Ethnicity and Race and Systemic Sclerosis: How It Affects Susceptibility, Severity, Antibody Genetics, and Clinical Manifestations

John D. Reveille, MD

Address
Division of Rheumatology and Clinical Immunogenetics, The University of Texas Health Sciences Center at Houston, 6431 Fannin Street, MSB 5.270, Houston, TX 77030, USA.
E-mail: john.d.reveille@uth.tmc.edu

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Most studies have suggested that ethnic factors impact significantly on systemic sclerosis. Extensive epidemiologic studies have been carried out in white individuals, and limited data suggest that blacks are affected twice as frequently; Japanese patients have a lower prevalence than whites. This highest rate that has been described has been in Choctaw Native Americans. Blacks have a lower age at onset, as well as a higher frequency of diffuse skin involvement, pulmonary disease, and an overall worse prognosis than whites. Limited data in Hispanics and Native Americans suggest that they have more severe disease than whites. Whites have the highest frequency of anti-centromere antibodies (associated with limited skin involvement and less pulmonary fibrosis), whereas blacks have a higher frequency of anti-ribonucleoprotein and fibrillarin autoantibodies; the latter is a nucleolar antibody associated with a poorer prognosis. Ethnic differences are also seen for associations with non–major histocompatibility complex genes, such as *FBN1* (fibrillin) genes, in Choctaws and Japanese and *SPARC* (osteonectin) in whites, Hispanics, and Choctaws. Although these facts do not entirely rule out socioeconomic factors associated with ethnicity, nevertheless ethnicity has an important impact on the pathogenesis of systemic sclerosis, perhaps because of genetic factors.

Introduction: Ethnicity and Disease–Is This A Relevant Factor?

Most anthropologists and population geneticists hold that homosapiens originated in Africa. The ancestors of anatomically modern humans left Africa between 35,000 and 89,000 years ago [1], departing through Egypt and the Middle East to populate the rest of the planet. In the ensuing time, regional differences occurred in homosapiens, probably in response to local environmental pressures, to give rise to the nine "racial" groups now considered. These groups vary among themselves in genetics factors that may affect immune response (such as human leukocyte antigen [HLA] alleles) and also in socioeconomic and cultural or behavioral domains that may affect how autoimmune diseases, such as systemic sclerosis (SSc), are manifest.

Ascribing an impact on disease pathogenesis to ethnicity (or to genetic factors associated therewith) is misleading because of these socioeconomic or behavioral confounders. Assigning an independent effect of ethnicity (or genetic factors associated therewith) is further confounded by gene-environment interactions, which are not considered in many outcome studies. A debate regarding the validity of racial or ethnic categories for biomedical and genetic research has emerged, and it has been proposed recently that such considerations are not valid [2]. However, Risch *et al.* [3] has more recently proposed that an epidemiologic perspective on the issue of human categorization in biomedical and genetic research would strongly support the continued use of self-identified race and ethnicity.

Ethnicity and the Epidemiology of Systemic Sclerosis

Most of the population studies of the prevalence of SSc have been conducted in white individuals, with prevalence ranging between 31 and 286 per million and incidences (per million/year) between three and 18.7 (Table 1) [4–13]. Among non-whites, few data exist. Steen *et al.* [7] identified 144 cases of hospital-diagnosed SSc in Allegheny County, PA during a 20-year survey from 1963 through 1982, and observed a total annual incidence of 13.9 per million population. Overall, the incidence rate doubled during 1973 to 1982 compared with the first time interval of the study, with the greatest increase occurring in women. Among the younger population (ages 15 to 24), black

Table 1. Studies of systemic sclerosis incidence and prevalence

Study and region	Study period	Incidence rate (new case per million per year)	Prevalence (total cases per million)
Medsger *et al.* [4]; Shelby County, TN	1947 to 1968	2.7	—
Michet *et al.* [5]; Rochester, MN	1950 to 1979	10	138
Steen *et al.* [7]; Pittsburgh and Allegheny County, PA	1963 to 1972; 1972 to 1982	9.6; 18.7	—
Maricq *et al.* [6]; South Carolina	1985	—	286
Mayes *et al.* [8]; Detroit, MI	1989 to 1991	18.7	242
Arnett *et al.* [14]; Oklahoma	1990 to 1994	—	660
Eason *et al.* [10]; Auckland, New Zealand	1970 to 1979	6.3	—
Silman *et al.* [9]; West Midlands, UK	1985 to 1986	3.7	31
Tamaki *et al.* [15]; Tokyo, Japan	1987	—	38
Geirsson *et al.* [13]; Iceland	1975 to 1990	3.8	71
Englert *et al.* [11]; Sydney, Australia	1974 to 1988	—	86
Roberts-Thomson *et al.* [12]; South Australia	1993 to 1999	22.8	233

(*From* Mayes and Reveille [58]; with permission.)

women had the highest incidence of SSc (21.2 per million population). Overall, the incidence ratio of women to men was 3 to 1, and was slightly higher (3.4 to 1) during the childbearing years (ages 15 to 44).

Mayes *et al.* [8] conducted a retrospective cohort study of women with SSc diagnosed in Michigan between 1980 and 1991. A total of 514 women with SSc were identified; 117 (23%) were black and 397 (77%) were white. The overall incidence of SSc was 14.1 per million per year; 22.5 per million per year in black women versus 12.8 per million per year in white women ($P<0.001$).

Arnett *et al.* [14] found Choctaw Native Americans in southeastern Oklahoma to have the highest prevalence of SSc (469 per 100,000). No data exist for other Native American groups.

Studies of the epidemiology of SSc in Asia are needed. Tamaki *et al.* [15] estimated the prevalence rate of SSc in Japan was between 2.1 and 5.3 per 100,000. The ratio of men to women was 14 to 1. This rate is somewhat lower than has been described in other ethnic groups.

Ethnicity and Clinical Features of Systemic Sclerosis

Most data from multiethnic cohorts suggest that nonwhites generally have a higher likelihood of more severe SSc (Table 2) [16••,17–19], especially with respect to diffuse skin and pulmonary involvement. Systemic sclerosis occurs at a younger age in black women than in European-American women [17,18]. Reveille *et al.* [16••] examined 54 Hispanics, 28 blacks, and 79 whites from Texas with recent-onset (less than 5 years) SSc enrolled in a prospective longitudinal study, and reported that Hispanics and blacks in the prospective cohort were more likely to have diffuse skin involvement, skin pigmentary changes, digital ulcers, early-onset pulmonary hypertension (blacks), and an overall lower sociodemographic status than whites, who had more facial telangiectasia and hypothyroidism. Laing *et al.* [17] conducted a retrospective cohort study of women with SSc in Michigan using 117 black (23%) and 397 white (77%) SSc patients. Among black women, the mean age at diagnosis was lower (44.5 years vs 51.5 years; $P<0.001$) and diffuse disease was more common (49.6% vs 24.9%; $P<0.001$) than among white women. Pericarditis ($P=0.009$), pulmonary hypertension ($P<0.001$), pleural effusions ($P=0.01$), myositis ($P=0.02$), and an erythrocyte sedimentation rate greater than 40 mm per hour ($P<0.001$) were more frequent among black women, whereas white women were more likely to have digital infarctions ($P<0.001$). Greidinger *et al.* [18] examined 101 patients with diffuse cutaneous SSc. Black patients with SSc were distinct from white patients by having younger age of onset and higher prevalence of antibodies to topoisomerase I.

Tager and Tikly [19] conducted a retrospective study of SSc in African blacks attending a tertiary hospital on the Witwatersrand, South Africa. The ratio of men to women in the 63 patients was 4.6 to 1, and the mean age of onset of SSc was 36.1 years. Forty-one patients had diffuse cutaneous SSc (dcSSc), 18 had limited cutaneous SSc (lcSSc), and four were unclassified. Overall, 56% had pulmonary fibrosis, 37% had myositis, and 98% were antinuclear antibody–positive, with a notable absence of anti-centromere antibodies. Seven of the eight known deaths occurred in patients with dcSSc. These findings, particularly the age of disease onset, predominance of the dcSSc subset, inflammatory features of myositis and a raised erythrocyte sedimentation rate, and absence of anti-centromere antibodies, were similar to those reported previously in black patients.

Limited data exist for Asian SSc patients, except possibly for Japan. Krishnamurthy *et al.* [20] described 78 southern Indian patients with progressive SSc seen over a period of 14 years. There was a female preponderance (3.9 to 1), and the peak age of occurrence was the fourth decade (32.1%). Arthralgia (53.8%) and

Table 2. Regional and ethnic differences in disease type and antibody expression

Group	Diffuse disease, %	Limited disease, %	Pulmonary fibrosis, %
Zimbabwean African blacks [19]	65	29	56
Michigan black women [17]	70	30	25
Texas blacks [16••]*	64	36	32
Texas Hispanics [16••]*	61	39	22
Oklahoma Choctaw Native Americans [14]	65	35	70
Japan [15]	75	25	45
Thailand [21]	70	30	43
West Midland, UK, whites [9]	61	39	No data available
Greek whites [28]	45	49	36
Michigan white women [17]	31	69	23
Texas whites [16••]*	46	54	14
Iceland [13]	28	72	No data available
Australia [12]	26	74	No data available

*Systemic sclerosis patients with disease duration of less than 5 years.
(*From* Mayes and Reveille [58]; with permission.)

skin thickening (70.5%) were the common presenting symptoms. Raynaud's phenomenon (28.2%) was less common. Joints were affected in 66.7% of patients; internal organs were involved in 52.6% of patients. Antinuclear antibody was positive in 56.8% of patients. Abnormal echocardiography (37.6%) and abnormal barium studies of the gut (20.4%) were seen. Restrictive airway pattern by pulmonary function test was present in 55% of patients.

Panicheewa *et al.* [21] reported clinical parameters in 69 SSc patients from Thailand, including 46 patients with diffuse SSc, two with lcSSc, two with linear SSc, 18 with overlap syndrome, and one with primary Raynaud's disease. The major clinical manifestations among the diffuse SSc patients were cutaneous (93.3%), musculoskeletal (69.6%), gastrointestinal (54.3%), and pulmonary (43.3%), although renal involvement (4.3%) was less common. These findings were further observed by McNeilage *et al.* [22] in a comparison of patients from Australia and Thailand.

Kuwana *et al.* [23] and Tamaki *et al.* [15] reported that the characteristic signs of SSc were as follows: proximal SSc (75%); sclerodactyly (91%); pitting scars (49%); short sublingual frenulum, 49%; pulmonary fibrosis, 45%; diffuse pigmentation (45%); and phalangeal contracture (35%). Raynaud's phenomenon was present in 93% of patients, and was the initial symptom in 59% of cases.

Prognosis

Early reports from the US suggested that black patients have a significantly increased mortality compared with white patients [4,24]. In fact, most studies of whites from the US and Europe have suggested a lower mortality compared with non-whites, in general, particularly black patients [4,23–27], with one notable exception [29].

Walsh and Fenster [25] determined whether elevated rates of mortality from SSc in the southeastern US result from local, multicounty clusters of the disease. From 1981 to 1990, significant excess mortality from SSc in the southeastern US occurred among white men (standardized mortality ratio [SMR]=1.2; P=0.0004] and black men (SMR=1.2; P=0.04), but not among white women (SMR=0.98; P=0.55) or black women (SMR=1.1; P=0.06). In combination, excess SSc mortality in the detected clusters accounted for 79% and 66.2%, respectively, of the excess deaths among white and black men across the whole southeast. They concluded that the elevation of SSc mortality rates in the southeastern US resulted from local clusters of concentrated mortality, possibly artifacts of regional variation in death certificate quality.

The probability of survival worse among non-whites and the rate of healthcare use greater. Nietert *et al.* [26] used the 1995 Healthcare Cost and Utilization Project national inpatient sample to identify 3621 SSc hospitalizations. They found population hospitalization rates were higher for non-whites compared with whites among those younger than 65, whereas rates were higher for whites compared with non-whites for those older than 65. The overall in-hospital death rate was 7.1%. These patterns are consistent with a greater burden and increased severity of disease among non-whites under 65 years of age with SSc.

Likewise, specific organ manifestations tend to be more severe in blacks. Greidinger *et al.* [18] examined 101 patients with dcSSc. In multivariate analyses accounting for gender, age, smoking history, years of SSc symptoms, and RNA polymerase II antibody status, race (blacks), and topoisomerase I antibody status independently predicted lower lung function. Steen *et al.* [27] reported that race, male gender, early disease, and primary cardiac involvement caused by SSc were the features most frequently associated with severe restrictive lung disease (by multiple logistic regression) in 890 SSc patients observed at the Uni-

versity of Pittsburgh. Vlachoyiannopoulos *et al.* [28] likewise described a lower frequency of severe pulmonary and renal disease among 254 SSc patients from Greece, and an estimated survival probability for this cohort, 4 years after the first visit, of 95%.

Kuwana *et al.* [23] reported that the frequency of *progressive* pulmonary interstitial fibrosis was lower, and cumulative survival rates were better in white patients compared with blacks and patients from Japan. In another report, they described 275 consecutive Japanese patients newly diagnosed as having SSc who were first evaluated during the period 1971 to 1990 [31]. Cumulative survival rates at 10 years after diagnosis of SSc were 93% in patients with anticentromere antibodies, 72% in those with anti-U1 ribonucleoprotein, 66% in those with anti-DNA topoisomerase I (anti-topo I), and 30% in those with anti-RNA polymerases I, II, and III (anti-RNAP). Major organ involvement linked to cause of death included biliary cirrhosis in patients with anticentromere antibodies, isolated pulmonary arterial hypertension, and cerebral hemorrhage in those with anti-U1 ribonucleoprotein, pulmonary interstitial fibrosis in those with anti-topo I, and cardiac and renal involvement in those with anti-RNAP.

Nishioka *et al.* [30] examined the prognosis of 496 Japanese patients with progressive SSc based on clinical data described in case cards provided by the members of the Scleroderma Research Committee of the Japanese Ministry of Health and Welfare. Ninety patients died (11 men, 79 women). The age of onset of the deceased patients was significantly higher than that of surviving patients (45.6 years and 41.3 years, respectively). Statistically significant factors for a poor prognosis included more diffuse skin involvement, anti-Scl-70 antibody positivity, and anticentromere antibody negativity. The survival rate at 5 years after the onset of the disease was 93.7%, followed by 82% at 10 years, 56.7% at 20 years, and 40% at 30 years after disease onset. The most common causes of death were heart failure, pulmonary insufficiency, lung fibrosis, and renal failure.

In contrast, Panicheewa *et al.* [21] reported 69 patients from Thailand with scleroderma. Overall, the Thailand patients with SSc appeared to have milder disease than those described in Western series. Given the paucity of data that otherwise exist in patients from Thailand and other southern and southeastern Asians, these data need further confirmation.

Ethnic Differences in Autoantibody Frequencies

Systemic sclerosis is a serologically heterogeneous disease, and these autoantibodies in turn are associated with clinical subsets. Anticentromere antibodies, which are associated with limited skin involvement and a lower frequency of pulmonary disease (summarized in [32••]), are significantly less frequent in Africans [33,34] and blacks in the US [16••], as well as Hispanics [16••] and in patients from Thailand [21] (Table 3). Anti-Scl-70, associated with diffuse skin involvement and a higher frequency of pulmonary fibrosis [32••], occurs in approximately in equal frequencies in all ethnic groups, although the highest frequencies of anti-Scl-70 have been described in SSc patients from Thailand (40.6%) [21] and Choctaw Native Americans (80%) [14].

Anti-ribonucleoprotein, which is associated with overlap syndromes, occurs in highest frequency in blacks with SSc [16••], and is as seen in systemic lupus erythematous [37].

Antifibrillarin antibodies (AFA) are associated with diffuse skin and internal organ involvement, and an overall worse prognosis [38,39]. Arnett *et al.* [38] and Reveille *et al.* [16••] described a higher frequency of AFA in blacks in two independent cohorts of SSc patients from Texas. Tormey *et al.* [39] investigated 1026 consecutive patients with SSc from the UK for the presence of AFA. Antifibrillarin antibodies were detected in 42 patients (4.1%) with early disease onset (mean age 36 years). Sixteen (38%) patients had lcSSc and 26 (62%) had dcSSc. Eight Afro-Caribbean patients with AFA had dcSSc, whereas the whites were equally divided between dcSSc and lcSSc.

Using a recombinant human fibrillin-1 protein, Tan *et al.* [40] detected the presence of autoantibodies to fibrillin-1 in the sera of Native American SSc patients that correlated significantly with the presence of SSc (as opposed to other connective tissue diseases). Autoantibodies to fibrillin-1 also were detected in sera from Japanese, white, and black SSc patients. Compared with other ethnic groups, Japanese and Native American SSc patients had significantly higher frequencies of AFA.

Ethnic Differences and Similarities in Genetic Factors

Major histocompatibility complex genes

Probably the most consistent association of SSc with HLA alleles has been with HLA-DR11 (*DRB1*11*), which has been previously known as HLA-DR5 [16••,28,42]. In fact, the *HLA-DRB1*1104* subtype of DR11 has been reported as associated with SSc in white patients from Pittsburgh [41], Greece [28], as well as with Hispanics from Mexico City (Table 4) [42]. In addition to this, white patients from the UK have an excess of HLS-DR3 (*DRB1*0301*) [43]. Tan *et al.* [44] implicated an extended HLA-DR2 (*DRB1*1602*, *DQA1*0501*, *DQB1*0301*, *DPB1*1301*) haplotype in Choctaw Native Americans.

*HLA-DQB1*0301* is in linkage dysequilibrium with *HLA-DRB1*11* and *DRB1*1602* haplotypes in these ethnic groups. Reveille *et al.* [16••] reported that *HLA-DQB1*0301* was significantly associated with SSc in Hispanics, blacks, and whites from Texas with recent-onset disease (less than 5 years).

Table 3. Autoantibody frequencies in systemic sclerosis patients by ethnic group*

Autoantibody	Texas Hispanics (*n*=77), %	Texas blacks (*n*=77), %	Texas whites (*n*=191), %	Choctaw Native Americans (*n*=21), %	UK whites (*n*=735), %	Australian whites (*n*=365), %	Zimbabwean blacks (*n*=63), %	Japanese (*n*=496), %	Thailand (*n*=69), %
ANA	86	84	79	100	92	95	98	92	90
Anti-Scl-70	19	16	13	71	21	2	18	32	41
ACA	18	4	32	12	30	34	0	17	3
Anti-Sm	4	9	0	0		No data	8	5	0
Anti-U1-RNP	11	29	5	0	7	7	10	16	18
Anti-Ro	4	6	3	17	4	No data	18	11	No data
Anti-nucleolar	34	34	23	0	No data	16	31	No data	No data
Anti-fibrillarin	7	17	4	0	4	No data	No data	3	No data
Anti-Th/To	9	0	6	0	No data	No data	No data	5	No data
RNA polymerase I	26	20	13	0	32	No data	No data	5	No data
RNA polymerase II	6	3	5	42	26	No data	No data	40	No data
RNA polymerase III	26	20	13	0	32	No data	No data	5	No data

*Frequencies of anti-Th/To and the RNA polymerase I through III autoantibodies were only available in 88 whites, 30 blacks, and 59 Hispanics; *P* value is based on the comparison of antibody distribution among whites, blacks, and Hispanics.
ACA—anticentromere antibodies; ANA—antinuclear antibodies; RNP—ribonucleoprotein.

Table 4. Major histocompatibility complex genes associated with systemic sclerosis in different ethnic groups

Group	DPB1	TAP	DQA1	DQB1	DRB1	C4	TNF
Whites*	Not studied	Not studied	**0501*	**0201*	**0301*	*A*Q0*	Not studied
Whites	**1301*	Not studied	**0501*	**0301*	**11*	Not studied	*a2, b3*
Blacks	Not studied	Not studied	**0501*	**0301*	**11*	Not studied	Not studied
Hispanics	Not studied	Not studied	**0501*	**0301*	**1104*	Not studied	Not studied
Choctaw Native Americans	**1301*	Not studied	**0501*	**0301*	**1602*	Not studied	Not studied
Japanese	**0901*†	*1A, 2A*	**0103*	**0601*	**1502, *0803*	*B*Q0*	*a13*

*From the UK and the Netherlands.
†Associated with anti-topoisomerase I autoantibody response
TAP—transporter-associated peptide; TNF—tumor necrosis factor.
(*From* Mayes and Reveille [58]; with permission.)

*HLA-DRB1*11*, *DRB1*0301* and *DRB1*1602* are infrequently found in eastern Asians (Japanese and Koreans), where different major histocompatibility complex associations have been reported. Most consistently seen is the association with the *HLA-DRB1*1502* and *DRB1*0803* alleles, which are in linkage dysequilibrium with *HLA-DQA1*0103* and *DQB1*0601* [45,46]. Panicheewa *et al.* [21] examined 69 patients from Thailand with scleroderma, including 46 patients with diffuse SSc, two with lcSSc, two with linear scleroderma, 18 with overlap syndrome, and one with primary Raynaud's disease. Human leukocyte antigen DR2 was significantly increased in diffuse SSc patients (P<0.01). Although the serologic analyses used precluded HLA-DR2 subtyping, this probably represented the same *HLA-DRB1*1502*, *DQA1*0102*, and *DQB1*0601* haplotypes described in the Japanese SSc patients.

However, it has been proposed that the HLA associations with SSc may be better explained by autoantibody subsets of the disease [47,48]. Reveille *et al.* [16••] found *HLA-DRB1*11* correlated with the anti-topo I antibody response, and *HLA-DRB1*01*, *DRB1*04*, and *DQB1*0501* with anticentromere antibodies. Kuwana *et al.* [49] reported that HLA-DRB1 alleles associated with anti-topo I antibody differed; that is, *DRB1*1101* to *DRB1*1104* in white and black patients, *DRB1*1502* (a subtype of HLA-DR2) in Japanese patients, and *DRB1*1602* (another subtype of HLA-DR2) in Choctaw Native American patients.

Before this, Kang *et al.* [46] reported that anti-topo I–positive SSc was strongly associated with *HLA-DRB1*1502* in 35 anti-topo I–positive compared with 39 anti-topo I–negative SSc patients and 200 healthy control individuals. Among anti-topo I–negative patients, diffuse and limited subtypes of SSc were significantly associated with *DRB1*0803* (47% vs 15% in control individuals; P<0.05) and DRB1*1501 (50% vs 17% in control individuals; P<0.01), respectively.

In addition to HLA class II genes, associations with tumor necrosis factor genes and transporter-associated peptide genes and SSc have been described in Japanese patients that have not been observed in white patients [50–52]

Non–major histocompatibility complex genes

Fibrillin-1 is an important structural protein that is expressed in many tissues, including skin, and is a major component of elastic microfibrils found in the extracellular matrix. Functional studies using pulse-chase labeling indicate that fibrillin-1 containing microfibrils from SSc fibroblasts are unstable and easily degraded [53]. The *tsk1* mouse, one of the few recognized animal models of SSc, possesses a genomic duplication of fibrillin-1 (*FBN1*) that maintains the reading frame [54]. Tan *et al.* [55] identified a multilocus 2-centimorgan haplotype on human chromosome 15q, homologous to the murine *tsk1* region, that showed a significantly increased frequency in SSc cases (38%) compared with controls (8%) (P=6.5x10^{-18}). In further work from the same group, Tan *et al.* [56] identified five single nucleotide polymorphisms (SNPs) in the *FBN1* genes, two of which were found only in SSc patients. These same *FBN1* SNP haplotypes were associated with SSc in the Japanese, consistent with the hypothesis that *FBN1* or a nearby gene on chromosome 15q is involved in SSc susceptibility in the Choctaw Native Americans and Japanese patients.

SPARC (secreted protein, acidic, and rich in cyteine) regulates the deposition or assembly of extracellular matrix components through induction of matrix metalloproteinases or their inhibitors, making it an attractive SSc candidate gene. Zhou *et al.* [57] found a twofold average increased gene expression compared with normal control individuals for *SPARC* of skin fibroblasts from SSc patients. Genotyping for five microsatellite markers around *SPARC* on chromosome 5q31-32 in four ethnic groups with SSc patients and ethnically matched control individuals (Choctaw Native Americans, whites, blacks, and Hispanics) revealed three of five microsatellite mark-

ers showed significant associations with SSc in Choctaw Native Americans. Analysis of *SPARC* SNPs in the four studied ethnic populations after adjusting for the effect of ethnic background indicated that homozygotes for the C-allele at SNP +998 were significantly increased in SSc cases compared with control individuals (P=0.0028) in Hispanics and Choctaw Native Americans, and another SNP was associated in whites, although no effect was seen in black patients.

Conclusions

Ethnicity impacts on the epidemiology, immunology, genetics, clinical features, and prognosis in SSc. The highest frequency of SSc has been described in Choctaw Native Americans, followed by black patients. The lowest frequency has been described in Japanese patients. Blacks (and Africans) and Choctaw Native Americans also appear to have more severe disease and a worse prognosis, as well as autoantibodies associated with more severe SSc and a worse prognosis. Furthermore, genetic factors that have been implicated in predisposition, such as HLA and non-HLA genes, differ from ethnic groups to ethnic group. These factors, and those from other diseases, suggest that ethnic factors may be an independent determinant of prognosis. However, the definition of ethnicity is becoming more blurred with time, as a result of intermarriage between different groups. Theories of race-based genetic susceptibility must be replaced with rigorous criteria to determine when a trait can be ascribed to some genetic origin [2], and efforts in the future should be directed toward defining those specific genetic factors and correcting their potential effect by considering potential socioeconomic or behavioral or cultural confounders. Tools are now being develop to make this possible, which will allow a better perspective of the true impact of "ethnicity" on SSc and perhaps allow novel approaches to treatment.

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