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Systemic lupus erythematosus: a genetic epidemiology study of 695 patients from China

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Abstract Our purpose was to explore potential genetic models for systemic lupus erythematosus (SLE) and analyze genetic epidemiologic characteristics of SLE in a Chinese population. Data for 695 patients with SLE were obtained by using a uniform questionnaire. Patients, clinical characteristics and their family history were analyzed using software. A complex segregation analysis was conducted to propose potential genetic models for SLE. The mean ± SD age of onset were 30.2 ± 10.5 years and mean time to progression to SLE was 32.5 ± 44.4 months. The most frequent initial manifestations were malar rash (61.3%). During the evolution of the disease, the main clinical features were arthritis in 73.6% of our patients, followed by malar rash (68.1%), and renal involvement (56.7%). As the first symptom, the late-onset group (onset of disease beyond the age of 50 years) less often showed malar rash (45% vs. 63.4% in the early-onset group; $p = 0.001$). There were no significant differences in the other cumulative clinical symptoms between late-onset and early-onset group, except for a lower prevalence of malar rash, photosensitivity and alopecia and a higher prevalence of mucosal ulcers in the late-onset group. A positive family history of SLE was obtained in 50 patients (7.2%). There were no statistical differences in clinical characteristics between familial SLE and sporadic SLE patients. The heritability of SLE was 43.6%, the genetic model of SLE could be polygenetic model and major gene mode is the best fitted one. SLE could be a multifactorial disease with polygenetic model.

Keywords China · Genetic epidemiology · Systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by a striking preponderance in females, multisystem involvement, and autoantibodies directed primarily against nuclear antigens. The prevalence of SLE is about 0.07% in China and more prevalent than Caucasian populations. The precise aetiology of SLE remains unclear. Through a variety of study designs, SLE shows a strong familial aggregation, with a much higher frequency among first-degree relatives of patients [1, 2, 7, 17, 29]. Studies of affected probands estimate the sibling recurrence risk (λs) to be approximately 20 [34]. In twins who usually shared the

same environment, the disease concordance rate is 2–5% for dizygotic twins and 24–58% for monozygotic twins [28, 31]. This suggests that multiple genes shared between each pair of twins greatly influence the susceptibility to SLE. Screenings of the genome were performed and several susceptibility loci were identified for the disease itself. Regions of linkage were detected on almost every chromosome, suggesting the contribution of several genes. For instance, the FcG receptor genes are located in one of the linked regions on human chromosome 1 and are believed to play an important role in SLE. The FcGRIIB gene was found to be associated with lupus in Asians, but not in Caucasians [25]. Studies of candidate genes, including MHC, Fcγ receptors, IL-6, complement genes, tumour necrosis factor-α and so on, suggest that genetic factors play an important role in the predisposition of the disease.

Relatively simple rules are used to describe modes of inheritance, including autosomal dominant, recessive or sex-linked inheritance. These rules make it possible to explain to patients in a simple and understandable way the risk of their children developing a particular disease. SLE is more prevalent among relatives of the affected patients but it does not appear to follow simple Mendelian inheritance patterns. The purpose of the present study is to validate or disprove this theory.

In this study, we try to explore the possible genetic model for SLE from China.

Materials and methods

Subjects and study design

We retrospectively analyzed the records of 695 China patients with SLE who were followed-up in the rheumatology and dermatology department of the First Affiliated Hospital of Anhui Medical University in China either as inpatients or outpatients between January 1999 and June 2005. All patients met at least four of the 1997 American college of rheumatology (ACR) revised criteria for SLE [15]. Patients with drug-induced SLE or pure cutaneous lupus were excluded.

After giving informed content, a structured questionnaire was designed and completed for each patient to gather information by the doctor with the patient. Age of onset, age at diagnosis, time to progression to SLE, the first symptom and cumulative clinical manifestations during the disease evolution, family history and numbers of affected first-, second- and third-degree relatives were recorded. Every proband was questioned in detail, using an identical questionnaire. They were scrutinized for missing items, inconsistent items, or both. Telephone interviews or follow-up letters were used to fill in missing items and resolve inconsistencies. Questionnaires with missing/inconsistent items that could not be corrected were excluded. The clinical data obtained by history and clinical examination included skin and mucosal manifestations, photosensitivity (by history), arthritis, serositis, renal and central nervous system (CNS) involvement and fever, Raynaud's phenomenon (RP), alopecia and antinuclear antibodies (ANA), anti-double-stranded-DNA (dsDNA), anti-Sm antibodies. The institutional review board of Anhui Medical University, Hefei, China, approved this study.

In total, 956 normal controls without any skin disease or other autoimmune diseases such as diabetes, rheumatoid arthritis, psoriasis, were recruited simultaneously with the SLE patients. Demographically similar controls matched for sex and age (within 5 years) were randomly selected from relatives of patients in the First Affiliated Hospital of Anhui Medical University.

Definitions

Age at onset of the disease was defined as the first time the patient showed clinical signs of SLE. Age at diagnosis was defined by the age of the patients when they fulfilled at least 4 of the 11 ACR criteria for SLE. Time to progression to SLE was defined as the time between SLE onset and diagnosis. SLE family history was defined as where at least two members satisfied at least four of the criteria for the classification of SLE. Patients with disease onset beyond the age of 50 years were identified—the late onset SLE group.

Malar rash: fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds.

Photosensitive: nonscarring dermatitis appearing as either papulosquamous or annular lesions.

Serositis: including pleuritis, pericarditis or both.

Renal involvement: (1) persistent proteinuria >0.5 g/d; (2) microhematuria and/or cellular casts; (3) otherwise unexplained elevation of serum creatinine >75 μmol/L.

CNS involvement: seizures, psychosis, chorea, and transverse myelitis in the absence of drugs or known metabolic disturbances.

Fever: temperature >38°C or 100°F in the absence of infection.

Statistical analysis

Data from 695 probands and their families were entered into a database created using software (EPI INFO, Version 6.0, Centers for Disease Control and Prevention, Atlanta, GA) and then converted to the proper format for analysis using software (SPSS, Version 10.0, SPSS Inc., Chicago, IL). Conventional Chi-square and Fisher exact tests were used for analyzing qualitative differences, and the Student t test was used for comparison of means in large, independent samples of similar variance; a value of $P < 0.05$ indicated statistical significance.

According to Falconer's method [9], we obtained values for heritability (h2) in relatives of probands. A complex segregation analysis was performed to evaluate possible models of inheritance of SLE using computer programs (REGTL) (segregation analysis of a truncated trait with logistic probability density function model 1 and 2) and statistical analysis for genetic epidemiology software (SAGE, Version 3.1, Case Western Reserve University). REGTL, based on the regression model of Bonney [5], is designed to conduct segregation analysis under a class A regressive model (with the possibility of including a common sibship component that depends on the proportion of sibs affected) either of a truncated trait (such as age of onset to a diseases) that follows a logistic distribution, possibly after transformation (model 1), or of susceptibility to the disease (model 2). The disease is thus a discrete trait with variable age of onset. Under model 1, genotype is presumed to influence age of onset through location susceptibility (defined as the probability of being affected by age 'infinity'). Susceptibility may be different for up to two affection classes. Under model 2, genotype is presumed to influence susceptibility to the affected state, but not to affect age of onset (referring to the user manual of the SAGE package, release 3.1) [30]. It is appropriate to use model 1 for analysis of SLE. Using a logistic model, the logarithm of the odds ratio (θ) for an affected member of a certain family was assigned based on type (y), sex (s), trait of mother (y_m), trait of father (y_f), and covariates (x_1~x_n). Thus, the logarithm of the odds ratio (θ) for a particular member i of a family is

$$\theta = \mathrm{Log}[P(y_i = 1/P(y_i = 0))] = \beta us\ (y) + \gamma_m(y_m) + \gamma_f(y_f) + \varepsilon_1 x_1 + \cdots + \varepsilon_n x_n$$

for βus, where u = alleles aa, ab, or bb. The a allele was presumed as the susceptibility gene for SLE.

We tested a series of competing models including Mendelian models (dominant, recessive and additive), an environmental model, a no-major-gene model. The natural logarithm of likelihood (LnL) of a general unrestricted model was calculated and compared with the hypothesis-bearing models specified above with one or more pertinent parameters restricted. To test a hypothesis about a specific mode of inheritance, the likelihood ratio test (LRT) statistic $\mathrm{LRT} = -2(\mathrm{Ln}\ L_{\mathrm{general}} - \mathrm{Ln}\ L_{\mathrm{specific}})$ was used, where 'specific' indicates the model for a specified hypothesis. The sampling distribution of this statistic is well approximated by a χ^2 with $n - k$ degrees of freedom where n and k equal the number of independent parameters estimated in the general model and the specific model, respectively. When more than one model was not rejected against the general model, the one with the lowest Akaike information criteria (AIC) [3] was considered the best model, where $\mathrm{AIC} = -2\mathrm{Ln}\ L + 2k$.

Results

General characteristics

The entire cohort consisted of 630 female (90.6%) and 65 male (9.4%) patients. Thus, the female to male ratio was 9.6:1. Mean age at disease onset (mean ± SD) was 30.2 ± 10.5 years (range 8–72) and mean time to progression to SLE (mean ± SD) was 32.5 ± 44.4 months (range 1–242). When patients were distributed according to the age at onset, a peak age of onset was seen between 21 and 40 years for both males and females. The most frequent initial manifestations were malar rash (61.3%), arthritis (55.1%) and fever (29.8%). Other typical SLE manifestations were expectable. During the evolution of disease, arthritis appeared in the vast majority of patients (73.6%), followed by malar rash (68.1%), renal involvement (56.7%), fever (47.6%), alopecia (28.7%), photosensitivity (27.6%), serositis (20.8%), mucosal ulcers (16.3%), RP (15.7%), discoid lesions (8.7%), and CNS involvement (7.3%). A positive result of ANA was found in 97.8%, anti-dsDNA levels were found in 52.2%, anti-Sm antibodies were found in 48.3%.

The number in the early-onset group was 615 (58 males and 557 females) with an average onset age of 27.78 ± 8.16 years (mean ± SD), comprising 88.5% of the total number of patients. The number in the late-onset group was 80 (7 males and 73 females) with an average onset age of 55.49 ± 5.44 years (mean ± SD), constituting 11.5% of the total patients. The mean time to progression to SLE was significantly higher in the late-onset group than in the early-onset group (47.61 ± 55.65 vs. 30.57 ± 42.4 months, $p < 0.005$). The

female to male ratio was nearly identical in both groups. We compared the clinical features and laboratory data of both groups. As the first symptom, the late-onset group less often showed malar rash (45% vs. 63.4% in the early-onset group, $p = 0.001$). During evolution of the disease, analysis of cumulative clinical symptoms showed that the significant difference between these two groups was a decreased prevalence of malar rash (56.3% vs. 69.6%; $p = 0.016$), photosensitivity (16.3% vs. 29.3%; $p = 0.014$), and alopecia (16.3% vs. 30.1%; $p = 0.01$) in the late-onset group. However, this group exhibited a significantly increased prevalence of mucosal ulcers (25.0% vs.15.0%; $p = 0.022$). No significant differences were found among the other clinical and laboratory features between the groups either the first symptom or cumulative clinical symptoms.

Family characteristics

A positive family history of SLE was obtained in 50 patients (7.2%). When we compared SLE patients who did and those who did not have relatives with SLE, we found no statistical differences in clinical characteristics. Of the 50 patients who had relatives with SLE, 11 had more than one and the rest had only one. Of 3,926 first-degree relatives of probands, 41 had SLE, giving a prevalence rate of 1.04%. Corresponding figures for second- and third-degree relatives are 12/9,596 (0.13%) and 9/14,722 (0.06%), respectively. The 956 controls had 5,080 first-degree relatives, of whom six had SLE, giving a prevalence rate of 0.12%. The prevalence rates in the second- and third-degree relatives of controls were 6/13,031 (0.04%) and 5/21,130 (0.02%), respectively.

Analysis of heritability

According to Falconer's method [9], the heritability (h^2) of SLE in first-, second- and third-degree relatives of probands was $43.60 \pm 3.53\%$, $22.78 \pm 9.5\%$ and $15.78 \pm 20.05\%$, respectively (Table 1). The weighted average of heritability in all relatives was $40.41 \pm 3.26\%$. Thus the prevalence rate in first-degree relatives was higher than that in second-degree relatives and third-degree relatives. This indicates a clear hereditary tendency in SLE.

Complex segregation analysis

To explore the possible genetic model of SLE, we performed complex segregation analysis using the REGTL program. Based on the REGTL results (Table 2), by both LRT and AIC, SLE follows polygenetic model and major gene mode is the best fitted one.

Discussion

Systemic lupus erythematosus afflicts all populations around the world with diverse incidence among different geographic regions and ethnic groups. In the present study, we have analyzed the most relevant clinical and immunologic features in a very large cohort of SLE patients and explored the genetic mode. In order to minimize possible interobserver or selection bias, all the participating physicians discussed the variables of this questionnaire on several occasions.

Systemic lupus erythematosus is much more common in women than in men although the ratio varies in different studies from 4.3 to 13.6 [26]. In our study, the female/male was 9.6:1. The peak age of onset (21–40 years) was similar to those reported earlier [24, 32]. In contrast, a peak incidence found by Johnson et al. [18] was between the ages of 18 and 19 years. The median time to progression to SLE was 32.5 months in our study, a shorter time than that reported by Hopkinson et al. [16], who found a mean interval between first definite SLE symptom and diagnosis of 61 months, varying between 0 and 518 months, however, longer than that reported by Vilar [32], who found a mean interval of 10 months. Overall, the prevalence of the major clinical features during the evolution of the disease in the present cohort is comparable to that reported in previous studies [10, 13, 32, 33], Arthritis and malar rash were the most common symptoms in our patients, although other features not specified in the ACR criteria also were frequent, including fever, RP, and alopecia.

Various reports made the division between 'old' and 'young' at the age of 50 years [4, 8, 11, 14, 22, 27], in our study, we defined disease onset beyond 50 years as late-onset SLE. We found that patients with late-onset had longer time to progression to SLE than patients with early-onset ($p < 0.01$). Similar results have been suggested previously [11, 14], this illustrates that late-onset SLE patients may present atypically at disease onset, leading to a delay in diagnosis. In late-onset lupus patients, we found a significantly lower frequency of malar rash, photosensitivity and alopecia, but a higher frequency of mucosal ulcers when compared with early-onset lupus patients. These findings were also noted in other report [21]. There was no other major clinical difference between both groups.

Table 1 Heritability ($h^2 \pm s$) in relatives of proband

	No. of subjects	No. of patients	Prevalence rate (%)	X	α	b	h2 ± s (%)
Proband							
Father	695	4	0.58				
Mother	695	15	2.16				
Sibs	1,801	19	1.05				
Children	735	3	0.41				
First-degree relatives	3,926	41	1.04	2.312	2.652	0.218	43.60 ± 3.53
Second-degree relatives	9,596	12	0.13	3.012	3.294	0.114	22.78 ± 9.5
Third-degree relatives	14,722	9	0.06	3.239	3.507	0.079	15.88 ± 20.05
Control							
Father	956	1	0.1				
Mother	956	2	0.2				
Sibs	2,245	2	0.08				
Children	890	1	0.11				
First-degree relatives	5,080	6	0.12				
Second-degree relatives	13,031	6	0.04				
Third-degree relatives	21,130	5	0.02				

Table 2 Complex segregation analysis of SLE using the SAGE-REGTL program

Item	Non-Mendel genetic model			Mendel genetic model			
	General model	Environment	Non-transmitted	Dominant	Additive	Recessive	Major gene
Q_A	0.5	1	–	0.823043	0.009455	0.262573	0.059253
Tau AA	1	0.416077	–	1[a]	1[a]	1[a]	1[a]
Tau AB	0.450616	0.416077	–	0.5[a]	0.5[a]	0.5[a]	0.5[a]
Tau BB	1	0.416077	–	0[a]	0[a]	0[a]	0[a]
β AA	–3.71679	–5.38089	–5.26389	–5.26411	–3.72637	–2.78221	–0.61182
β AB	–7.59282	–4.92826	–5.26389	–5.26411	–4.57863	–5.36587	–4.76529
β BB	–8.17208	–3.93306	–5.26389	–5.6354	–5.4309	–5.36587	–9.03319
α	0.189656	0.057104	0.133977	0.13397	0.137459	0.130513	0.216776
γ female	0.035498	0.203504	0.037895	0.037895	0.03779	0.038432	0.036447
γ male	0.00873	0.051094	0.009221	0.009221	0.008728	0.009388	0.009026
No. of parameter	10	7	3	4	5	5	5
df		3	7	6	5	5	5
–2 LN	818.8359	856.9784	826.7396	826.7321	826.6826	824.9819	815.9485
AIC		862.9784	840.7396	838.7321	836.6826	834.9819	825.9485
P value		<0.05	<0.05	>0.05	>0.05	>0.05	>0.05

[a] These values are fixed during model fitting

Q_A, frequency of allele A; Tau AA, the probability that a parent with genotype AA transmits allele A to an offspring; similarly for Tau AB and Tau BB; β AA, the baseline parameter for a subpopulation with the AA genotype; similarly for β AB and β BB; α, age coefficient; γ female susceptibility for females; γ male susceptibility for males;

LnL, natural logarithm of likelihood; *AIC* Akaike information criteria, *df* degrees of freedom

In SLE, support for the existence of genetic predisposition is derived from several lines of evidence. The first is based on the prevalence of SLE in families with multiple cases. Secondly, there is also greater concordance of SLE in monozygotic twins than in dizgotic twins. Further evidence is derived from the association between SLE and the HLA system. Several studies indicate a significant increase in the prevalence of SLE among relatives of patients with the disease compared with controls [6, 12, 20]. Approximately 10% of lupus patients have a first or second degree relative with SLE or closely related disease [6]. In this study, a positive family history of SLE was elucidated in 7.2% of our patients. This frequency was also noted in some other reports [12, 20]. Buckman et al. [6] reported a positive family history in 12% of patients with a sample of 340. Large families with many cases of SLE appear to be rare. Brunjes et al. [7] described a family with four sisters. Sestak et al. [29] described a large pedigree with eight female SLE patients and aggregation of other autoimmune features in several blood relatives, especially in women. We found 11 families had 2 or 3 affected relatives and the rest had only 1. This reflects both the low prevalence of SLE in the general population and the presumably low penetrance of SLE susceptibility genes.

To minimize the potential effects of bias in the selection of controls, we randomly selected controls from the same area, resulting in a cohort that was very similar to the SLE cohort in age, sex, race, education and ethnic composition. We estimate the heritability for SLE to be 43.6% according to the method of Falconer [9]. Lawrence et al. [19] had reported a heritability of 66% for SLE. These indicate that the effect of genetic factors is strong in SLE. Nevertheless, as heritability is lower than 70%, environmental factors may still play an important role. Thus environmental factors such as exposure to sunlight and estrogens may serve as precipitating factors in the pathogenesis of SLE.

At present, most researchers agree that the pathogenesis of SLE is intimately related to heredity, but they disagree on the genetic model of SLE. In a study of 125 multiplex French Caucasian families with SLE, an autosomal dominant mode of inheritance was predicted in one extended pedigree with a clinically affected member and a recessive pattern in five other families. No obvious mode of inheritance could be suspected in most of the remaining pedigrees [20], which is in agreement with other previous work [2]. A study of pedigrees of 340 patients with SLE by Buckman [6] and his colleagues suggested that several possible explanations for the mode of inheritance including dominant, recessive and sex-linked dominant inheritance. When all the pedigrees were considered as a group, multifactorial inheritance was suggested. For the first time, we propose a genetic model for SLE based on a large sample of Chinese individuals. The results suggest that the genetic model of SLE does not fit a single-gene recessive or dominant mode of inheritance. The environment and no-major-gene (sporadic) models of inheritance are both rejected. SLE follows polygenetic model and major gene mode is the best-fitted one, but excludes the possibility of single-gene inheritance.

In conclusion, analysis of the 695 SLE patients we have recruited to date suggests SLE follows polygenetic model and the best-fitted genetic mode is major gene mode. The major genes involved in SLE include HLA DR2 and DR3 genes, complement genes (C2, C4, and C1q), Fcγ receptors genes and so on [23]. Epidemiological investigation has provided evidence for the familial transmission of SLE. It has yielded interesting insights to the pattern of inheritance of the disease. New techniques of genetic studies combined with epidemiological tools may aid the localization of the SLE genes.

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