Mapping the Systemic Lupus Erythematosus Susceptibility Genes

Swapan K. Nath, Jennifer A. Kelly, John B. Harley, and R. Hal Scofield

Summary
Systemic lupus erythematosus (SLE) is a prototype systemic, autoimmune inflammatory disease that can involve virtually any organ or tissue type. The disease has a strong familial tendency but, like most human illness, has a complex pattern of inheritance that is consistent with multiple susceptibility genes as well as environmental risk factors. Association studies have been performed, especially for the major histocompatibility complex on chromosome 6 and for various complement components. Several large familial studies have begun to report results for genetic linkage. Linkage has been established for many genetic intervals. SLE is a complex clinical illness, and investigation of the genetics of the illness based on clinical manifestations revealed linkages not found without consideration of the phenotype of the disease.

Key Words: Autoantibodies; autoantigens; complement; genetic association; genetic linkage; HLA; systemic lupus erythematosus.

1. Introduction
Systemic lupus erythematosus (SLE) is a complex disease in which immune responses are directed against a multitude of self-antigens. SLE in humans manifests with a diverse array of clinical symptoms that potentially involve multiple organ systems. At least a portion of the pathophysiology is attributed to deposition of immune complexes, which are continuously formed by autoantigens and autoantibodies, in various tissues. Thus, pathogenesis is related to dysregulation of self-reactive B cells. In addition, immune dysfunction of the T lymphocytes involved in the adaptive immune system and elements of the innate immune system, such as complement protein deficiencies, are also involved in disease expression.
Although SLE is a clinically heterogeneous disease, current guidelines require a set of 4 of 11 American College of Rheumatology criteria for classification of a patient as having SLE (1); the hallmark feature is the production of autoantibodies against nuclear components. As a result, antinuclear antibody (ANA) testing is very sensitive for the disease, although not highly specific because ANAs are sporadically detected in as much as 2% of the female population over the age of 40 yr as well as in the sera of persons with other diseases.

On the other hand, antibodies to double-stranded DNA (dsDNA) and the Sm protein are very specific for SLE. The overall estimated prevalence in the United States is approx 12–64 cases per 100,000 individuals (2,3). Significant gender differences are observed in prevalence (female: male = 9:1), age at onset, premorbid conditions, clinical expression, course of illness, response to treatment, and morbid risk. In addition, there are important racial differences in disease manifestations. For example, at least a two- to fourfold higher incidence in non-Caucasian as compared with Caucasian population has been observed (4).

The familial nature of SLE suggests an underlying genetic susceptibility, but environmental, stochastic, or epigenetic factors must be important because even monozygotic twins are not always concordant for disease. Substantial evidence has shown that the disease clusters in families, with 7–12% increased risk among the first- or second-degree relatives of a proband (5). An increased concordance rate in identical twins (15–69%) as opposed to dizygotic twins (2–5%) (6) shows support for genetic basis. The relative risk ratio for the siblings of an affected proband $\lambda_s$ varies from 20 to 40 (7). Moreover, the complex pattern of inheritance of SLE suggests multigenic inheritance, requiring interaction of various combinations of contributing genes at multiple loci in individual patients; these combinations are likely to contribute to clinically diverse phenotypes. Finally, various environmental factors, perhaps interacting with specific genes, also may play a significant role in development of SLE.

Often, lupus shows familial cosegregation with other autoimmune diseases, like rheumatoid arthritis, Sjögren’s syndrome, or antiphospholipid antibody syndrome. In fact, studies show that 10–20% of lupus probands have at least one first or second-degree relative afflicted with other autoimmune diseases. In a classic study, Bias et al. (8) defined an “autoimmune phenotype” in lupus pedigrees based on the presence of an autoimmune disease or high titers of autoantibodies (e.g., rheumatoid factors, anti-smooth muscle antibodies, anti-acetylcholinesterase antibodies, thyroid insufficiency). Bias and coworkers found that the most parsimonious model for the mode of inheritance of this new phenotype was autosomal dominant with variable penetrance (92 and 49% for women and men, respectively). This led to the hypothesis that a single gene confers susceptibility to autoimmunity, and other genes (such as HLA, T-cell
receptors, immunoglobulin allotypes) bestow specificity to the autoimmune phenotype developed.

Becker et al. (9) compared linkage results from 23 autoimmune or inflammatory disease studies and showed clustering of mapped candidate autoimmune loci to 18 genomic regions, supporting the hypothesis of a possible shared genetic basis. Genes that predispose to SLE are undoubtedly related to key events in pathogenesis and may be involved in the expression of various other autoimmune diseases.

For disorders with a poorly known biochemical basis like SLE, identification of the genes is a prerequisite or key to an increased understanding of the biological basis. Therefore, identification of the genes contributing to susceptibility for SLE will contribute to understanding of the development and pathogenesis of the disease and may lead to novel therapeutic interventions. Such information may be valuable in predicting the course of SLE in individual patients, and this could prove to be an important guide to therapy and monitoring. In addition, genetic screening could be used to identify individuals who are at risk so that they can take advantage of early diagnosis and treatment.

2. Methods for Identifying Genes

The situation of gene discovery in humans changed markedly two decades ago when it was recognized that variations in human DNA could be assayed directly and used as genetic markers in linkage studies (10). The identification of restriction fragment length polymorphism (RFLP) markers and, subsequently, abundant highly polymorphic short tandem repeat (STR) microsatellite markers (11,12) led to the mapping and identification of many single-gene, Mendelian diseases.

Such mapping is based on the meiotic mapping process of recombination. Naturally occurring mutations are identified on the basis of their chromosomal location through meiotic events as manifested in families segregating for the disease. Typically, the markers closer to the disease gene show the strongest genotype–phenotype correlations. Markers showing the strongest correlation with disease in families are assumed to be closest to the disease locus. Such a strategy ultimately leads to positional cloning of the culprit gene.

The remarkable success of linkage analysis and positional cloning has generated a strong sense of optimism in identifying genes for a range of common, familial, and non-Mendelian diseases such as SLE. Currently, for complex diseases, two kinds of fundamentally different strategies have been used to identify genetic susceptibility factors: the whole genome search by linkage analysis and the study of candidate genes. In principle, both approaches are very simple.

When screening the whole genome, the objective is to find a genome area in which a disease risk factor is present. This is done by studying the entire
genome with a dense collection of genetic markers, typically 300–400. Then, linkage statistics are calculated either by parametric (penetrance-dependent) or nonparametric allele-sharing (penetrance-independent) model-free methods at each position of the genome. In this way, genomic intervals are identified in which the statistics show a significant deviation from what would be expected under independent assortment.

In contrast to relying on genomewide, evenly spaced linkage study, candidate gene studies focus on genes selected because of an a priori hypothesis about the candidate gene’s etiological role in the pathogenesis. Although a linkage study analyzes the cosegregation of two parameters (disease and marker) in families, the association study investigates the coexistence (nonindependence) of alleles in individuals. Thus, collection of families is not necessarily needed in this last method.

Although these methods have been relatively successful in identifying some suspected genomic regions, they have not yet been highly successful in identifying genes involved in the pathogenesis of SLE. In the single instance in which a specific disease-causing gene and allele have been identified, information from a knockout mouse phenotype greatly aided the gene discovery process. Lindqvist and colleagues (13) mapped, confirmed, and localized an SLE susceptibility gene on a chromosome. Genetic knockout of the programmed cell death 1 gene, which lies within the mapped interval, results in an SLE phenotype. Thus, this gene became a high-priority candidate, and a regulatory polymorphism upstream of the coding region of this gene appears to be the sequence predisposing to SLE (14).

The inability to identify susceptibility genes may be the result of a combination of the following causes. First, SLE varies in severity of symptoms, race, gender, and age at onset, which results in difficulty selecting the best populations to study. Second, SLE can vary in its etiological mechanisms, which might involve various biological pathways. Third, SLE, like other complex diseases, is more likely caused by several genes with small overall contributions and relative risks. Because of these factors, researchers now apply another approach, which is an association study based on a candidate gene approach.

2.1. Sources of Complexity and Clinical Heterogeneity in SLE

Clearly, SLE is a clinically complex disease such that two patients may share no common feature and yet still be diagnosed as having the illness. This fact is exemplified in the classification criteria, for which presence of any 4 of 11 criteria allows classification as SLE (1). SLE may involve almost any organ system with the mucocutaneous, musculoskeletal, neurological, hematological, immunological, cardiovascular, pulmonary, and renal systems all included in the criteria. Thus, the pattern of manifestations varies greatly between indi-
viduals, making the disease as clinically diverse as any single entity in modern medicine. So, it can easily be imagined that the complex clinical picture will have an impact on and produce an equally complex genetic etiology.

In general, SLE may range from not much more than a nuisance to an immediately life-threatening illness. Mortality in SLE is associated with several disease features, including thrombocytopenia most prominently (15, 16). Nonetheless, prediction of severity of disease or mortality in an individual remains virtually impossible. Thus, the disease has marked heterogeneity regarding its severity as assessed by mortality.

Another area in which there is great heterogeneity in SLE is the immunological manifestations. Although almost every patient has ANAs, the specificity of these autoantibodies varies widely. There are four prominent protein autoantigen specificities. Anti-Ro (or SSA) is found in the sera of about 40% of patients with SLE, some of whom also have anti-La (or SSB), which is never found without the simultaneous presence of anti-Ro. An analogous situation exists for anti-RNP and anti-Sm. Anti-RNP is found in the sera of about 40–50% of patients with SLE, and anti-Sm is found in 5–20% of sera but is always found in conjunction with anti-RNP. There are many clinical, immunological, and immunogenetic associations for each of these autoantibodies. For example, anti-Ro is strongly associated with genetic deficiency of early complement components, such as C2 and C4 (reviewed in ref. 17), and is associated with neutropenia (18). Of course, the other prominent autoantibody system in SLE is that binding native (double-stranded) DNA. The presence of anti-dsDNA is associated with kidney disease.

Overall, the large variety of clinical/immunological changes noted and the variability seen across subjects imply that SLE is an etiologically heterogeneous disease phenotype. In addition, the number of major anomalies observed in different body organs or systems demonstrates a very likely complex etiology for SLE. Because SLE is an extremely complex disease, genetic susceptibility to SLE is likely to be polygenic, involving several genes of low penetrance with allelic (different variants within the same gene) as well as locus (genetic variants in separate genes) heterogeneity and complicated epitasis, gene–environmental interactions.

2.2. Replication and Its Importance

A handful of susceptibility genes for common and complex diseases such as BRCA1 and BRCA2 in breast cancer (19, 20), Calpain10 in NIDDM (21), NOD2 in Crohn’s disease (22, 23), Neuregulin 1 in schizophrenia (24), and ADAM33 in asthma (25) have been identified. Despite these successes, linkage studies of complex diseases have been difficult to replicate. A review of the linkage findings of 31 complex human diseases based on whole genome scan concluded
that genetic localization of most susceptibility loci is still imprecise and difficult to replicate (26).

This difficulty is, in part, because of the inability to measure the precise underlying phenotype, small sample sizes, genetic heterogeneity, inaccurate genetic model, and statistical methods employed in analysis. In another similar review, Hirschhorn et al. (27) reviewed genetic association studies and concluded that only a few were reproducible. Success has been elusive because almost all complex diseases are the combination of multiple genes and environmental factors. Unlike the so-called monogenic diseases, there is no “smoking gun,” that is, associated disease mutations obviously deleterious to protein function. Instead, there are likely to be alleles with subtle functional changes that are neither necessary nor sufficient to cause disease.

Replication of initial linkage signals from independent samples is considered an important and crucial step toward distinguishing between true positives and false positives (28). The basis of all scientific research is hypothesis testing and validation of results by independent researchers or data. Independent replication is typically viewed as the sine qua non for accepting a hypothesis, but this is an extremely difficult issue in genetic studies for a complex disease, especially when genetic effects are weak and possibly context dependent (e.g., incidence may vary by sex, ethnicity, or precision of diagnosis), even with a reasonably large sample (29-30).

2.3. Application of Association to SLE

Association studies are used to localize genetic effects and identify differences in the distribution of allele frequencies according to the phenotypic status within a population. To date, there have been numerous candidate genes studied with SLE. Efforts have focused on genes identified based on some theoretical or actual knowledge of disease mechanisms associated with biologic pathways implicated in SLE. Because the loss of immune tolerance to self-components is the basis of disease etiology, many genes encoding proteins with significant functions in the immune system have been considered as candidates. Several reviews (31–34) provide a comprehensive catalog of potential candidate genes. An updated list of candidate genes showing significant association with SLE is given in Table 1.

Evidence supporting associations has been observed for numerous genes and genomic regions, including within the major histocompatibility complex in both class II and class III as well as for several cell surface immunoglobulin receptors, among others. However, there has been no, or very few, consistent replication of positive findings for any of these disease genes. There is a potentially good explanation for this phenomenon. Inconsistencies in these genetic association studies may stem from reliance on the population genetic property
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Table 1

Association Studies in SLE

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p36</td>
<td>C1q</td>
<td>44</td>
</tr>
<tr>
<td>1q22-23</td>
<td>FcGR2A</td>
<td>45</td>
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<tr>
<td>1q22-23</td>
<td>FcGR3A</td>
<td>46</td>
</tr>
<tr>
<td>1q22-23</td>
<td>TcR-ζ</td>
<td>47–49</td>
</tr>
<tr>
<td>1q31-32</td>
<td>IL10</td>
<td>50–52</td>
</tr>
<tr>
<td>2q33</td>
<td>CTLA-4</td>
<td>53</td>
</tr>
<tr>
<td>6p21</td>
<td>HLA-DR3, HLA-DR2</td>
<td>54, 55</td>
</tr>
<tr>
<td>6p21</td>
<td>TNF-α</td>
<td>56–58</td>
</tr>
<tr>
<td>6p21, 19p13, 6p21</td>
<td>C2, C3, C4</td>
<td>59</td>
</tr>
<tr>
<td>10q11.2-q21</td>
<td>MBP</td>
<td>60–62</td>
</tr>
<tr>
<td>10q24, 1q23</td>
<td>FAS/FASL</td>
<td>63</td>
</tr>
<tr>
<td>18q21</td>
<td>Bcl-2</td>
<td>50</td>
</tr>
</tbody>
</table>

of linkage disequilibrium to detect an association between what is actually a “marker” polymorphism in a candidate gene and the unobserved true SLE-predisposing variant. Moreover, the complexity of SLE demands studies that have very strong statistical power. The sample sizes of most of the candidate gene studies to date have been inadequate to make conclusive statements about the role of the specific alleles in a complex clinical phenotype.

Although population-based association methodology is statistically powerful, similar to other disease association studies, false-positive results may occur if cases and controls are not drawn from the same population with a matched genetic history. In addition, modest genetic effects and allelic heterogeneity contribute to difficulty in replication and confirmation of the candidate genes implicated in SLE in the last several years.

2.4. Application of Linkage to SLE

There are several different study designs with variable ascertainment approaches that have been used for genomewide scan to identify novel susceptibility loci for SLE. Some of the study designs involve (a) sibling pairs who may or may not have parents available or (b) small and large pedigrees with several generations. Numerous genome scans have been made by the four major scientific groups (located in California, Oklahoma, and Minnesota in the United States and in Sweden), revealing many loci spread across the genome (reviewed in refs. 33 and 34). There are seven major cytogenetic locations, which show significant evidence of linkage to SLE based on the recommended criteria.
for genome scan. These key regions, along with several suggested regions identified by at least two independent groups, are summarized in Table 2 and Fig. 1.

However, for the reasons discussed, linkages to many loci have not been replicated across different population groups and studies, although replication in SLE may be better than that in many other genetically complex human diseases (see ref. 34 for complete details of these data). Thus far, genomewide scanning has led to the identification of only one susceptibility gene for SLE, the programmed cell death 1 gene (PDCD1, also called PD-1) (14).

<table>
<thead>
<tr>
<th>Study center</th>
<th>Study design</th>
<th>Number of families</th>
<th>Major ethnicity (%)</th>
<th>Major linkage findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMRF 1</td>
<td>Extended pedigrees</td>
<td>94</td>
<td>Caucasian (58), African American (33)</td>
<td>1q23, 1q25, 1q32, 20q13</td>
<td>64</td>
</tr>
<tr>
<td>OMRF 2</td>
<td>Extended pedigrees</td>
<td>126</td>
<td>Caucasian (63), African American (27)</td>
<td>4p16-16, 1q22-24</td>
<td>65</td>
</tr>
<tr>
<td>UMN 1</td>
<td>Sibpairs</td>
<td>105</td>
<td>Caucasian (80), Hispanic (8), African American (5)</td>
<td>6p11-21, 1q13, 1q21, 20p12</td>
<td>66</td>
</tr>
<tr>
<td>UMN 2</td>
<td>Sibpairs</td>
<td>82</td>
<td>Caucasian (78), African American (15), Hispanic (6)</td>
<td>7p22, 7q21, 10p13, 7q36</td>
<td>67</td>
</tr>
<tr>
<td>UMN 1 + 2</td>
<td>Sibpairs</td>
<td>187</td>
<td>Caucasian (79), African American (10), Hispanic (7)</td>
<td>6p11-12, 1q13, 2p15</td>
<td>67</td>
</tr>
<tr>
<td>USC</td>
<td>Extended pedigrees</td>
<td>80</td>
<td>Caucasian (46), Hispanic (54)</td>
<td>1q43</td>
<td>68</td>
</tr>
<tr>
<td>Uppsala</td>
<td>Extended pedigrees</td>
<td>17</td>
<td>Caucasian (100)</td>
<td>2q27, 4p15-13, 19p13, 19q13</td>
<td>13</td>
</tr>
</tbody>
</table>

OMRF, Oklahoma Medical Research Foundation; USC, University of Southern California; UMN, University of Minnesota; Uppsala, Uppsala University, Sweden.
2.4.1. Pedigree Stratification Strategy

As discussed, SLE is a complex autoimmune disease with a definite genetic predisposition. However, the exploration of SLE genetics is in its infancy. SLE is an extremely complicated clinical illness with a wide range of manifestations. Clinical manifestations of SLE can be very diverse, with glomerulonephritis, dermatitis, thrombosis, vasculitis, seizures, arthritis, hemolytic anemia, and thrombocytopenia counted among the disease’s manifestations. Consequently, the variation between patients is incredible. Indeed, it is possible to have two patients afflicted with SLE who satisfy the classification criteria three different ways with no features in common. This degree of clinical heterogeneity may be because of the involvement of multiple major and modifier genes. Thus far, the genome scans have been performed using a general SLE phenotype.

As an alternative, a set of “etiologic classes” could be considered, reflecting different genes or interactive combinations resulting in SLE for particular subsets of individuals or families (the “pedigree stratification approach”). Detection of a main effect will depend on the relative proportion of individuals carrying a particular genetic variant (or interactive combination that includes that gene) among the individuals studied. As this proportion is likely to fluctuate between data sets, it is unlikely that a particular linkage finding could be replicated in many other data sets, even if the same underlying model were at play. This is because the combination of families from different “classes” in the same linkage or association study will reduce the ability to detect the effects of any particular gene. The well-known example is the BCR1 gene, found only when early-onset breast cancer was considered among families that also had ovarian cancer.

The strategy of using pedigree stratification as a way to discover linkage effects has only been pursued by our Oklahoma group. We have taken the advantage of a pedigree stratification strategy from our huge collection of pedigrees with relevant clinical and medical information available for each individual, especially for the patients with SLE. Therefore, the extraordinary clinical heterogeneity in lupus is consistent with this phenotype as a treasure trove of genetic linkages based on stratifying pedigrees by clinical or demographic features. The rationale behind the subgrouping of the SLE families with a common clinical feature is to make the SLE families more genetically homogeneous. It was anticipated that, regardless of the actual number of genes involved in SLE, decreasing sample heterogeneity by subgrouping families based on race and common associated traits would increase the likelihood of identifying genes for SLE. Although this approach has many advantages, the major disadvantage is the reduced sample size after phenotype stratification, which urgently requires independent verification of the findings.
Fig. 1. Several groups have performed independent genomewide linkage studies. Results established and confirmed, or with suggestive conformation, are shown by chromosomal location. Oklahoma, Oklahoma Medical Research Foundation; Uppsala, Uppsala University, Sweden; California, University of Southern California; Minnesota, University of Minnesota.
2.4.2. Effect of Stratification

Because we are using a pedigree stratification strategy and dealing with a very low number of families, there is always a chance for false-positive results. Here, we have used an *ad hoc* criterion to adjust the critical value for declaring the significance of a linkage. For example, we performed the linkage analyses on a subset from our total pedigree collection, in which pedigrees were ascertained by the presence or absence of a certain phenotype (e.g., rheumatoid arthritis positive or negative, although study phenotype for linkage was maintained as SLE), and six different parametric models (based on different penetrances because the true model is unknown) along with a nonparametric model were tested in initial genome screen so that several genome scans were performed. This is a case of a multiple testing problem in which 14 \[2 \times (6 + 1)\] tests were performed.

To assess the significance of any linkage findings, we may use two types of experimental solutions. First, we took a simulation-based approach. We randomly selected \(n\) (number of pedigrees used for subset analysis) pedigrees from the total available pedigrees 10,000 times (sampling with replacement) and calculated the logarithmic odds (LOD) score at the peak marker for each resampled set of \(n\) to determine an empirical distribution of LOD scores. Therefore, this gives an empirical \(p\) value for our original \(n\) selected pedigrees from the observed LOD score distribution.

Second, we have used an *ad hoc* correction designed to maintain the overall genomewide significance level (5% level) to detect the significant linkage by raising the LOD score limit to 4.4. This is calculated as LOD(new) = LOD(conv) + \(\log_{10}(\#\text{test})\) \((35,36)\), where LOD(conv) is the conventional LOD score to be significant at 3.3. To date, we have identified many genomic regions with high statistical significance that may harbor genes predisposing to SLE. Some of the most convincing linkage results (Table 3) have been found by subgrouping the SLE families based on a specific autoimmune feature, for example, thrombocytopenia, hemolytic anemia, or diagnosis of rheumatoid arthritis.

3. Discussion and Future Directions

We anticipate that family-based classical linkage analysis followed by the association-based positional cloning approach will continue to advance the understanding of the biology of SLE disease phenotypes by identifying the underlying susceptibility genes. The availability of the human genome sequence, as well as that of model organisms, should expedite this effort. The full-scale analysis of genetic variation of genes in regions linked to disease will require the development of cost-effective, high-throughput single-nucleotide polymorphism genotyping. Considering the present advancement in the field, these advanced technologies and appropriate and powerful study designs will bring success to SLE genetics.
As discussed here, individuals affected with SLE are extraordinarily different from one another by clinical and laboratory measures. This variation may have a genetic basis; if so, it is advantageous to incorporate measures of between-family clinical variability as covariates in a genetic linkage analysis of affected relative pairs to allow for locus heterogeneity. This approach was applied to genome scan marker data from the Oklahoma Medical Research Foundation and identified some new genetic linkage for SLE (37). So, allowing for locus heterogeneity through the incorporation of covariates in linkage analysis is a useful way to dissect the genetic contributions to SLE and uncover new genetic effects. A few other variants of this method have been developed that take into account the locus heterogeneity measured by covariates, thereby allowing the discovery of evidence for linkage that might otherwise be obscured (38–40).

It is estimated that the human genome contains approx 30,000 genes. It seems likely that one day there will be the capacity to assess each individual gene and its significance to SLE in a very inexpensive way. Finding the predisposing genes may then be less difficult than it is today. But, the major challenge will be in understanding the biology and characterization of the genetic mechanisms responsible for SLE susceptibility. Consequently, a significant amount of time will be required to understand the biology of many of the real genetic effects now being discovered. For example, HLA-B27 and its significant association with ankylosing spondylitis have been known for 30 yr (41), yet the biology, disease mechanism, and why the association exists are not understood.

### Table 3

<table>
<thead>
<tr>
<th>Region</th>
<th>Marker</th>
<th>Race</th>
<th>No. of pedigrees</th>
<th>Phenotype</th>
<th>LOD/ p value</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>2q34.3-5</td>
<td>D2s1384-D2s434</td>
<td>AA</td>
<td>40</td>
<td>Renal</td>
<td>$1 \times 10^{-4}$</td>
<td>68</td>
</tr>
<tr>
<td>4p16.1-5</td>
<td>D4s3007</td>
<td>EA</td>
<td>23</td>
<td>Neuropsychiatric</td>
<td>5.19</td>
<td>69</td>
</tr>
<tr>
<td>5p15.3</td>
<td>D5s2505</td>
<td>EA</td>
<td>14</td>
<td>Rheumatoid arthritis</td>
<td>6.9</td>
<td>70</td>
</tr>
<tr>
<td>10q22.3</td>
<td>D10s2470</td>
<td>EA</td>
<td>31</td>
<td>Renal</td>
<td>$8 \times 10^{-7}$</td>
<td>68</td>
</tr>
<tr>
<td>11p13</td>
<td>D11s1392</td>
<td>AA</td>
<td>13</td>
<td>Thrombocytopenia</td>
<td>5.72</td>
<td>16</td>
</tr>
<tr>
<td>11q14</td>
<td>D11S2002</td>
<td>AA</td>
<td>16</td>
<td>Hemolytic anemia</td>
<td>4.70</td>
<td>71</td>
</tr>
<tr>
<td>11q14</td>
<td>D11S2002</td>
<td>AA</td>
<td>12</td>
<td>Nucleolar ANA</td>
<td>5.62</td>
<td>72</td>
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<tr>
<td>17p13</td>
<td>D17s974-D17s1298</td>
<td>EA</td>
<td>16</td>
<td>Vitiligo</td>
<td>$3 \times 10^{-4}$</td>
<td>73</td>
</tr>
<tr>
<td>19p13.3</td>
<td>D19s714</td>
<td>EA</td>
<td>37</td>
<td>dsDNA</td>
<td>4.93</td>
<td>74</td>
</tr>
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</table>

The DNA-based approach is also not without its shortcomings. This is particularly apparent when complex diseases like SLE are considered, for which the disease phenotype is more likely influenced by many different genes together with a modifying effect of the environment. These gene–gene and gene–environment interactions that combine to cause the disease complicate the interpretation of the data generated from family-based linkage and association studies.

As an alternative to this, an RNA-based approach could also be used to identify the important genes that are responsible for the development of the complex phenotype for SLE. By comparing gene expression in normal and disease states, differentially expressed genes are identified and may represent candidate genes for further investigation. For example, this technology has identified the Nba2, a murine SLE susceptibility locus (42). The use of gene expression arrays in human SLE has identified a pattern of interferon-inducible gene expression signature (43). So, this new approach will likely complement the DNA-based approach and further advance the knowledge about SLE biology.

Acknowledgments

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