ARTHRITIS & RHEUMATISM
Vol. 44, No. 6, June 2001, pp 1359–1362
© 2001, American College of Rheumatology
Published by Wiley-Liss, Inc.

Familial Occurrence Frequencies and Relative Risks for Systemic Sclerosis (Scleroderma) in Three United States Cohorts

Frank C. Arnett,[1] Mimi Cho,[1] Soumya Chatterjee,[2] Martha B. Aguilar,[1] John D. Reveille,[1] and Maureen D. Mayes[2]

Objective. **To determine the frequency with which scleroderma (systemic sclerosis; SSc) recurs in families and the familial relative risk (λ) in the US.**

Methods. **Family histories of SSc were prospectively surveyed in 3 large US cohorts of SSc patients, 2 in Texas and 1 in Michigan. Diagnoses of familial SSc were verified by rheumatologist evaluation and/or review of medical records. Familial relative risks for first-degree relatives (λ1) and siblings (λs) were calculated using actual reported counts of first-degree relatives in 2 cohorts and recent estimates of SSc prevalence in the US.**

Results. **Compared with the estimated prevalence of SSc in the US (2.6 cases/10,000 population [0.026%]), the disease occurred in 1 or more first-degree relatives in 1.5–1.7% of SSc families in the 3 cohorts (or 11 of 703 families [1.6%]), a significant increase. Familial relative risks in first-degree relatives in the 3 cohorts ranged from 10 to 16 (13 combined), and in siblings they ranged from 10 to 27 (15 combined).**

Conclusion. **SSc occurs significantly more frequently in families with scleroderma (1.6%) than in the general population (0.026%). A positive family history of SSc is the strongest risk factor yet identified for SSc; however, the absolute risk for each family member remains quite low (<1%).**

The familial occurrence of scleroderma (systemic sclerosis; SSc) has been reported infrequently and usually only in the form of case reports of 1 or several families (for review, see refs. 1 and 2). Other autoimmune diseases also have been reported to occur frequently in SSc families, as have positive antinuclear antibodies (ANA) but not SSc-specific autoantibodies (1–3). Only 1 systematic survey of familial relative risk has been reported. Englert et al (4) confirmed 10 instances of SSc occurrence (1.4%) in first-degree relatives of 710 SSc probands in the Sydney, Australia, population. No such reports of familial relative risks are available from centers in the US, where a recent prevalence estimate by Mayes et al (5) suggests an SSc prevalence higher than in several other countries surveyed (6). The familial relative risk of a disease (λ), particularly in intragenerational siblings (λs), has become a useful tool for geneticists in determining the sampling design for genetic linkage studies, especially when little evidence exists for a strong environmental contribution to disease risk (7). The purpose of this study was to determine the familial relative risk of SSc in several US cohorts of SSc patients in order to establish a foundation for studies of genetics versus environment in the etiopathogenesis of this disease.

PATIENTS AND METHODS

Three large cohorts of SSc patients who fulfilled the American College of Rheumatology (formerly, the American Rheumatism Association) criteria for SSc (8) were prospectively surveyed for similarly affected first-degree relatives

Supported by grant M01-RR-02558 from the University of Texas–Houston General Clinical Research Center. Dr. Arnett's work was supported by NIH grant P50-AR-44888 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases Specialized Center of Research (SCOR) in Scleroderma and by a grant from the RGK Foundation, Austin, Texas. Dr. Mayes' work was supported by NIH grant N01-AR-52217 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases Michigan Scleroderma Registry.

[1]Frank C. Arnett, MD, Mimi Cho, MD, PhD, Martha B. Aguilar, MD, John D. Reveille, MD: The University of Texas–Houston Health Science Center; [2]Soumya Chatterjee, MD, Maureen D. Mayes, MD: Wayne State University, Detroit, Michigan.

Address correspondence and reprint requests to Frank C. Arnett, MD, The University of Texas–Houston Medical School, 6431 Fannin, Houston, TX 77030.

Submitted for publication June 14, 2000; accepted in revised form February 6, 2001.

Table 1. Demographic features of 3 US cohorts of systemic sclerosis patients

Feature	Cohort 1 (n = 190)	Cohort 2 (n = 175)	Cohort 3 (n = 338)
Female/male, %	85/15	87/13	84/16
Race, %			
White	69	46*	75
African American	14	18	22
Hispanic	15†	33‡	2
Other	2	3	1
Mean age, years	ND§	48.9	47.6
No. of first-degree relatives¶	957	881	1,840
No. of siblings (mean/family)	577 (3.0)#	531 (3.0)	1,164 (3.4)

* $P \leq 0.001$ versus cohorts 1 and 3.
† $P \leq 0.001$ versus cohort 3.
‡ $P \leq 0.001$ versus cohorts 1 and 3.
§ ND = not determined.
¶ Includes parents and siblings.
# Assumed based on 3.0 siblings/family in Texas cohort 2.

(Table 1). Cohort 1 consisted of 190 consecutively evaluated patients with SSc (SSc cases) entered into immunogenetic studies of SSc by members of the Division of Rheumatology at the University of Texas–Houston (UTH) Health Science Center between 1986 and 1996. Familial SSc status had been ascertained and recorded at entry, as had sex and race but not age. Cohort 2 consisted of the first 175 patients with relatively early-onset SSc (duration of <5 years) entered from February 1997 to September 2000 into a prospective, longitudinal study of genetic, immunologic, and sociodemographic factors influencing disease outcome (GENISOS study) as part of the UTH Specialized Center of Research in Scleroderma (9). Those originally from cohort 1 who had been entered into GENISOS were counted only in cohort 2. Extensive family histories concerning SSc, Raynaud's phenomenon (RP), and other autoimmune diseases were obtained at the time of entry into this study, as was information on total numbers and relationships of all first-degree family members. Cohort 3 consisted of 338 patients with SSc entered into the Michigan SSc Registry from 1988 through 1998 who responded to a questionnaire detailing family histories of SSc, RP, and other autoimmune diseases, as well as numbers of relatives.

Numbers of siblings were obtained from direct counts provided by the cases. Children of the probands were not included because of the usual late age of onset for SSc. Therefore, first-degree relatives in this study are defined as parents and siblings. Because the numbers of total siblings were unknown in cohort 1, the rate of 3.0 siblings per family found in cohort 2 (both cohorts were from Texas) was extrapolated to cohort 1 (Table 1).

All familial SSc cases in cohorts 1 and 2, and 5 of 7 cases in cohort 3, were verified by examination by a rheumatologist or review of medical records. Two familial cases reported in cohort 3 could not be verified because of a lack of available medical records, and they were excluded from the family analyses. For statistical comparisons and calculations of familial relative risk in first-degree relatives and siblings, the prevalence of SSc in the US population was estimated to be 2.6 cases/10,000 based on averaging the mean of the prevalence rates in the 2 most recent surveys, 1 from Detroit, Michigan, and the other from South Carolina (5,10). Familial relative risks for SSc in the total number of first-degree relatives (parents and siblings but not children) ($\lambda 1$) and siblings (λs) were calculated by dividing them by the estimated population frequency of SSc, as described by Risch (7). Fisher's exact tests and 95% confidence intervals comparing familial SSc with the population frequency of SSc were calculated using Epi-Info (Version 6.04a; Centers for Disease Control and Prevention, Atlanta, GA).

RESULTS

The demographic features and numbers of family members in the 3 cohorts are shown in Table 1. No significant differences among the cohorts were found for sex distribution or mean age at disease onset (in the 2 cohorts for which this information was obtained). There were, however, significant differences in ethnic background of the cases among the 3 cohorts. Cohort 2 (Texas) had significantly more Hispanic cases than cohorts 1 (Texas) and 3 (Michigan), probably because the GENISOS study specifically targets minorities and collects SSc cases from all of the south Texas region, where more Hispanics reside than in the Houston, Texas, area or in Michigan. The numbers of siblings per SSc case averaged 3.0 for cohort 2 (which was extrapolated to cohort 1) and 3.4 for cohort 3.

SSc recurred in 1.5–1.7% of families of SSc cases in the 3 US cohorts studied and averaged 1.6% in the total 703 SSc families surveyed (Table 2). Compared with the estimated US population prevalence of ~2.6 cases/10,000 for SSc, the frequencies of familial SSc were significantly increased in each of the 3 cohorts. The familial relative risks for SSc in siblings ranged from 10 to 27 (average 15), and in first-degree relatives it ranged

Table 2. Familial occurrence frequencies and relative risks of systemic sclerosis in 3 US cohorts

Cohort	No. of multiplex families (%)	Affected/total siblings (%)	λs*	*P*	95% CI	Affected/total first-degree relatives (%)	λ1*	*P*	95% CI
1: Texas	3/190 (1.6)	4/577 (0.7)	27	0.0003	5.2–103.0	4/957 (0.4)	16	0.002	2.7–78.5
2: Texas	3/175 (1.7)	2/531 (0.4)	14	0.02	1.5–92.2	3/881 (0.3)	13	0.009	1.8–70.4
3: Michigan	5/338 (1.5)	3/1,164 (0.3)	10	0.02	1.4–53.2	5/1,840 (0.3)†	10	0.003	1.9–47.8
Combined	11/703 (1.6)	9/2,272 (0.4)	15	0.00003	3.3–61.6	12/3,678 (0.3)	13	0.00003	2.9–48.6
Whites	7/466 (1.5)	5/1,366 (0.4)	12	0.001	12.2–64.5	8/2,298 (0.3)	12	0.0001	11.6–55.3
African Americans	4/133 (3.0)	4/518 (0.8)	26	0.0001	4.9–145.7	4/784 (0.5)	17	0.0008	17.1–95.9

* Compared with population frequency for systemic sclerosis of 0.026% (λs = relative risk in siblings; λ1 = relative risk in first-degree relatives, defined as parents and siblings).
† Additional 2 families (parent-offspring) reported, but had no medical records to confirm; if correct, λ1 = 15, $P = 0.0001$, 95% confidence interval (95% CI) 3.0–62.0.

from 10 to 16 (average 13) (Table 2). No significant differences in the familial occurrence rates or familial relative risks were found among the 3 cohorts despite the differences in ethnic composition noted above.

Adjustments for race showed that familial SSc was found more frequently in African American SSc families (3%) than in white SSc families (1.5%) (Table 2). The λs was 26 in African Americans compared with 12 in whites, and the λ1 was 17 in African Americans compared with 12 in whites. These differences, however, were not statistically significant. No familial cases were found in Hispanic families.

Familial relationships in the 11 multiplex SSc families included 6 sister-sister pairs, a set of 3 affected sisters, 1 sister-brother pair, and 3 mother-daughter pairs. An additional 2 mothers and daughters were reported in cohort 3, but the mothers were deceased and had no medical records available for review.

DISCUSSION

This study is the first to document that in the US, familial SSc occurs significantly more frequently in siblings and first-degree relatives of cases of SSc (~1.6% of families) than in the population as a whole (0.026%). These results are consistent with those reported in Australia (4). Although the absolute risk for SSc in each first-degree relative and sibling is low (<1%), the familial relative risks (λ1 = 10–16 and λs = 10–27) are high and are comparable with those of other autoimmune diseases (11). Although the confidence intervals for the λ values in each of the 3 cohorts are wide (Table 2), the similarity of the results among the 3 study groups, as well as those reported elsewhere (4), suggests that they are reasonably accurate. In fact, the only methodologically similar study, from Australia by Englert et al (4), estimated a λ1 ranging from 11 to 158 based on population prevalence estimates of SSc there.

The expected US prevalence rate for SSc used to calculate these familial rates was based on the results of 2 recent population studies (5,10), which showed a higher prevalence than in earlier studies (6). If data based on earlier studies (6) were used as the basis for the calculations reported here, then the increased familial occurrence and relative risks would be even more striking—in fact, at least 10-fold higher. Moreover, family members not reported to have SSc were not examined for the disease. It is possible that some additional familial cases were not discovered and the rates reported here represent underestimates. In addition, there may be ethnic differences in both the population prevalence and the familial risk of SSc; however, prevalence estimates in American ethnic minority groups are based on small numbers, and the increased familial risk found in African Americans in this study was not statistically significantly different from that in whites.

A positive family history of SSc appears to confer a risk that is at least 10–16-fold higher than normal for SSc in first-degree relatives and 10–27-fold higher than normal for SSc in siblings (λs) and thus represents the strongest susceptibility factor yet reported for this disease (6). It should be noted, however, that the number of cases studied remains relatively small and the confidence intervals are wide.

The higher-than-expected familial occurrence of SSc could be the result of shared genetic predisposition and/or common environmental exposures, although many epidemiologic studies have provided little support

for an environmental cause (for review, see ref. 12). Studies of concordance rates in monozygotic versus dizygotic twins could provide more definitive evidence for genetic versus environmental effects; however, studies of twins to date are limited and inconclusive. Of 8 pairs of monozygotic twins reported in the literature, 2 (25%) have been concordant for SSc, while the twin of 1 SSc case had an SSc-like illness, and another had systemic lupus erythematosus (13). A preliminary survey of 16 monozygotic and 14 dizygotic twin pairs showed only 1 concordant pair in each twin group, although RP and ANA positivity occurred more frequently in the clinically unaffected monozygotic twins than in their unaffected dizygotic counterparts (14). Given the low familial occurrence rates reported here and elsewhere, a very large number of twins will need to be studied to provide statistically valid results either way. Nonetheless, the significantly higher-than-expected familial occurrence rates and relative risks found here provide the impetus for further genetic studies.

REFERENCES

1. Arnett FC. HLA and autoimmunity in scleroderma (systemic sclerosis). Int Rev Immunol 1995;12:107–28.
2. Manolios N, Dunckley H, Chivers T, Brooks P, Englert H. Immunogenetic analysis of 5 families with multicase occurrence of scleroderma and/or related variants. J Rheumatol 1995;22:85–92.
3. Maddison PJ, Stephens C, Briggs D, Welsh KI, Harvey G, Whyte J, et al. Connective tissue disease and autoantibodies in the kindreds of 63 patients with systemic sclerosis. Medicine (Baltimore) 1993;72:103–12.
4. Englert H, Small-McMahon J, Chambers P, O'Connor H, Davis K, Manolios N, et al. Familial risk estimation in systemic sclerosis. Aust N Z J Med 1999;29:36–41.
5. Mayes MD, Laing TJ, Gillespie BW, Cooper BC, Lacey JV Jr, Hirschenberger WS, et al. Prevalence, incidence and survival rates of systemic sclerosis in the Detroit metropolitan area [abstract]. Arthritis Rheum 1996;39 Suppl 9:S150.
6. Mayes MD. Scleroderma epidemiology. Rheum Dis Clin North Am 1996;22:751–64.
7. Risch N. Linkage strategies for genetically complex traits. I. Multilocus models. Am J Hum Genet 1990;46:222–8.
8. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581–90.
9. Reveille JD, Fischbach M, McNearney T, Friedman A, Aguilar MB, Lisse J, et al. Systemic sclerosis in three U.S. ethnic groups: a comparison of clinical sociodemographic, serologic and immunogenetic determinants. Semin Arthritis Rheum. In press.
10. Maricq HR, Weinrich MC, Keil JE, Smith EA, Harper FE, Nussbaum AI, et al. Prevalence of scleroderma spectrum disorders in the general population of South Carolina. Arthritis Rheum 1989;32:998–1006.
11. Vyse TJ, Todd JA. Genetic analysis of autoimmune disease. Cell 1996;85:311–8.
12. Mayes MD. Epidemiologic studies of environmental agents and systemic autoimmune diseases. Environ Health Perspect 1999;107: 743–8.
13. McHugh NJ, Harvey GR, Whyte J, Dorsey JK. Segregation of autoantibodies with disease in monozygotic twin pairs discordant for systemic sclerosis: three further cases. Arthritis Rheum 1995; 38:1845–50.
14. Feghali CA, Wright TM. Epidemiologic and clinical study of twins with scleroderma [abstract]. Arthritis Rheum 1995;38 Suppl 9:S308.