Summary: Systemic lupus erythematosus (SLE) is a prototypic systemic autoimmune disease in which glomerulonephritis represents one of the most severe clinical presentations. Numerous linkage and association studies, as well as the analysis of murine models, have provided ample evidence for a genetic basis for SLE. Genetic susceptibility to SLE results from the combined actions of multiple alleles, each of them conferring a modest incremental risk. SLE susceptibility genes have been identified in 3 major pathways: apoptosis, lymphocyte activation, and clearance of immune complexes and/or apoptotic debris. There also now is evidence that, within SLE patients, renal end-organ targeting also has a genetic basis, which can be divided into 2 branches. There is evidence that susceptibility alleles that are associated with a greater disease severity also are associated with lupus nephritis. There also is evidence for a set of kidney-specific genes that are likely to amplify or to sensitize to the autoimmune pathology.

Systemic lupus erythematosus (SLE) susceptibility is a complex trait in which both genetic and environmental components play a role. A $\lambda_v$ value, which compares the relative risk of disease in siblings of patients with that of the population at large, of 15 to 20 for SLE indicates a strong genetic basis, comparable with that of other major autoimmune diseases such as type 1 diabetes and multiple sclerosis. The inheritance of this type of diseases has been coined threshold liability. Contrary to Mendelian inheritance, in which there is an obligate and simple relationship between the inheritance of an allele and a specific phenotype, a threshold liability disease develops when an individual accumulates a number of genetic and environmental factors that is greater than the disease threshold. The involvement of nongenetic factors in SLE susceptibility is shown clearly by a concordance rate between monozygotic twins of 34% to 50%, which would be close to 100% if SLE susceptibility were purely genetic.

Genetic analyses of inbred murine models of systemic autoimmunity also strongly argue in favor of a genetic basis for SLE susceptibility. It is unlikely, however, that exactly the same genes mediate lupus in mice and in human beings, but the coincidence of functional pathways that have been identified in both the human disease and its animal models provides a powerful support to the notion that the identification and characterization of murine susceptibility genes will illuminate the genetic pathways to human lupus.

The exact number of genes involved in SLE susceptibility currently is unknown, and it is most likely that SLE susceptibility results from various combinations of different genes. With a few exceptions, the identity of these genes also is unknown. Rapid progress is being made, however, toward the identification of these genes, largely benefiting from the completion of the human and mouse genome sequencing projects, and the development of high-throughput genotyping techniques. As with any complex trait, 2 strategies have been used to identify lupus susceptibility genes.

Association studies evaluate candidate genes that have been selected based on their
function in the immune system (eg, Fc fragment of IgG, low affinity IIIa, receptor [FcgRIIIa]), or their aberrant expression in lupus patients (eg, interleukin [IL]-8). Statistical associations then are evaluated on sequence variations within these genes (most often single-nucleotide polymorphisms [SNPs]) between patients and controls (Table 1). The most obvious limitation of this approach is that it is biased toward genes with an expected contribution to the disease. In addition, a number of statistical issues, such as population stratification, can hinder result interpretation, which may explain why independent studies have reached opposite conclusions on the association of specific polymorphisms with SLE or lupus nephritis (LN) (Table 1).

Association studies correspond conceptually to the analysis of genetically engineered mice in which a gene of interest is either overexpressed as a transgene or knocked-out. This approach is obviously drastic, and does not correspond to the more subtle functional variants that are likely to occur in spontaneous mouse models or in SLE patients. Nonetheless, these studies have been very informative to identify the functional pathways that are defective in SLE because overexpression or deficiency in a large number of genes results in a lupus-like syndrome in mice, in many cases including LN. Moreover, some of these genes have been found to be involved in human SLE.

Linkage analyses rely on genome-wide scans of families of SLE patients with anonymous DNA markers. Subsequent statistical analyses have mapped the location of genomic regions named quantitative trait loci (QTL)-linked SLE or LN susceptibility (Table 2). In contrast to association studies, genome scans have the potential to identify any susceptibility genes without prejudice. The functional significance of a QTL is the probability that one or several susceptibility alleles are contained within this region. Validation of these statistical results is achieved through independent replications with other family sets. Several scans have been performed on SLE families that met the 4 American College of Rheumatology (ACR) criteria, and to date, 8 QTLs have been validated, out of more than 50 independently identified. The identification process for each of the genes responsible for these QTLs, however, is a daunting task that has not yet been completed.

A third strategy, the whole genome association analysis (WGA), is moving rapidly to the forefront of the genetic analysis of complex traits in general, and that of lupus in particular. This approach relies on the ongoing converging of (1) the development of a dense SNP haplotype map, known as HapMAP, and (2) the production of high-throughput affordable screening SNP chips that allow the simultaneous genotyping of 100,000 SNPs per individual. Because association studies offer more statistical power than linkage analyses, and the whole genome approach is not hindered by preselection of genes flagged by their known function, WGA studies hold the promise to deliver the key to complex trait genetics in the near future, including lupus susceptibility.

**IS THERE A GENETIC PREDISPOSITION TO LN?**

SLE is a heterogeneous disease affecting various target organs, including the kidneys. It is still a matter of debate whether end-organ targeting has a genetic basis. A number of studies, however, favor a genetic basis for renal involvement in SLE. The risk of developing end-stage renal disease is 2.6- to 5.6-fold greater in African Americans than in European Americans, and a number of studies have shown a genetic component to end-stage renal disease, either in general, or associated with diabetic nephropathy or LN. In addition, susceptibility to experimental immune-mediated nephritis varies greatly among mouse and rat strains, which implies a genetic basis.

Because LN is one of the most serious clinical outcomes of SLE, it is possible, however, that renal involvement represents a marker of disease severity rather than a distinct genetic cause. LN also is associated strongly with a number of other disease markers, most notably with the production of nephrophyllic autoantibodies such as anti–double-stranded DNA immunoglobulin (Ig) G. It is therefore possible that some of the LN susceptibility genes are in
<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Allele</th>
<th>LN*</th>
<th>Comments†</th>
<th>LN Negative‡</th>
<th>Comments§</th>
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<td>FcγRIIIA</td>
<td>V/F158</td>
<td>25</td>
<td>Meta-analysis</td>
<td></td>
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<td>-675 4G4G INDE</td>
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<td>Intron 4 repeat</td>
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<td>A-2518G</td>
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<td>Swedes and CA</td>
<td>70</td>
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<td>Vitamin D receptor</td>
<td>bb BsmI RFLP allele</td>
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<td>Japanese</td>
<td>79,80</td>
<td>Taiwanese</td>
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<td>82</td>
<td>Koreans</td>
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</table>

*Reference number of the study reporting a significant association with LN.
†Ethnic groups analyzed in the study reporting significant association with LN.
‡Reference of the study reporting a lack of association with LN.
§Ethnic groups analyzed reporting a lack of association with LN.
‌Association with SLE, but not LN.
fact genes that predispose to the production of these antibodies.

As detailed later, there is evidence that LN genetic basis is supported both by genes that target the pathogenic autoimmune effector response to the kidneys and by genes that increase the global severity of the autoimmune pathology, and therefore increase the likelihood of renal disease in these patients.

**GENES ASSOCIATED WITH LN**

Polymorphisms in more than 20 genes have now been associated significantly with increased LN frequency or severity (Table 1 and Fig. 1). Most of these studies were conducted with relatively small data sets and most likely were underpowered. It is therefore not surprising that for nearly half of these genes, independent studies on unrelated data sets did not find any association. In addition, the disparity of these results may be the consequence of ethnic-specific associations. Allele frequency varies among populations, making the ethnic stratification of the case and control populations a critical parameter and a common source of statistical error in association studies.

### Table 2. QTL Loci Linked to LN

<table>
<thead>
<tr>
<th>QTL</th>
<th>Position</th>
<th>Ethnicity</th>
<th>Reference</th>
<th>SLE QTL*</th>
<th>Candidate gene†</th>
<th>Mouse QTL‡</th>
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<td>SLE2B</td>
<td>PCDC1</td>
<td>Bxsb1</td>
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<td>3q21-23</td>
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<td>47,48</td>
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<tr>
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<td>11p13</td>
<td>AA</td>
<td>47</td>
<td></td>
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<tr>
<td>SLEN3</td>
<td>11p15.6</td>
<td>AA</td>
<td>47</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AA, African Americans; CA, Caucasian Americans.

*Overlap with a QTL identified in SLE patients ascertained with 4 ACR criteria (see Fig. 1).
†Genes with polymorphisms significantly associated with LN colocalizing with the SLEN loci (see Table 1).
‡Overlap with a mouse locus that has been linked to glomerulonephritis (GN).52

**Figure 1.** Position of genes and QTLs associated with LN in the human genome. Each chromosome is represented by 2 vertical bars separated by the centromere. In addition to genes presented in Table 1, this figure shows the location of 5 QTLs linked to LN (white bars on the right of chromosomes), 2 of (SLEN1-2) which have been confirmed independently.
Genes That Increase Kidney Susceptibility to Autoimmune Pathogenesis

Among the genes that have been associated with LN, angiotensin-converting enzyme (ACE) and angiotensinogen (AGT), 2 essential genes from the renin angiotensin system, are the best illustration of the existence of renal-specific factors. Two polymorphisms in the ACE gene that correlate with ACE serum levels have now been associated with LN in multiple studies.18-21 In the 2 studies performed on the largest cohorts,18,19 both the Alu D and (CT)2 alleles were associated significantly with increased LN frequency and severity in non-Caucasian patients, especially among Asians. The M235T polymorphism in the AGT gene also was associated with LN in Asians.19 Interestingly, the ACE Alu D allele also was associated with an increased frequency of SLE,18 probably because angiotensin II, whose production is dependent on ACE, is a potent proinflammatory modulator in renal and nonrenal tissues. This result illustrates the difficulty in delineating genetic factors that promote LN independently of SLE.

LN is a prototypic immune complex–mediated disease and it has been proposed that the low-affinity IgG receptor FCγRIIIa (CD16) plays an essential role in immune-complex clearance, preventing the deposition of pathogenic autoantibodies in the kidney, without being involved in immune regulation. This hypothesis was based largely on the fact that autoimmune mice rendered deficient in the FCγRIII and FCγRI receptors, were protected from kidney disease, although the production of pathogenic autoantibodies was unchanged.22 These results and others23,24 have now shown that glomerular binding of pathogenic autoantibodies is FCγRIII-dependent.

A meta-analysis of 11 association studies of the V/F158 polymorphism in FCGRIIIa showed that the F158 allele, which binds IgG1 and IgG3 with a lower affinity, was associated significantly with LN (odds ratio [OR], 1.2; 95% confidence interval [CI], 1.06–1.36). When comparing FF versus VV homozygotes, the risk was higher (OR, 1.47; 95% CI, 1.11–1.93).25 This analysis, however, did not find a significant association between V/F158 and SLE, confirming the involvement of this gene with local renal pathology rather than systemic autoimmunity.

The association of FCGRIIIa with LN is complicated by the fact that in addition to IgG3, IgG2 is the most common isotype forming the immune complexes that are deposited in the kidneys of LN patients. IgG2 is bound by FCγRIIa (CD32), an inhibitory Fc receptor that is encoded by a gene, FCGRIIa, located in close proximity to FCGRIIIa. We have assigned FCγRIIa to the group of factors that amplifies the autoimmune reactions because its deficiency has been shown to contribute to murine lupus by allowing the differentiation of autoreactive B cells.26 Two meta-analyses have been conducted on the association between the FCGRIIa R/H 131 polymorphism and LN. Although the first analysis concluded a significant association,27 the validity of the statistical methodology was questioned. A subsequent meta-analysis conducted on the same data set concluded that R/R homozygosity at FCGRIIa was significantly more frequent in SLE patients than in controls (OR, 1.30; 95% CI, 1.10–1.52), but this allele was associated significantly with protection from LN (OR, 1.27; 95% CI, 1.04–1.55).29 It has been suggested that the FCGRIIa-H/R131 and FCGRIIIa-V/F158 polymorphisms are in linkage disequilibrium.30 Polymorphisms in these 2 genes may therefore interact with other susceptibility alleles of genes affecting immune-complex clearance to enhance SLE risk.31

Another Fc receptor gene, FCGRIIIb, has been implicated recently in both induced nephritis in rats and LN in human beings.16 Interestingly, susceptibility or resistance is associated with the copy number of this gene. The rat-resistant strain carries a duplication of the Fcγ3 gene, Fcγ3-rs, that is missing in the susceptible strain. Among SLE patients, a low FCGR3B copy number was associated significantly with nephritis. Although gene copy number is known to be a major type of genetic variation in mammals, its association with disease susceptibility is novel. Because FCGR3B is located in close proximity to the other Fcγ receptor genes, it will be of interest to determine the genetic relationship between the var-
ious susceptibility alleles, which may be in linkage disequilibrium and act synergistically.

One should note that the relative risk associated with each individual FCGR allele is typically low, despite the associations being highly significant. It has been suggested that genotyping errors caused by the high degree of sequence homology between the FcγR genes might contribute to underestimated OR values. Nonetheless, the OR values for these alleles falls within the range reported for other individual susceptibility alleles in SLE or other autoimmune diseases. Epistatic interactions, in which the co-expression of 2 susceptibility alleles results in a phenotype with a greater amplitude than would be expected from the simple sum of the 3 individual phenotypes, have been shown with congenic murine models of SLE. Similar interactions are suspected to occur in human beings, although they have been difficult to show, largely because of genetic heterogeneity.

The only other gene-enhancing renal susceptibility to LN for which association has been validated independently is monocyte chemoattractant protein-1 (MCP-1). MCP-1 attracts leukocytes to inflamed tissues, and its expression is upregulated in the kidneys of LN patients. This gene may represent an effector mechanism by which locally increased inflammation in the kidney favors the development of nephritis in SLE patients.

**Genes That Amplify Autoimmune Pathogenesis and Increase LN Incidence or Severity**

The mechanism by which genes listed in this category contribute to LN is undefined. For most of them, however, their known function in the regulation of the immune system suggests that they contribute to the severity of the systemic autoimmune pathology. This severe disease combined with other renal-specific genetic or environmental factors fosters the development of LN.

Most autoimmune diseases have been associated with specific major histocompatibility complex (MHC) alleles. For SLE, significant association has been reported with human leukocyte antigen (HLA) class II (DRB1 and DQA) or class III (C4 and tumor necrosis factor α) genes. In addition, a genome-wide analysis has provided a strong evidence of linkage between the MHC locus and SLE. The association between these genes and LN has been more tenuous, which might be explained, at least in part, by the small number of LN patients considered. Significant associations have been reported, however, between DRB1, DQA, DQB, and LN (Table 1). In the most extensive study reported to date, conducted on 244 Italian Caucasian LN patients, a very high risk factor was found for the combination of the DRB1*1501 and DQA1*0101 alleles (OR, 65.96; 95% CI, 9.35–1,326.25), illustrating how epistatic interactions between alleles can alter disease susceptibility drastically. Association studies within the MHC locus, however, have to be interpreted with great caution. About 40% of the 180 genes expressed in this locus have a known function in immune regulation. Moreover, many of these genes are in tight linkage disequilibrium, which means that combinations of alleles of these genes are inherited in blocks, the size of which depends on the population structure. Consequently, association studies cannot discriminate among genes in close linkage disequilibrium, which one contributes to the disease. To start to address this question, the HLA locus in 334 SLE families was genotyped with 158 markers. Three DRB1/DQB haplotypes were identified as significantly associated with SLE, and 2 of these haplotypes were narrowed down to an approximately 500-kb region. The same type of analysis is still lacking for LN, but there is a strong likelihood that DRB1 and DQB, or genes in close proximity, correspond to SLE and LN susceptibility alleles. The definitive identification of these genes and alleles will require the upcoming completion and mining of the human MHC HapMap.

The only other immune-related gene whose association with LN has been validated independently is IL-10. IL-10 is a pleiotropic cytokine with both potent anti-inflammatory and B-cell growth factor properties. It is not clear whether the susceptibility alleles identified in the association studies correspond to functional variants, and therefore the mechanisms by which they confer LN susceptibility (by increas-
ing systemic or local inflammation, or by promoting B-cell effector functions) is not clear.

GENOMIC REGIONS LINKED WITH LN

A phenotype stratification strategy has been applied to genome scan results to address the genetic basis of various specific clinical manifestations.46 By using this approach, 6 SLEN QTLs have been linked to LN, 3 of them in African Americans and 3 in Caucasian Americans (Fig. 1 and Table 2).47 Among them, SLEN2 (2q34-35) and SLEN1 (10q22.3) subsequently have been validated in an independent data set.48 Interestingly, only 1 of the SLEN loci, SLEN2, overlaps with a validated SLE QTL, SLE2B, at 2q35-37.6 PDCD1, which is a strong candidate gene for SLE2B,49 produces an inhibitory receptor on T cells, and its deletion in C57BL/6 mice results in a lupus-like disease.50 The overlap between SLEN2 and SLE2B does not entail that the same gene accounts for both linkages because the genomic intervals typically are not precisely defined in linkage analysis and contain a large number of genes. Obviously, finer mapping will be required to solve this issue. Another potential overlap is at 3q21-23, a region in which nominal evidence of linkage has been obtained in 2 family collections ascertained with the 4 ACR criteria,1 and in one family collection stratified by LN.47

Interestingly, SLEN2 also overlaps with the mouse QTL Bxsb1 defined in the BXSBYaa model.51,52 The BXSBYaa strain is unique among the lupus models in that disease is greatly accelerated by the expression of Yaa (Y-linked autoimmune-accelerating locus), which corresponds to an as yet unidentified gene.53 Bxsb1 linkage to LN in females (without Yaa expression) has not been evaluated. SLEN2 was identified in a data set in which the female: male ratio was likely to reflect the typical 9:1 ratio observed in SLE patients. If SLEN2 and Bxsb1 correspond to the same gene, it would imply that other genes in the human genome could functionally replace Yaa and synergize with SLEN2.

Based on the association studies, IL-8 and SPP1, the genes encoding for IL-8 and osteopontin, respectively, are candidate genes for the SLEN locus that peaks at 4q13.1 (Fig. 1). This locus was linked significantly to LN in Caucasian Americans,47 which fits with the ethnicity of the population in which SPP1 was associated with LN.54 The association study for IL-8 did not stratify by ethnicity among a mixed US population.55

It is noticeable that the 6p11-23 HLA locus was not found to be linked to LN, despite its significant linkage to SLE and the strong association between HLA class II genes and LN. LN linkage analysis was performed only by one group, although on 2 independent data sets. It is therefore not clear whether this discrepancy between linkage and association studies reflects population heterogeneity, and/or statistical distortion resulting from the stratification scheme, or if it indicates that HLA genes contribute essentially to SLE susceptibility, but not as much to nephritis.

CONCLUSIONS

The analysis of the genetic basis of complex diseases such as LN is a difficult task. In addition to the inherent complexity of human polygenic traits, the analysis of a specific clinical manifestation, such as renal pathology, compounds the level of complexity for multiple reasons, the most obvious one being the lower statistical power as a result of reduced cohort size. Progress is being made in the identification of genes such as PTN22 and CTLA-4, which are involved in autoimmune pathology.56 Although these specific genes do not appear to be involved specifically in LN, their identification provides a road map toward the validation of existing LN candidate genes and the identification of new ones. In addition, extensive research is being conducted in parallel on the genetic basis of LN in animal models, either in spontaneous models of lupus57 or in induced models of immune-mediated nephritis.15,16 The active pursuit of these models will be likely to play an important role in the elucidation of the genetic mechanisms responsible for LN.

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