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Familiality and Co-Occurrence of Clinical Features of Systemic Lupus Erythematosus

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Objective. **To evaluate familiality of 15 clinical and laboratory features in systemic lupus erythematosus (SLE)–affected sibpairs, and to estimate correlations with the age at SLE diagnosis in affected sibpairs and parent–offspring pairs.**

Methods. **Concordance rates and sibling risk ratios were used as indicators of familiality for 15 manifestations of SLE. Pearson's correlations and paired *t*-tests were used to compare the age at SLE diagnosis in affected sibpairs and in parent–offspring pairs.**

Results. **Increased sibling risk ratios (1.9–3.9) for thrombocytopenia, discoid rash, neurologic disorder (defined as seizure or psychosis), and hemolytic anemia were observed in 159 SLE-affected sibpairs. Among these clinical features, paired expression of hemolytic anemia plus thrombocytopenia and hemolytic anemia plus neurologic disorder appeared to be more frequent in 709 SLE patients than would be expected by chance ($P < 0.00001$ and $P < 0.007$, respectively). The ratio of the presence of both hemolytic anemia and neurologic disorder was ~13 times higher in the younger affected sib than in the older affected sib ($P < 0.02$). Familiality of patient age at SLE diagnosis, as observed by relative correlations, was greater in 125 affected sibpairs (r = 0.67, $P < 0.0001$) than in 37 affected parent–offspring pairs (r = 0.47, $P = 0.003$). The median ± SD age at SLE diagnosis was significantly lower in offspring (21.5 ± 10.1 years) than in their parents (41.6 ± 15.8 years) ($P < 0.0001$) but was not different in sibpairs. The combined non-Caucasian sibpairs had a younger mean age at SLE diagnosis compared with Caucasian sibpairs ($P = 0.014$).**

Conclusion. **Evidence for familiality of thrombocytopenia, discoid rash, neurologic disorder, hemolytic anemia, and co-occurring neurologic disorder plus hemolytic anemia in SLE was observed in 159 affected sibpairs. Familiality of the age at SLE diagnosis in relative pairs suggests that shared genes and/or shared environmental exposures impact disease susceptibility. Shared immediate environmental triggers appear less compelling, because the average time between dates of diagnosis was 11 years in parent–offspring pairs and 7.5 years in affected sibpairs. The significantly earlier age at disease diagnosis in offspring compared with their parents suggests that some forms of anticipation might play a role in susceptibility to SLE. Stratifying families by subphenotypes that are familial may reduce heterogeneity and facilitate identification of genetic risk factors for SLE.**

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Susceptibility to systemic lupus erythematosus (SLE) has been attributed to complex interactions between multiple genetic and environmental factors (1–3). The influential effect of a genetic predisposition on susceptibility to SLE is supported by its familial aggregation. Siblings of SLE patients have a 20–40-fold greater risk for developing SLE compared with the general population (2% versus 0.05–0.1%) (3–6). Studies of monozygotic twins show a concordance rate for SLE ranging from 24% to 57% (5,6). Because most twin pairs share similar environments, the 10-fold lower concordance rate for SLE in dizygotic twins (2–5%) compared with that in monozygotic twins strongly suggests that genes predispose to SLE (5,6). Candidate gene studies have shown associations between SLE and many genetic factors, including complement gene deficiency (C1q, C2, or C4), and polymorphic alleles of major histocompatibility class II, Fcγ receptors, mannose-binding ligand, interleukin-10, and tumor necrosis factor α (3).

In recent years, collections of multiplex families for linkage analyses have facilitated studies of familial SLE. In several such collections, no differences in clinical manifestations and laboratory findings between familial and sporadic cases of SLE were observed (7–9). Thus, results of genetic analyses using multiplex SLE families may be extrapolated to sporadic cases of SLE, which represent most patients with SLE. Linkage analyses of multiple cohorts of SLE multiplex families have thus far identified 6 genomic loci (1q22–24, 1q41–42, 2q37, 4p15–16, 6p11–22, and 16q12–13) that meet the criteria for significant linkage and have been supported in independent cohorts (for review, see ref. 1). Considering the relatively small numbers (from 17 to 187) of families in each independent cohort (10–17), the effects of at least some SLE susceptibility genes appear to be quite consistent.

Strategies to facilitate the transition from linkage analyses to the identification of susceptibility alleles are being developed. One approach is to minimize phenotypic heterogeneity of the disorder. Patients with SLE present with a diverse array of clinical manifestations, including variable serology and organ involvement, leading to fulfillment of at least 4 of the 11 criteria for the classification of SLE (18,19). We reason that clinical features that run in families are likely to be genetic, and subphenotypes of SLE may be the result of fewer genes compared with overall disease susceptibility. Thus, assessment of the clinical manifestations among SLE-affected sibpairs displaying sibling concordance or a correlation may be useful for the stratification of families in an effort to reduce heterogeneity in linkage analysis. In this study, we evaluated sibling concordance of 15 SLE manifestations in 159 SLE-affected sibpairs as well as correlations between the age at diagnosis of SLE in 125 affected sibpairs and 37 affected parent–offspring pairs.

PATIENTS AND METHODS

SLE families. This study was approved by the Human Subjects Protection Committee of the University of California–Los Angeles (UCLA). Our cohort contained 189 families, including 109 Caucasian, 34 Asian, 23 Hispanic, and 19 African-American families, and 4 families of mixed ethnicity. Affected relative pairs of these 189 SLE multiplex families include SLE-affected sibpairs (present in 159 families) and affected parent–offspring pairs (43 families); in 13 relative pairs, parent–offspring families overlapped with sibpair families ([159 + 43] − 13 = 189 families). Among the 159 sibpair families, 34 were from the Lupus Multiplex Registry and Repository (LMRR cohorts A and B), and the remaining 125 families were recruited from UCLA and other collaborating sites. For this study, confirmation of classification of patients as having SLE (fulfillment of at least 4 of the 11 criteria recommended by the American College of Rheumatology [ACR]) (18,19) was performed as previously described (17). Neurologic disorder was defined as seizures and psychosis, according to the ACR criteria for classification of SLE. The clinical manifestations of the 2 eldest affected siblings and/or of the affected parent–offspring pair of each family were used in this study. Because of missing data (e.g., age at diagnosis or date of birth to deduce the time of SLE diagnosis) or missing serum samples of the studied subjects (for anti-SmD1$_{83-119}$ enzyme-linked immunosorbent assay [ELISA]), various numbers of affected relative pairs were used in the study.

Statistical analysis. We assessed familiality of clinical and laboratory features of SLE, using the presence at any time during the disease course of ACR criteria for SLE (18,19), Sapporo's criteria for antiphospholipid syndrome (APS) (20), and autoantibodies to Ro/SSA, La/SSB, cardiolipin, and double-stranded DNA (dsDNA), all documented by a rheumatologist. The frequency of SLE manifestations was estimated by regarding each sib independently. Sibling concordance rates were estimated according to the methods described for twins (21); that is, the number of concordant affected pairs was divided by the number of pairs having at least one affected sib. We also estimated familiality using an alternative approach, similar to that used to assess familiality in the general population. According to this approach, S1 is the estimated frequency of the clinical feature among the older sibs of the SLE-affected pairs, and S2 is the frequency among the younger SLE-affected sibs of the older SLE positive sibs. The sibling risk ratio, which is similar to that described by Risch (22), is estimated as S2/S1. This method quantifies how many times the rate of occurrence of the clinical feature is increased in the younger affected sibs whose elder affected sibs already manifest it and thus provides additional insight into familiality. The statistical significance of each estimate of the risk to the younger affected sib was evaluated by Fisher's exact

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Table 1. Familiality of clinical features in systemic lupus erythematosus (SLE)–affected sibpairs*

Clinical feature	Frequency	Sib concordance	S1	S2	Risk ratio, S2/S1	*P*
Thrombocytopenia	0.17	0.20	0.17	0.33	1.9	0.008
Discoid rash	0.18	0.18	0.16	0.31	1.9	0.008
Neurologic disorder	0.1	0.15	0.09	0.27	3.0	0.012
Hemolytic anemia	0.12	0.12	0.08	0.31	3.9	0.033
Anti-Ro/SSA	0.29	0.33	0.31	0.47	1.5	NS
Renal disease	0.36	0.35	0.37	0.51	1.4	NS
Anticardiolipin	0.29	0.26	0.29	0.41	1.4	NS
Anti-SmD1$_{83-119}$	0.36	0.38	0.41	0.59	1.4	NS
Anti-dsDNA	0.54	0.52	0.56	0.66	1.2	NS
Anti-La/SSB	0.12	0.12	0.14	0.17	1.2	NS
Photosensitivity	0.59	0.54	0.55	0.68	1.2	NS
Leukopenia	0.41	0.32	0.40	0.49	1.2	NS
Malar rash	0.56	0.48	0.57	0.62	1.1	NS
Serositis	0.43	0.41	0.50	0.51	1.0	NS
Secondary APS	0.08	0.04	0.08	0.08	1.0	NS

* The frequency of SLE manifestations was estimated treating each sib as independent. Sib concordance is the ratio of the number of affected sibpairs sharing the condition and the number of affected sibpairs in which at least 1 sib has the condition. S1 is the frequency of the clinical feature in older affected sibs in 159 SLE-affected sibpairs. S2 is the frequency of the clinical feature among younger SLE-affected sibs of older SLE-affected sibs. Proportions were compared using Fisher's exact test. NS = not significant; anti-dsDNA = anti–double-stranded DNA; APS = antiphospholipid syndrome.

test (Table 1). Co-occurrence of hemolytic anemia, thrombocytopenia, neurologic disorder, and discoid rash in 709 SLE patients was assessed by an analysis of proportions, using Fisher's exact test (Table 2). Pearson's product-moment correlations were used to assess the relationships of the age at SLE diagnosis in SLE-affected sibpairs and parent–offspring pairs. We are conducting multiple hypothesis-generating tests, and unadjusted *P* values are reported. However, we draw inferences concerning only those results that are significant after correcting for multiple testing.

ELISA for detection of anti-SmD1$_{83-119}$ antibodies. Anti-SmD1$_{83-119}$ peptide (VEPKVKSKKREAVAGRGRGRGRGRGRGRGRGRGGPRR) antibodies were detected as previously described, with minor modifications (23). Briefly, Costar polystyrene well plates (Corning, Corning, NY) were coated with 50 μl of 5 μg/ml SmD1$_{83-119}$ peptide dissolved in 0.1*M* carbonate buffer, pH 9.7, and incubated overnight at room temperature. After 3 washes in phosphate buffered saline (PBS), 0.1% Tween 20 (PBST), nonspecific binding sites were blocked for 1 hour at room temperature by using 1% dry nonfat milk in PBST (sample buffer). Sera were diluted 1:100 in sample buffer and added to the wells for 2 hours at room temperature and assayed in duplicate. After repeated washings, alkaline phosphatase–conjugated goat anti-human IgG (Fc-specific; Caltag, South, San Francisco, CA) was added 1:500 in sample buffer for 2 hours at room temperature. The final reaction was visualized by 1 mg/ml paranitrophenyl phosphate (PNPP; Sigma, St. Louis, MO) dissolved in PNPP buffer, pH 9.8 (1% diethanolamine, 0.1 μg/ml $MgCl_2$; Sigma). Optical density values were measured at 410 nm by MRX microplate reader (Dynatech, Chantilly, VA).

The standard curve was established by using a highly reactive serum from one specific SLE patient. Reactivity of this serum at a dilution of 1:100 was defined as 1,000 arbitrary units. The upper limit of the normal range was defined as mean value +2 SD of the observed values among 55 normal human sera, which was 53 units/ml.

Table 2. Co-occurrence of familial clinical features in patients with systemic lupus erythematosus*

Co-occurring clinical feature	All patients (n = 709)	Patients with specific clinical feature: Discoid rash (n = 99)	Neurologic disorder (n = 69)	Hemolytic anemia (n = 85)	Thrombocytopenia (n = 147)
Discoid rash	14	–	21	12	16
Neurologic disorder	10	15	–	20†	14
Hemolytic anemia	12	10	25†	–	29‡
Thrombocytopenia	21	24	31	51‡	–

* Values are the %.
† $P < 0.007$ versus all patients.
‡ $P < 0.00001$ versus all patients.

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RESULTS

The mean ± SD duration of disease was similar in SLE-affected sibpairs (11.1 ± 9.4 years in older SLE-affected sibs and 10.1 ± 10.3 years in younger SLE-affected sibs). Clinical features of SLE that were assessed for familiality included malar rash, discoid rash, photosensitivity, serositis, hemolytic anemia, thrombocytopenia, leukopenia, renal disease, neurologic disorder (defined by seizures and/or psychosis), APS as defined by Sapporo's criteria (20), anti-dsDNA, anticardiolipin, anti-Ro/SSA, anti-La/SSB, and anti-SmD1$_{83–119}$ (23). Anti-Sm is an autoantibody exhibiting high specificity but low sensitivity for SLE. Recently, the C-terminal peptide (amino acid 83–119) of the SmD1 protein was identified as a major target for the autoantibody response in patients with SLE, with a sensitivity of 70% and an SLE specificity of 94% (23).

Thus, IgG anti-SmD1$_{83–119}$ ELISA was performed using serum samples from 159 SLE-affected sibpairs. The 2 most prevalent signs of SLE, antinuclear antibodies and arthritis, were not included because of insufficient variation among SLE patients. Lymphopenia was not included because data were frequently either missing or confounded by medication usage. Familiality of the expression of a clinical feature was estimated by sibling concordance (21), which is the ratio of the number of affected sibpairs sharing the clinical feature compared with the number of affected sibpairs in which at least 1 sib has the feature. As shown in Table 1, sibling concordance for each of the 15 features was correlated with the frequency of each manifestation in 159 SLE-affected sibpairs. Clinical features that occur frequently in SLE patients appeared to have higher concordance rates than those that occur less frequently.

An alternative method to assess familiality, the sibling risk ratio, compares the frequency of the clinical feature among older affected sibs and the frequency among the younger SLE-affected sibs of the older SLE-affected sibs displaying it. Using Fisher's exact test, no evidence of an increased sibling risk ratio was observed for the presence of autoantibodies to dsDNA, Ro/SSA, La/SSB, or SmD1$_{83–119}$ or for renal disease, photosensitivity, leukopenia, malar rash, serositis, or APS. In contrast, increased risk ratios (1.9–3.9) were observed for thrombocytopenia, discoid rash, neurologic disorder, and hemolytic anemia among 159 SLE-affected sibpairs, as shown in Table 1.

To address the question of whether any pair of the familial conditions (including thrombocytopenia, discoid rash, neurologic disorder, and hemolytic anemia) tends to co-occur in SLE patients, we assessed the frequency of each condition in our cohort of 709 SLE patients from both SLE multiplex and SLE simplex families. The frequencies of thrombocytopenia, discoid rash, neurologic disorder, and hemolytic anemia were 21%, 14%, 10%, and 12%, respectively. Among the SLE patients who exhibited discoid rash (n = 99), the frequencies of co-occurring neurologic disorder, hemolytic anemia, or thrombocytopenia were 15%, 10%, and 24%, respectively. These frequencies among patients with SLE and discoid rash were not significantly different from those among SLE patients expressing each single manifestation (15% versus 10% for neurologic disorder, 10% versus 12% for hemolytic anemia, and 24% versus 21% for thrombocytopenia) (Table 2). After stratifying SLE patients according to each of the 4 clinical features, the results indicated that hemolytic anemia and thrombocytopenia co-occurred more frequently than would be expected by chance ($P < 0.00001$) (Table 2). Similarly, hemolytic anemia and neurologic disorder co-occurred more frequently than expected ($P < 0.007$). Other combinations of these 4 clinical features showed no significant overlap in SLE patients.

We also evaluated whether the co-occurrence of hemolytic anemia and thrombocytopenia as well as hemolytic anemia and neurologic disorder was familial in our sample of 159 SLE-affected sibpairs. Although the sample size was small, we estimated the sibling risk ratio of co-occurring hemolytic anemia and neurologic disorder as 12.9 (S1 = 0.031, S2 = 0.4, S2/S1 = 12.9; $P < 0.02$). Thus, if the older affected sib expresses this combined phenotype, the younger affected sib has an ~13-fold increased risk to develop both hemolytic anemia and neurologic disorder. However, similar analysis of the combined phenotype of hemolytic anemia plus thrombocytopenia failed to show an increased sibling risk (S1 = 0.02, S2 = 0). This negative finding may be attributed to the low frequency of co-occurrence and to our limited sample size.

Quantitative levels of serum autoantibodies to SmD1$_{83–119}$ from affected sibpairs were assessed for familiality by estimating sibling correlations. A modest sibling correlation (r = 0.211, $P = 0.022$) was observed in serum levels of IgG anti-SmD1$_{83–119}$ in 117 SLE-affected sibpairs. Considering that serum levels of anti-SmD1$_{83–119}$ fluctuate with disease activity (23), the observed correlation between sibpairs using blood samples drawn at one time point is possibly conservative. Estimating sibling correlations of serum levels of autoantibodies to dsDNA, cardiolipin, Ro/SSA, and La/SSB was not feasible in this sample, because quantitative data

extracted from chart reviews were incomparable due to use of nonstandardized assays at various clinics and hospitals.

Familiality of age at SLE diagnosis among 125 pairs (those for whom the age at SLE diagnosis was documented) was significant (r = 0.67, $P < 0.0001$) (Figure 1A). Stratifying by sex, the earliest ages at diagnosis (6 and 7 years old) were in the only pair of affected brothers. Significant sibling correlations of the age at SLE diagnosis were observed in the 24 brother–sister pairs (r = 0.79, $P < 0.0001$) and the 100 sister–sister pairs (r = 0.61, $P < 0.0001$). Figure 2 shows the distribution of the age at SLE diagnosis in the older and younger affected sibpairs separately. The mean ± SD age in the older sibpairs was 29.2 ± 11.9 years, and in the younger sibpairs it was 28.6 ± 11.4 years. A paired *t*-test showed no significant difference (mean difference = 0.58 years) in the age at SLE diagnosis between the older and younger affected sibs. However, at the mean age at which SLE was diagnosed, most sibs were likely to live apart. A significant familiality of sibling age at time of SLE diagnosis suggests that shared genes and/or shared early environmental exposures impact disease susceptibility.

Several studies have noted younger ages at disease onset in African-American SLE patients compared with Caucasian patients (24–26). Therefore, we stratified sibpairs by ethnicity to determine the mean age at diagnosis in Caucasian, Asian, Hispanic, and African-American patients as well as in patients of other ethnic origin (Table 3). The mean age at which SLE was diagnosed was younger among the combined non-Caucasian sibpairs than among Caucasian sibpairs ($P = 0.014$). Both non-Caucasian and Caucasian affected sibpairs showed significant correlations between the age at diagnosis of older affected sibs and younger affected sibs ($P < 0.0001$ for both, r = 0.63 and 0.67, respectively).

We also assessed whether the ages at SLE diagnosis in affected parent–offspring pairs were correlated. As shown in Figure 1C, ages at SLE diagnosis in the 37 parent–offspring pairs were correlated (r = 0.47, $P = 0.003$), and the correlation was mainly attributable to the 29 mother–daughter pairs (r = 0.52, $P = 0.004$). The mean ± SD age at SLE diagnosis of parents (41.6 ± 15.8 years) was significantly older than that of their offspring (21.5 ± 10.1 years) (mean difference 20.1 years; $P < 0.0001$ by paired *t*-test) (Figure 2). The significant familiality of the age at diagnosis in SLE-affected parent–offspring pairs might be attributed to shared genes or shared environment. The mean ± SD difference in the

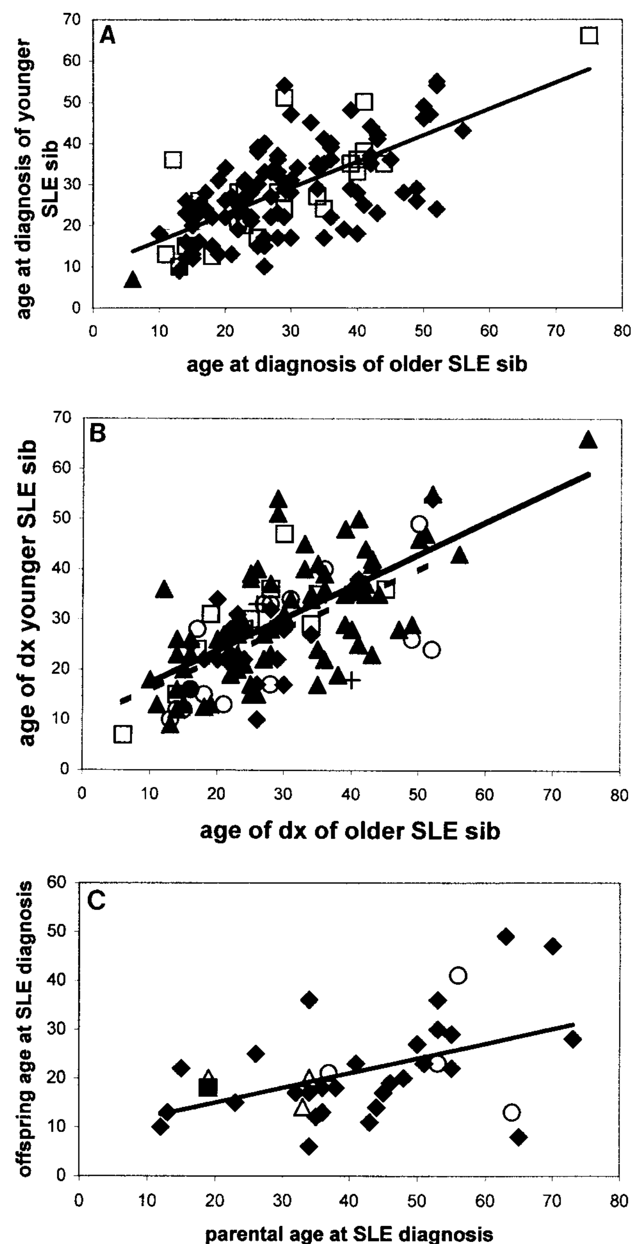

Figure 1. Correlation of ages at diagnosis in systemic lupus erythematosus (SLE)–affected relative pairs. **A,** Stratification by sex. A significant correlation ($P < 0.0001$, r = 0.67) was seen in 125 affected sibpairs (female–female [◆], male–female [□], male–male [▲]. ▬ = combined regression. **B,** Stratification by ethnicity. Both Caucasian (▲) and non-Caucasian (Asian [◆], African American [□], Hispanic [○], other ethnic group [+]) SLE-affected sibpairs showed significant correlations between age at diagnosis of older affected sibs and younger affected sibs ($P < 0.0001$ for both, r = 0.63 and r = 0.67, respectively). ▬ = regression for Caucasian sibpairs; ▬ ▬ = regression for non-Caucasian. **C,** Stratification by family relationship. A correlation ($P = 0.003$, r = 0.47) was seen in 37 parent–offspring pairs (29 mother–daughter pairs [◆], 3 mother–son pairs [△], 4 father–daughter pairs [○], 1 father–son pair [■]). ▬ = combined regression.

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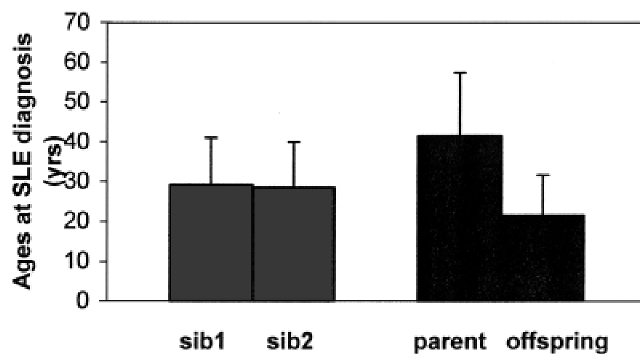

Figure 2. Average age at diagnosis of systemic lupus erythematosus (SLE) in 125 affected sibpairs and 37 affected parent–offspring pairs. The age at diagnosis was significantly greater in affected parents than in their affected offspring ($P < 0.0001$, by paired t-test). Bars are the mean and SD.

date at which SLE was diagnosed was 11.0 ± 10.5 years in 36 affected parent–offspring pairs and 7.5 ± 7.3 years in 80 sibpairs for whom we could identify the year of disease diagnosis. The lapse in the time of disease diagnosis within these affected relative pairs made a hypothesis of immediate shared environmental factors triggering the overt expression of SLE less compelling. Taken together, these data suggest that shared genes may have a stronger influence than shared environmental triggers on the development of SLE.

DISCUSSION

Evidence suggesting the familiality of thrombocytopenia, discoid rash, neurologic disorder, hemolytic anemia, and co-occurring hemolytic anemia and neurologic disorder was observed in 159 SLE-affected sibpairs. Younger affected sibs expressed each of these clinical features 1.9–12.9 times more frequently than did their older affected sibs ($P = 0.008$–0.033). Some familial clinical features co-occurred more frequently than expected, including hemolytic anemia plus thrombocytopenia ($P < 0.00001$) and hemolytic anemia plus neurologic disorder ($P < 0.007$) (Table 2). The simultaneous or sequential concurrence of autoimmune hemolytic anemia and immune thrombocytopenia is recognized as Evans's syndrome. The frequency of Evans's syndrome in 2 studies of SLE patients (n = 126 and n = 186, respectively) was 2–3% (27,28). The 6% rate of co-occurrence of hemolytic anemia and thrombocytopenia that we observed among ~700 SLE patients is likely to include those with Evans's syndrome. This rate of co-occurrence of hemolytic anemia and thrombocytopenia is similar to the 5% rate reported in a Mexican study of 500 consecutive SLE patients (29). In that study, a history of thrombocytopenia, hemolytic anemia, or both was associated with the presence of antiphospholipid antibodies (29).

Co-occurring hemolytic anemia and neurologic disorders (defined as seizures or psychosis) in SLE patients has not been well described. The lack of sibling concordance for many clinical/laboratory features in our study is in general agreement with a lack of concordance for clinical symptoms in a smaller study of 16 affected sibpairs (30). Concordance in autoantibody and disease profiles has been noted in a smaller study of SLE-affected sibpairs who share both HLA haplotypes (31). The heritability of SLE (the fraction of disease that can be attributed to genes) has been estimated to be 66% (32), consistent with the role of genes in familial features of SLE.

Ethnic differences in genetics and clinical manifestations among SLE patients have been well established (3,33). We combined all of the non-Caucasian groups, because each separate group was too small to allow assessment of familiality of clinical features. Comparisons between 88 Caucasian and 71 non-Caucasian SLE-affected sibpairs resulted in a more than 2-fold difference in sibling risk ratios for neurologic disorders, hemolytic anemia, and anti-La/SSB (data not shown). This difference might be attributable to ethnic differences and/or stochastic variation in smaller samples. We also observed ethnic differences according to the age at SLE diagnosis. Non-Caucasian affected sibpairs as a group had significantly younger ages at diagnosis than did Caucasian sibpairs ($P = 0.014$) (Table 3). Despite the limited size of our current sample of each non-Caucasian ethnic group (Asian, Hispanic, or African-American sibpairs), we are able to observe possible ethnic differences in ages at SLE diagnosis.

Table 3. Ethnicity and age at diagnosis of systemic lupus erythematosus among sibpairs*

Ethnicity	No. of affected sibpairs	Age at diagnosis, years, mean ± SD
Caucasian	73	30.6 ± 12.2
Non-Caucasian	52	26.5 ± 10.3†
Asian	23	26.6 ± 8.75
Hispanic	16	25.8 ± 12.2
African American	11	27.0 ± 10.8
Other	2	29.2 ± 9.43

* The mean age at diagnosis of the oldest affected sibpair of each family was used for these calculations.
† $P = 0.014$ versus Caucasian.

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Correlations in the age at SLE diagnosis in SLE-affected sibpairs and parent–offspring pairs were significant (Figures 1A and B). A possible explanation is that after a diagnosis of SLE is established in one family member, the other family member is more likely to seek medical consultation, thus facilitating diagnosis. The nearly identical ages at diagnosis in the older and younger affected sibs (Figure 2) may be attributable to the possibility that siblings who share a common genetic predisposition to SLE tend to reach the threshold for manifestation of SLE within similar time periods, during which each has stochastically accumulated predisposing environmental events. As shown in Figure 2, affected parents developed SLE significantly later in life compared with their affected offspring. The average 20-year difference is consistent with the observation of Arnett and Shulman that the average age at SLE diagnosis is 39 years for parents (10 parent–offspring pairs) and 19 years for their offspring (30).

Earlier age at disease diagnosis in offspring than in their affected parents is referred to as "anticipation," which has been reported in multiple studies of rheumatoid arthritis (RA) (34,35). Genetic anticipation has been well studied in several neurodegenerative diseases in which the expansion of unstable trinucleotide repeats (coding for polyglutamine) within susceptibility genes in subsequent generations is implicated (36). It is possible that genetic anticipation may also play a role in the susceptibility to rheumatic autoimmune diseases such as RA and SLE. Other potential reasons for an earlier diagnosis in offspring than in their parents might include improvements in recognition and diagnosis of SLE over the last few decades, and selection bias of parents who were well, had children, and then developed SLE later in life. Because most studied parents were mothers, and because most (29 of 33 [83%]) gave birth to their offspring before the mother developed SLE, fetal cell microchimerism in mothers might contribute to the pathogenesis of systemic autoimmunity (37,38). Maternal cell microchimerism might also predispose to the development of SLE in offspring.

Age at disease diagnosis may be used to stratify families into more homogenous subsets that can facilitate the identification of susceptibility genes—a common approach for the analysis of genetically complex diseases. Familiality has been addressed in a relatively small sample of multiplex families. Support for these findings in additional multiplex family panels is essential to successful stratification.

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