associated with a most striking risk to developing SLE [5–10]. Deficiency of *C4A*, so called C4Anull allele, is probably the most common inherited complement deficiency, occurring at varying frequency in different population groups [9]. In some populations 50–80% of SLE patients have *C4A* deficiency [9,10]. The molecular basis of the C4A deficiency is heterogeneous, but the most common C4Anull allele in Caucasians is a 28 kb deletion removing both the *C4A* and *21-OH* genes, which occurs on the HLA B8-DR3 haplotype commonly associated with SLE [10]. *C2* deficiency is associated with SLE but at a lower frequency and with a milder clinical picture than in deficiencies of *C1q* and *C4* [5,6,8].

Polymorphisms within the genes encoding Fcγ receptors II and III have been investigated for association to SLE. The Fc receptors, which are active in immune complex clearance, have been considered candidate genes for the disease, since the formation and deposition of immune complexes are characteristic of SLE. Low affinity variants of both *Fcγ* receptor *IIA* and *IIIA* have been shown to be associated with nephritis in SLE patients [11,12]. In particular, the *FcγRIIA* gene (*CD32*) has two expressed isoforms that differ by a single amino acid at position 131 [11] and have different abilities to bind aggregated immunoglobulin-G2 and IgG1. An arginine (R131) results from a G instead of a histidine (H131). The R131 has a lower Fc

affinity than H131. Thus, this polymorphism has a functional potential in determining immune complex clearance. The results of association with *CD32* have been controversial although the strongest evidence exists for lupus nephritis [11,12]. Association with *FcγRIIIA* (*CD16*) has also been proposed but linkage disequilibrium has not been excluded [12].

Mannose-binding protein is a serum acute-phase protein, which activates the classical and alternative pathways of complement independently of antibody. An allele of *MBP* unable to activate the classical pathway of complement has a moderate association with SLE in two different ethnic populations [13]. Most interesting is the strong association shown between high morbidity and mortality of patients with SLE, through infections and a functional polymorphism related with lower serum levels of MBP due to a substitution in position 54 resulting in aspartic acid [14].

Since it is possible that dysfunctional programmed cell death is involved in the pathogenesis of SLE, genes participating in that process, such as *bcl-2*, *IL10* and *Fas-L*, have been investigated. A first study described the association between an intragenic microsatellite in the promoter of the *IL-10* gene, called the *IL-10G* microsatellite, and SLE in a Scottish population [15]. A second study analyzed alleles of all three genes in Mexican-Americans [16]. In the same study, a synergistic effect between alleles of the *IL-10* and *bcl-2* genes in determining susceptibility to SLE [16] was detected, but no association was obtained for the *Fas-L*. A study in the Italian population analyzed *IL-10* and *Bcl-2* among other genes, and could only determine association with the *IL-10G* microsatellite in two independent sets of patients, but were unable to confirm any synergistic effect between *IL-10* and *Bcl- 2* [17]. Another study in a much larger set of Mexican patients could not detect association between SLE and the *IL-10G* microsatellite [18]. In addition, there was no association with *Bcl-2* when the gene was analyzed with at least three different polymorphisms in Mexicans, and consequently no synergistic effect with *IL-10* was observed [19]. A more recent study analyzing the *IL-10G* microsatellite in patients from various populations showed associations in Caucasians and African-Americans, but could not determine an association in Mexican-Americans, suggesting the difficulty in the use of admixed populations for case-control association studies [20]. Studies on the *IL-10* gene, which analyzed single nucleotide polymorphisms found within the gene promoter, have given more consistent results. Association has been shown between these and some clinical manifestations, such as presence of Ro autoantibodies, nephritis and central nervous system SLE [21,22]. Thus, the type and number of polymorphisms analyzed in an association study is of importance, since it is the number of patients used in the analysis and the choice of controls. A large number of other genes has been analyzed for association with SLE, however due to space constraints those will be not reviewed here.

Ig = immunoglobulin
MBP = mannose-binding protein

Genome scans and linkage studies in SLE

A different strategy to localize genes, in contrast to association analysis of candidate genes, is to map a phenotype to a segment of a chromosome by screening the whole genome with genetic markers, such as microsatellite markers, using linkage analysis. Microsatellites are abundant, randomly distributed repeated sequences, usually dinucleotides such as (CA)n, which are highly polymorphic. When performing a genome screen, no a priori assumptions are made about the location or the function of genes involved in the disease studied.

Complex diseases often aggregate in families but do not follow classical Mendelian dominant or recessive inheritance. Most likely, several genetic factors interact in various ways and result in the development of the disease. Typical also is the presence of genetic heterogeneity, demonstrated by the fact that different susceptibility loci may be involved in the development of the same disease in different ethnic populations. Consequently, the genetic heterogeneity can affect the power to detect linkage depending on the population material studied.

The first step towards attempting to analyze genetic linkage in human SLE was conducted by Bias et al. [23]. Based on the observation that several autoimmune diseases show familiar clustering, the authors postulated that a major autoimmunity gene interacts with secondary genes in the development of autoimmunity, where the secondary genes confer the specificity of the phenotype. Examples of secondary genes would be the genes within the MHC. Bias et al. used overt autoimmune disease or high titers of autoantibodies as a definition of autoimmunity. Under these conditions, the autoimmunity was shown to segregate as a Mendelian autosomal dominant trait by goodness of fit [23]. Linkage analysis was performed with genetic markers as HLA, red cell antigen, red cell enzymes and serum proteins, but without significant linkage results probably due to marker paucity and the few families studied.

More recently, a linkage study in human SLE used prior knowledge of the localization of murine lupus susceptibility loci on mouse chromosome 1 [24]. The murine loci *Sle1*, *Nba2* and *Lbw7* have been mapped to the telomeric end of mouse chromosome 1 [25–28], which is syntenic to the telomeric end of human chromosome 1 (1q23–1q42). The authors analyzed genetic markers located on the interval 1q31–q42 in 52 affected sibpairs from three ethnic groups [24]. Evidence of linkage to SLE as well as to the presence of IgG antichromatin autoantibodies was detected for several markers within the 1q41–q42 region. In a follow-up study, association with SLE was demonstrated with a microsatellite polymorphism in the *PARP* gene in an extended multi-ethnic cohort as well as in the Caucasian material alone [24]. Although the locus at 1q42 has been confirmed by others [30,31] and is now generally accepted as *SLEB1*, no group has been able to replicate the association with *PARP* [31 and our unpublished observations].

MHC = major histocompatibility comples

Table 1. Family material used in the five genome screens of human SLE

Study	No. of families	Family type	No. affected	Total no. of individuals	Linkage analysis methods
Moser et al. [30]	Total 94 31 African-American 55 European-American	Pedigrees	220	533	Two-point parametric and non-parametric multipoint analysis
Gaffney et al. [33]	Total 105 84 Caucasian 8 Hispanic 6 African-American 3 Asian 4 mixed heritage	Sibpairs	220	375	Non-parametric multipoint analysis
Gaffney et al. [34]	Second cohort of 82 and combination with the first cohort, total 187. Added: 78 Caucasian 6 Hispanic 15 African-American 1 mixed heritage	Sibpairs	179	280	Non-parametric multipoint
Shai et al. [35]	Total 88 43 Mexican-American 37 Caucasian	42 sib pairs, 38 affected relative pairs	188	434	Non-parametric multipoint
Lindqvist et al. [36]	Total 17 6 Icelandic 11 Swedish	Pedigrees	61	158	Two-point parametric

Five complete genome screens for human SLE [30,33–36] were recently performed. The family materials analyzed by each group are summarized in Table 1 and cover various ethnicities. The results are summarized in Table 2. All five studies generated several chromosomal regions indicating possible linkage with SLE (LOD scores >1.0), which we describe in more detail below.

The Oklahoma group [30] identified 16 loci with LOD scores >1.5 using American families that were stratified as European-Americans and African-Americans. Of these, the markers FcγRIIA (LOD=3.45), D13S779 (LOD=2.50) and D20S481 (LOD=2.49) had the greatest effects in the combined family material [30]. The effect of the FcγRIIA was predominated by the African-American families (LOD=3.37). In the Minnesota study [33], four loci were identified with LOD scores >2.6 (6p11–21, 14q21–23, 16q13 and 20p12) and an additional nine loci with LOD scores between 1.0 and 1.68 [33]. The group from Minnesota performed a second genome scan [34] on an independent cohort consisting of 82 multi-case families. New intervals were revealed on chromosome 7, 7p22 (LOD score Z=2.87), 7q21 (LOD score=2.40) and 7q36 (LOD score=2.15), as well as on chromosome 10p13 (LOD score=2.24). Combining the first and second cohorts (a total of 187 sibpair families) confirmed their own previous regions in chromosome 6p11–21 (D6S426, LOD score=4.19) and 16q13 (D16S415, LOD score=3.85), and some other weaker intervals at 2p15, 7q36 and 1q42 (*SLEB1*, D1S235, LOD score Z=1.51). The results of both Minnesota cohorts are shown in Table 2 as well as those obtained when the sets were combined.

The study from Los Angeles [35] using European-American and Mexican-American sibpair families identified 11 regions of interest with NPL scores >1.0. Worth noting is that a NPL score of 1.0 corresponds to a LOD score of 0.22; the results from the latter study are converted to LOD scores in Table 2 to facilitate the comparisons. Overall, very weak LOD scores were detected in this study. The highest LOD score was found at 1q44 (D1S2785, LOD score=1.54). The Swedish study that analyzed two sets of families from Iceland and Sweden, respectively [36], identified four regions with LOD scores above 2.0 in the Icelandic material (2q37, 4p15, 19q13 and 19p13) and another four with LOD scores above 1.0 [5p15, 6p21 (below HLA region), 7p15 and 21q21]. Two more regions were identified in the Swedish material with LOD scores above 2.0 (2q11 and 2q3) and another six with LOD scores above 1.0 [1q31, 5p15, 6p21 (HLA region), 6q23, 11q23 and 18q21]. The locus at 4p15 identified in the Icelandic families showed a LOD score of Z=3.20. The combination of the two family sets gave a highly significant LOD score at 2q37 with the marker D2S125 (LOD score=4.24) [36].

This region was initially denoted *hSLE1* and has officially been renamed *SLEB2* (www.gene.ucl.ac.uk/cgi-bin/nomenclature). This region has been fine-mapped in 31 families of Nordic origin to an interval between the original marker D2S125 to D2S2585 towards the very end of 2q37, with a multi-point LOD score of Z=6.03 [37]. Thus, two defined SLE loci have been confirmed on the basis of their strong linkage result and/or their presence in various studies, *SLEB1* in chromosome 1q42 and *SLEB2* in 2q37.3. It is worth noting that the Swedish study did not detect linkage to 1q42 or to the FcγRIIA interval (1q23). These two loci were observed in sets of families with a predominant African-American and

Table 2. Regions with LOD score higher than 2.0 and/or where linkage was detected in at least two genome scan studies

	SW [36]		UCLA [35]		OK I [30]		MN I [33]		MN II [34]		MN I + II [33,34]		OK II [38]	
Region	**LOD**	**Marker**	**LOD**	**Marker**	**LOD**	**Marker**	**LOD**	**Marker**	**LOD**	**Marker**	**LOD**	**Marker**	**LOD**	**Marker**
1q22–24			1,4	D1S484	**3,5**	FcγRIIA							**2,8**	D1S1679
1q31	1,6	D1S1660			**2,0**	Iamc1								
1q42–44			**2,4**	D1S2785	**3,5**	D1S3462	1,51	D1S235			1,9	D1S235		
2p15							1,7	D2S337			**2,1**	D2S337		
2q11	**2,1**	D2S436												
2q32					**2,1**	D2S1391								
2q37	**4,2**	D2S125											1,5	D2S1363
4p16–15					**2,2**	D4S403			1,5	D4S403			**3,8**	D4S2366
4p13	**3,2**	D4S1627												
4q31–33					1,5	D4S2431	**2,0**	D4S424			1,5	D4S1597		
6p24-23											1,6	D6S2434	**2,1**	D6S2434
6p22–11	1,9	TNFa					**3,9**	D6S257	**2,87**	D6S426	**4,2**	D6S426	1,7	D6S2439
6q11													**2,4**	D6S1053
6q15							**2,2**	D6S462						
6q27	1,4	D6S503			**2,0**	D6S1027								
7p22–21	1,8	D7S513							**2,9**	D7S517				
7q21									**2,4**	D7S669				
7q36									**2,15**	D7S798	**2,2**	D7S798		
9p24	**2,3**	GATA62F03											**2,1**	D9S925
10p13	1,8	D10S1423							**2,2**	D10S548				
11q21					**2,1**	D11S2002								
11q24					**2,2**	D11S912								
12p12					**2,0**	D12S1042							1,79	D12S1042
12q24													**2,0**	D12S395
13q32					**2,5**	D13S779			1,5	D13S159				
14q11					**2,2**	D14S742								
14q22							**2,8**	D14S276						
15q26	**2,0**	D15S657					**2,1**	D15S127						
16q13							**3,6**	D16S415	**3,2**	D16S415			**3,9**	D16S415
18q21	1,2	D18S851	1,4	D18S64										
19p13	**2,6**	D19247												
19q13	**2,1**	D19S246			**2,1**	D19S246								
20p12							**2,6**	D20S186			1,77	D20S186		
20q13					**2,5**	D20S481								

Asian admixture [25,30,35], which could explain the different result in the Swedish study with a homogeneously Caucasian cohort [35].

A recent study combining the analysis of 126 multiplex families and 175 affected relative pairs (all family materials were used in the previous studies and therefore cannot be considered as independent) was performed with the multi-point Haseman-Elston regression method that considers concordant and discordant sibling pairs [38]. A new locus was identified at 4p16–15.2 (close but probably different from the Icelandic locus at 4p15–13) with a LOD score of $Z = 3.84$ and an epistatic interaction with a region at 5p15 [38]. Of interest, a region at 5p15, albeit with a weak LOD score, was identified at 5p15 in the Icelandic (gata84e11, LOD score $Z = 1.26$) and Swedish families (D5S1492, LOD score $Z = 1.52$) [38]. Several other regions identified in this study were observed in the genome scans described previously. In summary, regions at 1q41 [24,30,31], 2p13–q12 [30,36], 2q35 [30,33], 5p15 [36,38], 6p11–21 [30,33,34,36], 7q36 [30,34], and 21q21 [30,36] have been found in various genome scans. In addition, six regions fulfill the criteria of Lander and Kruglyak [39] of LOD score > 3.3 for linkage: 1q23 [30], 1q41 (*SLEB1*) [24,30], 2q37 (*SLEB2*) [36,38], 4p16–p15 [38], 6p21–11 [33,34,36] and 16q13 [33,34].

All studies detected linkage in regions at chromosome 1: 1p13–p21, 1q21–23, 1q31 and 1q42–44. All these regions have synteny to mouse chromosome 1 [Figure 1]. In addition, the interval 2q32–2q37 in human chromosome 2 is represented in mouse chromosome 1 as well [Figure 1] (go to for human/mouse homology maps). This opens the possibility of studying mouse chromosome 1 in order to understand the function and regulation of many important genes involved in susceptibility for SLE. Chromosome 1 harbors a large number of candidate genes of interest, including the *FcγRIIA* (1q21), *IL-10* and its homologue *IL-19* [40], (1q31) and *PARP* (1q42) as well as the complement receptors CR1 and CR2 among many other interesting candidate genes.

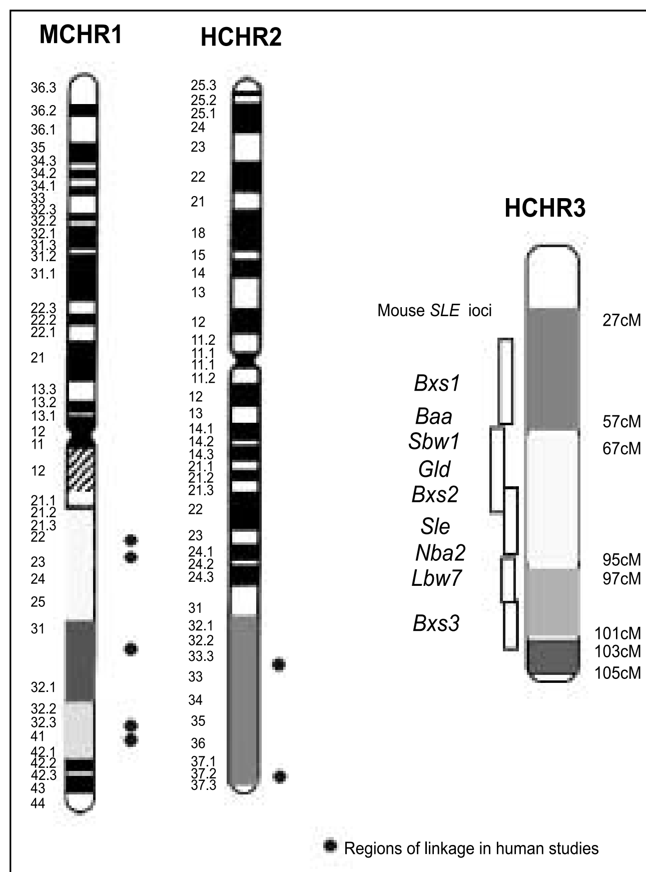

Figure Legends

Synteny between mouse and human chromosomes. HCH1 = human chromosome 1, HCH2 = human chromosome 2, and MCH1 = the mouse chromosome 1. The regions found in human chromosomes 1 and 2 that have homologous genes in the mouse chromosome 1 are shadowed. The dots represent the human linkages detected in multi-case families for SLE. The white bars represent the intervals of linkage in mouse genetic studies and crosses with mouse models of SLE: New Zealand strains, MRL-lpr and BXSB. Of interest, linkages for SLE are well represented in the mouse chromosome 1.

Conclusion

SLE is a genetically complex disease with contribution from both MHC and non MHC-genes. Substantial work has been done to unravel these genetic factors both in murine lupus models and in human SLE. The results from the genetic analysis of SLE in humans support the data from murine lupus models, suggesting that SLE is a polygenic disorder. Although the actual genes identified in human and murine SLE may not be identical, it is possible that the immunological pathways are similar. Identification of the genes involved in the development of SLE will provide important insight into the development of the disease, the development of autoimmunity, and opportunities to improve diagnosis and treatment.

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Correspondence: Dr. M.E. Alarcón-Riquelme, Phone: (46-18) 471-4805, Fax: (46-18) 471-4808, email: marta.alarcon@genpat.uu.se