The Genetics of Systemic Sclerosis

*Randall W. Johnson, MD, Monty B. Tew, MD, and Frank C. Arnett, MD**

Address
*University of Texas Health Science Center, Department of Internal Medicine, 6431 Fannin MSB 5.260, Houston, TX 77030, USA.
E-mail: Frank.C.Arnett@uth.tmc.edu

Current Rheumatology Reports 2002**, 4:**99–107
Current Science Inc. ISSN 1523–3774

The etiopathogenesis of systemic sclerosis (SSc) is unclear. With no definitive evidence supporting an environmental cause, recent attention has focused on genetic factors. Familial clustering and ethnic influences have been demonstrated. Human leukocyte antigen (HLA) associations exist but are more related to the presence of particular autoantibodies rather than to the disease. In addition, no single major histocompatibility complex (MHC) allele predisposes to SSc in all ethnic groups. The role of microchimerism in SSc is a novel yet unproven hypothesis that may be related to intergenerational HLA compatibility. Recent studies investigating polymorphisms in genes coding for extracellular matrix proteins and cell-signaling molecules implicate non-MHC areas in SSc pathogenesis. The data reviewed suggest that SSc is a multigenic complex disorder.

Introduction

Despite the expanding molecular knowledge of extracellular matrix (ECM) abnormalities, endothelial dysfunction, cytokine dysregulation, and autoantibody production in scleroderma or systemic sclerosis (SSc), the etiopathogenesis of this protean disease remains obscure. Multiple anecdotal reports and case series have implicated an initiating environmental event (*ie*, infections, hormonal manipulation, and exposures to pesticides, silica, or organic solvents). However, with the possible exception of estrogen replacement in postmenopausal women contributing to a small increased risk of disease development, there are no conclusive case-controlled evidence indicating that any known environmental agent causes SSc [1••]. Therefore, increasing attention is being focused on genetic factors in SSc.

Although no increased disease concordance has been demonstrated consistently in monozygotic versus dyzygotic twins [2,3], the number of twin pairs studied remains too small to draw a definitive conclusion. The hypothesis that genetic factors strongly influence the development and expression of SSc is based on the following observations: the firm demonstration of familial clustering of SSc; frequent observations of other autoimmune diseases and antinuclear antibodies in relatives of patients with SSc; increased frequency of major histocompatibility complex (MHC) or human leukocyte antigen (HLA) alleles in certain subsets of SSc; and differences in prevalence rates, clinical manifestations, and serologic features influenced by ethnic background [4–6]. Furthermore, the irrefutable presence of disease-specific autoantibodies infers that SSc has an autoimmune basis and thus represents a complex genetic disorder similar to diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). With the presence of genetic abnormalities found in structural proteins of the ECM in the tight skin mouse [7], animal models support a genetic hypothesis. A multitude of genetic abnormalities are being identified in patients with SSc, including polymorphisms in cytokines, growth factors, and constituents of the ECM. However, it is undetermined how these genetic variants are translated to altered cell signaling, fibroblast activation, and endothelial cell dysfunction.

Familial Aggregation and Ethnic Influence

With the establishment of the American College of Rheumatology criteria for classification of scleroderma in 1980 [8], the incidence of SSc in the United States has been estimated at 18.2 cases/million population. The most recent prevalence rates have been estimated at 242 to 286 cases/million population [9]. Disease prevalence appears to differ geographically, with European and Japanese rates for SSc far less than those in the United States or Australia [10]. Although these geographic discrepancies may represent methodologic differences, variations in genetic predisposition and environmental exposures may be the explanation.

Although possibly confounded by shared and potentially ubiquitous environmental exposures, the increasing number of reported cases of familial clustering suggests a genetic contribution to the development of SSc. Many families have been identified with multiple cases, including SSc or related fibrotic disorders [4,11]. In addition, several concordant twin pairs have been presented [3]. However, a formal study of 34 twin pairs revealed a concordance rate of only 6.9% and no statistically significant difference between monozygotic and dyzygotic twins [2].

A recent study from Sydney, Australia, evaluated 710 families with at least one index case of SSc and 371 age- and gender-matched control families [12••]. Whereas no cases of SSc were detected in the control cohort, SSc affecting a first-degree relative was validated in 10 of 710 families (1.4%), which exceeded the point prevalence of SSc in the

Sydney population (0.009%). Furthermore, the relative risk for recurrence of SSc within first-degree relatives was estimated to range from 11- to 158-fold greater than in the general population. Similar familial prevalence rates recently have been found in three large US cohorts (1.6%–1.7% in two SSc cohorts studied at the University of Texas-Houston and 1.5% in the Michigan Scleroderma Registry) with estimated familial relative risks of 10 to 27 [13••]. These studies suggest that a positive family history of SSc confers the highest relative risk yet identified for SSc.

Ethnic differences appear to influence the development, observed manifestations, expressed autoantibodies, and survival rates seen in patients with SSc. Laing *et al.* [14] reported that black women were significantly more likely to develop scleroderma, suffer severe systemic manifestations, and have a worse age-adjusted survival rate. Similar findings were found in a multi-ethnic cohort in which black and Japanese patients with SSc had higher frequencies of progressive pulmonary interstitial fibrosis and lower cumulative survival rates [6]. Correlating with these clinical findings, the frequency of anticentromere antibodies (which have been associated with limited SSc) has been found to be significantly increased in whites versus blacks (36% vs 4%, respectively), whereas antitopoisomerase I antibodies (typically associated with diffuse SSc disease and thus worse outcome) were found more frequently in blacks versus whites (37% vs 17%, respectively) [10].

Perhaps the most compelling evidence of an ethnic susceptibility to SSc comes from the strikingly high prevalence of scleroderma in the Choctaw American Indian population in Oklahoma (469 cases/million population) [5]. Among the SSc cases studied there was considerable homogeneity of disease expression with most cases exhibiting diffuse scleroderma, pulmonary fibrosis, and antitopoisomerase I antibodies. Genetic contributions to SSc in this relatively isolated population is suggested by identifying common ancestral founders in the 1700s, the presence of an American Indian HLA haplotype identified in 100% of the SSc cases versus 54% of the controls, and several other genetic associations. The contribution of ethnicity in SSc is multifactorial because it likely reflects genetic variances, geographic exposures, and variations in customs.

Human Leukocyte Antigen Associations

With the demonstrated influence of racial background on SSc, several studies have investigated variances in MHC or HLA alleles or haplotypes among different ethnic groups. The most consistently described associations of HLA with SSc in American and European whites include the HLA-DR5 haplotypes (*DRB1*1101* and **1104*, *DQA1*0501*, *DQB1*0301*) and the DR3 haplotype (*DRB1*0301*, *DQA1*0501*, *DQB1*0201*) [4,15]. Another study demonstrated a strong association between *DRB1*1104* and Greek patients with SSc [16]. However, a recent report by Reveille *et al.* [17•] that evaluated a large multi-ethnic US cohort could not substantiate the increased frequency of any HLA-DRB1 allele in whites alone. Among blacks, *HLA-DRB1*08* was more common in patients with SSc versus ethnically matched controls (27% vs 11%, respectively). In addition, Mexican American patients with SSc were similar to whites with an increased frequency of *HLA-DRB1*1104*. The only HLA allele that crossed ethnic lines and was associated with SSc in all three groups was *HLA-DQB1*0301*, which is in linkage disequilibrium with HLA-DR5 (DR11) and DR4 haplotypes. In other studies, Japanese patients demonstrated increased frequencies of two HLA-DRB1 alleles (**1502* and **0802*), and *DQB1*0601*, but with a stronger concomitant association with antitopoisomerase I antibodies [4,17•]. Further evidence for a correlation between the MHC and ethnically influenced SSc derives from a uniquely American Indian HLA haplotype (*DRB1*1602*, *DQB1*0301*, and *DQA1*0501*), which confers a strong risk for SSc in Choctaw American Indians [5]. The *HLA-DQA1*0501* allele, a component of several SSc-associated haplotypes (DR5 and DR3), recently was reported to be significantly more common in men with SSc [15]. By virtue of the diversity in frequencies of HLA haplotypes in the various ethnic populations, there does not appear to be a single MHC haplotype or allele that predisposes to SSc. Instead, it seems likely that the MHC effects relate more to specific immune responses, as evidenced by the strong associations with autoantibodies found in patients with SSc (Table 1) [4,6,17•,18,19].

Antitopoisomerase I antibodies

Antitopoisomerase I antibodies, which are unique to SSc and have been correlated with diffuse cutaneous involvement and pulmonary fibrosis, appear to occur more frequently in Mexican American, black, American Indian, Thai, and Japanese patients with SSc [4]. Extensive variances among different ethnic populations exist, but in whites and blacks, several reports have described increased frequencies of *HLA-DRB1*1101-*1104* [17•,18]. Among Mexican Americans, Reveille *et al.* [17•] revealed increased frequencies of *HLA-DRB1*1104* in antitopoisomerase I-positive patients. However, it has been suggested that the antitopoisomerase I response is determined by the presence of certain HLA-DQB1 alleles, with *DQB1*0301* being in linkage disequilibrium with the DR11 allele in most populations [4]. Among Choctaw American Indians who have a high frequency of antitopoisomerase I antibodies, *HLA-DQB1*0301* was found in all patients with SSc, often in a homozygous state [5]. Among Japanese patients with antitopoisomerase I response, there are increased frequencies of HLA-DRB1 alleles (**1502* and **0802*) and DQB1 alleles (**0601* and **0301*), which are in linkage disequilibrium, respectively [4]. *HLA-DPB1*1301* also has been associated with antitopoisomerase I autoantibodies in several populations [20–22]. Various shared amino acid sequences within these disease-specific, autoantibody-associated alleles have been proposed as crucial sites

Table 1. Major human leukocyte antigen-class II haplotypes associated with systemic sclerosis-related autoantibodies in various ethnic groups [3,5,16]

		Human leukocyte antigen haplotype			
Autoantibody		**DRB1**	**DQA1**	**DQB1**	**Ethnicity**
Topoisomerase I		*1101-*1104	*0501	*0301	White
		*1101-*1104	*0501	*0301	Black
		*1502, *0802	*0102	*0601, *0301	Japanese
		*1104	*0501†, *0401†	*0301†, *0402	Hispanic
		*1602	*0501	*0301	Choctaw
Centromere		*0101, *0401	*0101	*0501, *0301	White
		*0101, *0401		*0501	Hispanic
U1-ribonucleoprotein		*0401		*0302	White
		*0401, *1502		*0302, *0601	Japanese
PM-Scl		*0301	*0501	*0201	White
Fibrillarin		*1302	*0102	*0604	White
		*1302†	*0102†	*0604†	Black
		*1302†	*0102†	*0604†	Japanese
Th/To		*1104		*0301	White
RNA polymerases	I	*0401			White
	II	*0301†		*0201†	
	III	*0301†		*0201†	

†Trend toward significance.

determining stereotactic and charge prerequisites that influence T-cell receptor and processed antigen binding resulting in the autoimmune response [4].

Anticentromere antibodies

Anticentromere antibodies (ACA) are found predominantly in whites and typically are associated with limited forms of scleroderma with a good long-term prognosis. Unlike antitopoisomerase I antibodies, ethnicity does not appear to influence the HLA haplotypes associated with ACA. Initial studies revealed a correlation predominantly with HLA-DR11 but also with HLA-DR1, -DR4, and -DR8 [4,20]. More recent studies suggest that the primary susceptibility to the anticentromere response correlates with HLA-DQB1 alleles that are encoded with polar amino acids (glycine or tyrosine) at position 26 [4]. Homozygosity of this polymorphism appears to exert a powerful effect on predisposition to the anticentromere response.

Anti–U1-RNP antibodies

Anti–U1-RNP, typically detected in blacks, Mexican Americans, and Japanese, can occur in patients with SSc and correlates with myositis and arthritis. Kuwana *et al.* [6] initially reported an association with the *HLA-DRB1*1502* and *DQB1*0601* haplotype in a small cohort of Japanese patients with SSc. This was followed by a large case-control study that revealed a correlation between anti–U1-RNP antibodies and *HLA-DRB1*0401* and *DQB1*0302*, which are in linkage disequilibrium [18]. Among African-Americans, Reveille *et al.* [17•] reported no significant HLA association with the U1-RNP response, albeit the number of patients studied was small.

Antinucleolar antibodies

Although relatively infrequent, several antinucleolar antibodies have been described in patients with SSc and generally are found exclusive of one another.

Anti–PM-Scl antibodies, which occur in fewer than 5% of patients with SSc, are almost uniquely detected in whites and correlate with myositis and arthritis, and overlap features of SSc. Studies have shown a striking association (nearly 100%) with the *HLA-DRB1*0301*, *DQA1*0501*, and *DQB1*0201* haplotype [4].

Anti–U3-RNP (fibrillarin) antibodies occur in approximately 5% of all patients with SSc but are more frequently detected in blacks versus whites and Japanese [23]. Antifibrillarin antibodies have been associated with diffuse skin involvement, gastrointestinal dysmotility, pulmonary hypertension, and cardiac involvement. The *HLA-DRB1*1302* and *DQB1*0604* haplotype has been associated with antifibrillarin antibodies in one study [24], but no associations were found in another study that measured anti–U3-RNP antibodies by an alternative method [23].

Anti–Th-ribonucleoprotein (anti-Th/To) antibodies appear specific for SSc, occur primarily in whites, and are associated with limited skin involvement. The only HLA association recognized thus far with anti-Th/To is with *DRB1*1104* [25].

Autoantibodies to the RNA polymerases (anti-RNAP) I, II, and III have been described in approximately 20% of whites with SSc in the United States [23]. Anti-RNAP III has been associated with diffuse cutaneous involvement, arthritis, and scleroderma renal crisis. Although initial studies suggested an association with *HLA-DQB1*0201*, a cohort of 81 patients with SSc who had anti-RNAP did not

demonstrate any significant HLA-DR or HLA-DQB1 associations [23]. Analysis of each anti-RNAP subtype revealed a trend for correlation between anti-RNAP II and III with HLA-DR3, whereas anti-RNAP I antibodies were associated with an increased frequency of HLA-DR4.

Microchimerism

Recently the novel hypothesis of microchimersim has been suggested in the pathogenesis of SSc [26,27]. The theory suggests that allogenic hematopoietic fetal cells cross the placenta, persist in maternal circulation as a result of HLA class II (DRB1) compatibility, and subsequently mount a graft-versus-host response. Supporting this hypothesis, retained fetal cells detected using Y chromosome-specific sequences or disparate HLA alleles have been identified in the tissue and blood of women with SSc and have been demonstrated to exceed that found in healthy control patients. Although persistent fetal cells would not pertain to the occurrence of SSc in men or nulliparous women, it subsequently was demonstrated that HLA-disparate maternal cells persist in male offspring, albeit in patients with SSc and in healthy controls [28].

Lambert *et al.* [29] demonstrated that HLA-DRB1 compatibility between mother and child significantly increased the risk of subsequent SSc in the mother by 2.6-fold. In addition, a recent report demonstrated that fetal microchimerism among T lymphocytes was associated with *DQA1*0501* haplotypes [30]. However, no increase of maternal HLA compatibility in male patients with SSc has been demonstrated [15]. It cannot be concluded that microchimerism is involved in the development of SSc.

Extracellular Matrix

Collagen

Type I collagen is the predominant protein in SSc-associated fibrotic lesions. It is encoded by two genes, *COL1A1* and *COL1A2*. Each type I collagen molecule consists of two α1 and one α2 chains derived from these respective genes. Control of transcription is likely the most important regulatory mechanism determining the fibrotic phenotype [31]. Studies of the promoter region of *COL1A1* and *COL1A2* demonstrate up-regulated transcription factor binding in SSc versus normal fibroblasts and increased basal collagen mRNA levels [32,33]. Fibroblast-specific regulatory elements in the upstream region of murine *COL1A2* appear to be present in the *tight skin 1* (*tsk1*) mouse model of SSc [34]. Increased transcription of *COL1A2* may be controlled by the Sp1 transcription factor in SSc fibroblasts [35,36]. Mithramycin, which specifically inhibits the binding of Sp1 to DNA, diminishes collagen mRNA transcription and may have some therapeutic relevance in SSc. No studies have clearly documented germline mutations that influence Sp1 transcription factor binding in SSc fibroblasts or alterations in the *COL1A1* gene that are heritable factors important in SSc. In contrast, dinucleotide repeated segments in the upstream region and first intron of *COL1A2* correlating with increased gene expression were recently shown to occur more frequently in patients with SSc [37]. The dinucleotide repeats were associated most with male patients with SSc who had antitopoisomerase I, anticentromere, or anti–U1-RNP autoantibodies (Table 2) .

Progressive accumulation of collagen and other ECM constituents could occur secondary to an alteration in the activity or production of normally occurring degradative enzymes such as the matrix metalloproteinases (MMPs). Johnson *et al.* [38] showed that the frequency of the functionally relevant genotype in the promoter of *MMP1* was unaltered in patients with SSc compared with ethnically matched controls. Other MMP genes may be more important contributors to SSc, or inhibitors of the degradative enzymes' function may exist.

Fibrillin-1, *tsk1*, and human scleroderma

Fibrillin-1, the predominant microfibrillar component of elastic fibers and mutations that cause Marfan syndrome, has numerous epidermal growth factor-like binding domains and binds transforming growth factor-beta (TGFβ) in a latent form. A genomic duplication of exons 17–40 of the mouse fibrillin-1 gene (*fbn1*) has been responsible for the scleroderma-like phenotype of the *tsk1* mouse model [7,39]. Similarly, microsatellite markers near the human fibrillin-1 gene (*FBN1*) on chromosome 15q segregate with patients in the Choctaw cohort with SSc [40••]. While no gross duplications are present in *FBN1* from patients with SSc on the Southern blot [40••], specific single nucleotide polymorphisms (SNPs) and their resultant haplotypes were shown recently to be significantly more common in Choctaw and Japanese patients with SSc than in ethnically matched controls [41]. Studies of these same SNPs in other ethnic groups are in progress.

There are numerous potential functional consequences of abnormal fibrillin-1. Abnormal mouse fibrillin-1–containing microfibrils bind more TGFβ than the wild type protein [42]. In human SSc dermal fibroblasts, metabolic and electron microscopic studies have suggested that fibrillin-1 is unstable and more susceptible to degradation, which could lead to enhanced release of bound latent TGFβ and other cytokines [43]. *Tsk* mice [44] and most patients with SSc produce autoantibodies to fibrillin-1 [45,46•], which could be an effect of the unstable protein revealing cryptic epitopes to an activated immunologic milieu and causing an autoimmune response. Antifibrillin-1 autoantibodies tend to recognize different regions of fibrillin-1 depending on ethnic background [46•]. Nonetheless, studies have shown them to be highly specific for diffuse and limited forms of SSc [45] and localized scleroderma [47]. Whether they are pathogenic has yet to be determined.

Recent evaluations of the interaction between abnormal fibrillin-1 and the immune system in the *tsk* mouse may

Table 2. Genetic polymorphisms associated with systemic sclerosis

Gene	Polymorphism	Function of polymorphism	Association with SSc	Reference
COL1A2	Repeat haplotype	Increased output of type I collagen	Increased frequency in SSc (RR 6.93–32)	Hata *et al.* [37]
FBN1	SNP haplotypes	Unknown	Certain haplotypes more common in SSc	Tan *et al.* [41]
FN	RFLP genotypes	Unknown	Certain genotypes more common in SSc with fibrosing alveolitis (RR 1.99)	Avila *et al.* [53]
SPARC	MM	Unknown	Certain markers more frequent in SSc	Zhou *et al.* [54]
TGFβ1	Genotype	Increased output of TGFβ	Increased frequency in SSc (OR 3)	Crilly *et al.* [60]
TGFβ2	MM	Unknown	Certain markers more frequent in SSc	Susol *et al.* [58]
TGFβ3				
TIMP-1				
IL-4Rα	Missense mutation	Unknown	Mutation more common in SSc (RR 3.3)	Youn *et al.* [69]
CXCR2	SNPs	Unknown	Certain mutations more common in SSc (OR 2.33–2.67)	Renzoni *et al.* [71]
TNFβ	RFLP genotypes	Decreased output of TNFβ	More frequent in SSc	Pandey and Takeuchi [74]
TNFα	MM	Unknown	Increased frequency in Japanese SSc with anti-*Scl-70* antibodies	Takeuchi *et al.* [76]

FBN1—human fibrillin-1; FN—fibronectin; IL-4Rα—interleukin-4 receptor alpha; MM—microsatellite marker; OR—odds ratio; RFLP—restriction (enzyme) fragment length polymorphism; RR—relative risk; SNP—single nucleotide polymorphism; SPARC—secreted protein, acidic and rich in cystein; SSc—systemic sclerosis; TGF—transforming growth factor; TIMP-1—tissue inhibitor of metalloproteinase-1; TNF—tumor necrosis factor.

provide insight into the pathogenesis of human SSc. Studies of bone marrow transplantation from *tsk* mice to MHC-matched control mice suggest that abnormal fibrillin-1 leads to a state of autoimmunity in which activated cellular constituents of the immune system contribute significantly to the scleroderma-like phenotype [48]. To determine which cytokines are necessary for this process to occur, McGaha *et al.* [49] developed a *tsk* mouse line with targeted mutations in the interleukin-4 receptor alpha (IL-4Rα) or TGFβ genes. Both cytokine systems were implicated as inducers of fibroblast collagen production. The IL-4Rα knockout mice had essentially normal skin thickness and dermal hydroxyproline content and negative antitopoisomerase I antibodies. Likewise, heterozygous TGFβ knockout mice did not develop the typical *tsk* phenotype. Both knockout lines developed low levels of antifibrillin-1 antibodies and pulmonary emphysema, features of the *tsk* syndrome. The authors proposed that alternative activating factors may be present in the lung parenchyma of the mice as opposed to the skin.

The utility of mouse models in determining the pathogenesis of human SSc is debatable. Considerable evidence suggests that human SSc is a disease of autoimmunity. In addition, the bone marrow transplant studies mentioned previously suggest that the immune system has a significant pathogenic role in *tsk*. However, the *tsk* phenotype has been demonstrated experimentally in the absence of a functioning immune system [50,51], suggesting the existence of alternative sources of profibrotic cytokines such as mastocytes or the fibroblasts.

Fibronectin

Fibronectin (FN) is a complex glycoprotein involved in mediating the interactions between cells and their surrounding ECM. In the lung, FN is secreted by macrophages and serves as a chemoattractant and adhesive molecule for fibroblasts. Macrophages from patients with idiopathic pulmonary fibrosis produce 20 times as much FN as those from normal controls [52]. Certain FN restriction fragment length polymorphisms of unknown functional relevance are more common in patients with SSc than in controls, with essentially all of the differences in genotype frequency observed in those patients with SSc who have fibrosing alveolitis [53].

SPARC

SPARC (secreted protein, acidic and rich in cysteine) or osteonectin is a protein secreted by endothelial cells in response to injury that may be important in ECM remodeling. Highly significant differences were found in allele

frequencies for several microsatellite markers around SPARC between patients with SSc and controls in the Choctaw population, although the functional relevance of this finding is unknown [54].

Cytokines and Cell-signaling Molecules

Transforming growth factor-beta

Growth factors of the TGFβ family (TGFβ isoforms 1, 2, and 3) have been implicated in the pathogenesis of SSc and other fibrosing disorders because of their ability to stimulate the synthesis of ECM constituents and inhibitors of ECM degradation. Anti-TGFβ therapies, including monoclonal antibodies [55] and the *tsk* mouse knockout mentioned previously [49], can prevent fibrosis in animal models. The enhancing effects of TGFβ on collagen types I, III, VI, VII, and X, fibronectin, proteoglycan, and glycoprotein transcription may be mediated by connective tissue growth factor (CTGF), which is also abnormally upregulated in response to TGFβ in SSc fibroblasts [56].

Several recent investigations evaluated the association of polymorphisms in TGFβ family-related genes to SSc. No clear association was found in the Choctaw SSc cohort between the disease and microsatellite marker polymorphisms near the genes for TGFβ1, latent TGFβ1-binding protein, TGFβ receptors 1 and 2, PDGFα, or PDGFβ and their respective receptors [57]. In contrast, in the United Kingdom, a similar study of white patients reported associations between microsatellite markers for TGFβ2, TGFβ3, and tissue inhibitor of metalloproteinase-1 (TIMP-1) and SSc [58].

Two SNPs in the TGFβ1 gene have been shown to correlate with high TGFβ1 production and to have a propensity toward pulmonary fibrosis before and after lung transplantation [59]. Crilly *et al.* [60] recently showed that these same high output-associated SNPs are more common in patients with diffuse, but not limited, SSc. Other studies have focused on the importance of TGFβ receptors in mediating this cytokine's fibrosing effects in SSc. The expression of TGFβ receptors on SSc fibroblasts is upregulated [61], suggesting that some component of the fibroblasts' hyperresponsiveness to TGFβ stimulation [62] may be the result of autocrine signaling. Whether this high expression of receptors is related to genetic mutations or polymorphisms is unknown.

Recent work in elucidating the genetic basis of familial primary pulmonary hypertension (PPH) may have some relevance for SSc. Through extensive genetic mapping it has been demonstrated that heterozygous, pleomorphic mutations in the gene coding for bone morphogenetic protein receptor type 2 (*BMPR2*) are responsible for most cases of familial and many sporadic cases of PPH [63,64,65••]. *BMPR2* is a member of the TGFβ type 2 receptor family. Pathologically, the vascular lesions of PPH appear identical to those seen in the pulmonary hypertension of SSc and other connective tissue diseases. Tew *et al.* (unpublished observations) recently sequenced *BMPR2* in 12 patients with concomitant connective tissue diseases and pulmonary hypertension (nine of whom had SSc) and found no genetic abnormalities compared with ethnically matched controls or the published sequence.

Interleukin 4

Interleukin 4 (IL-4), which is secreted by T cells, activates and induces differentiation of B cells and promotes a T_H2 response, which is thought to contribute to human autoimmune disease. IL-4 also stimulates collagen production by fibroblasts [66]. The administration of anti–IL-4 antibodies diminishes collagen deposition in the *tsk* mouse model [67]. IL-4 mRNA transcription is upregulated in the peripheral blood leukocytes of patients with SSc [68]. In addition, SSc fibroblasts overexpress IL-4Rα [62]. Several potentially functionally relevant IL-4 gene polymorphisms exist, but they have not been evaluated systematically in patients with SSc. A mutation in the IL-4 receptor that leads to a more avid T_H2 response than the wild type receptor was shown recently to occur more commonly in patients with SSc, primary Sjögren's syndrome, and SLE [69].

Interleukin 8

Interleukin 8 (IL-8) is a potent chemoattractant for neutrophils, the accumulation of which in the lower respiratory tract is thought to be critical in the pathogenesis of pulmonary fibrosis. Bronchoalveolar lavage fluid from patients with SSc-related fibrosing alveolitis, and those with idiopathic fibrosing alveolitis, demonstrates higher concentrations of IL-8 compared with controls [70]. Homozygosity for two SNPs in the 3′ untranslated region of the gene coding for CXCR2, a member of the IL-8 receptor family, is more common among patients with SSc with and without fibrosing alveolitis compared with controls [71]. However, CXCR2 binds chemokines besides IL-8.

Tumor necrosis factor

The genes for TNF map within the HLA complex and code for pro-inflammatory cytokines. TNF polymorphisms have been studied extensively in RA; promoter region and intragenic polymorphisms have been described. An elevated serum TNFα level has been associated with pulmonary fibrosis in SSc [72]. The role of TNFα in other aspects of SSc makes the implications of this observation unclear. Studies of differential gene regulation suggest that TNFα acts to counter the deleterious effects of TGFα on CTGF and downstream transcription at the level of the skin fibroblast [73]. One study evaluating the frequency of TNFα and TNFβ gene polymorphisms in SSc showed that homozygous genotypes of the $TNFβ^{+252}$ locus were significantly different between patients and controls [74]. The homozygous TNFβ1 genotype is associated with low levels of TNFα production and would theoretically be protective against pulmonary fibrosis. The frequency of

this genotype was decreased in the patients with SSc, the frequency of TNFβ2 homozygosity (associated with the highest levels of TNFα production [75]) was increased in patients relative to controls [74]. In a related study, the *TNFa13* microsatellite was shown to be a genetic marker for Japanese patients with SSc who had antitopoisomerase I autoantibodies but not for German patients with SSc [76]. However, *TNFa13* was in positive linkage disequilibrium with *DRB1*1502*, an HLA marker associated with SSc, underscoring that studies of TNF polymorphisms must be interpreted cautiously given the location of TNF within the MHC complex.

Metabolic Enzymes

Two studies of enzymes involved in the metabolism of external (organic solvents) and internal substances (products of oxidative metabolism) proposed to be associated with SSc pathogenesis illustrate the dichotomy of genetic effects in this disorder. A specific cytochrome P450 allele was found to be statistically more common among individuals who developed SSc in the setting of organic solvent exposure as opposed to those with sporadic SSc and normal controls. However, the number of subjects was small, resulting in extremely wide 95% confidence intervals for the odds ratio associated with this allele (*CYP2E1*3*) [77]. In contrast, a study of glutathione S-transferase (GST) genotypes revealed no increased frequency of null alleles in those with SSc from three ethnic groups compared with ethnically matched controls. However, null alleles for one isotype (GST-T1) were associated with hypertension and SSc-related pulmonary involvement [78]. Genetic polymorphisms influence the course of SSc without influencing one's likelihood of developing the disease, and the converse is most likely true.

Conclusions

As in other systemic autoimmune disorders, a multitude of genetic factors may be important in the predisposition to or manifestations of SSc. SSc is among a select group of autoimmune diseases in its apparent dependence on immunologic and extracellular matrix protein abnormalities for the development of its characteristic features, but genetic similarities between SSc and other systemic autoimmune illnesses probably exist. Genome-wide scans show that SLE, RA, autoimmune thyroid disease, insulin-dependent diabetes, and other diseases demonstrate genetic linkage to similar regions of chromosomes that likely contain genes responsible for loss of immune tolerance [79,80,81•]. A genome-wide scan for SSc genes is in progress in the Choctaw population and other US families. A paradigm to explain how such dissimilar diseases could share one origin would invoke elements in the remainder of the host's genetic background as the determinant of which illness would develop.

The impact of genetic factors—such as those that determine how people recognize and react to their environment, how cytokines communicate among cellular components within and outside the immune system, and how ECM components create the materials between cells—have been reviewed here. How powerful new technologies to assess the workings of individual cells in diseases such as SSc can explain pathogenesis remains to be seen. For example, will microarray studies provide diagnostic utility, identifying the characteristic gene activation "fingerprint" of SSc? Will their data eventually lead to the discovery of an underlying genetic anomaly that explains the alteration in gene expression? The recognition of which genes are activated or suppressed in the course of a disease does not explain the underlying cause, but clearly such knowledge is one step closer to the discovery of the source.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.•• Mayes MD: **Epidemiologic studies of environmental agents and systemic autoimmune diseases.** *Environ Health Perspect* 2000, **107:**743–748.

A critical review of epidemiologic studies that demonstrates a lack of evidence supporting an environmental exposure significantly contributing to the development to systemic sclerosis.

2. Feghali CA, Wright TM: **Epidemiologic and clinical study of twins with scleroderma [abstract].** *Arthritis Rheum* 1995, **38:**S308.
3. McHugh NJ, Harvey GR, Whyte J, *et al.*: **Segregation of autoantibodies with disease in monozygotic twin pairs discordant for systemic sclerosis: three further cases.** *Arthritis Rheum* 1995, **38:**1845–1850.
4. Arnett FC: **HLA and autoimmunity in scleroderma (systemic sclerosis).** *Int Rev Immunol* 1995, **12:**107–128.
5. Arnett FC, Howard RF, Tan FK, *et al.*: **Increased prevalence of systemic sclerosis in a Native American tribe in Oklahoma: association with an Amerindian HLA haplotype.** *Arthritis Rheum* 1996, **39:**1362–1370.
6. Kuwana M, Kaburaki J, Arnett FC, *et al.*: **Influence of ethnic background on clinical and serologic features in patients with systemic sclerosis and anti-DNA topoisomerase I antibody.** *Arthritis Rheum* 1999, **42:**465–474.
7. Siracusa LD, McGrath R, Ma Q, *et al.*: **A tandem duplication within the fibrillin 1 gene is associated with the mouse tight skin mutation.** *Genome Res* 1996, **6:**300–313.
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:**581–590.
9. Tan FK, Arnett FC: **Genetic factors in the etiology of systemic sclerosis and Raynaud phenomenon.** *Curr Opin Rheumatol* 2000, **12:**511–519.
10. Mayes MD: **Scleroderma epidemiology.** *Rheum Dis Clin North Am* 1996, **22:**751–764.
11. Manolios N, Dunckley H, Chivers T, *et al.*: **Immunogenetic analysis of 5 families with multicase occurrence of scleroderma and/or related variants.** *J Rheumatol* 1995, **22:**85–92.
12.•• Englert H, Small-McMahon J, Chambers P, *et al.*: **Familial risk estimation on systemic sclerosis.** *Aust N Z J Med* 1999, **29:**36–41.

The first study using a large population-based study from Sydney, Australia, that formally assessed the relative risk for familial recurrence of systemic sclerosis.

13.•• Arnett FC, Cho M, Chatterjee S, *et al.*: **Familial occurrence frequencies and relative risks for systemic sclerosis (scleroderma) in three United States cohorts.** *Arthritis Rheum* 2001, **44:**1359–1362.

From Houston, Texas, and the Michigan Systemic Sclerosis Registry, this study is the first from the United States to formally estimate the familial recurrence rate of systemic sclerosis (SSc) from three large SSc cohorts.

14. Laing TJ, Gillespie BW, Toth MB, *et al.*: **Racial differences in scleroderma among women in Michigan.** *Arthritis Rheum* 1997, **40:**734–742.

15. Lambert NC, Distler O, Müller-Ladner U, *et al.*: **HLA-DQA1*0501 is associated with diffuse systemic sclerosis in Caucasian men.** *Arthritis Rheum* 2000, **43:**2005–2010.

16. Vlachoyiannopoulos PG, Dafni UG, Pakas I, *et al.*: **Systemic scleroderma in Greece: low mortality and strong linkage with HLA-DRB1*1104 allele.** *Ann Rheum Dis* 2000, **59:**359–367.

17.• Reveille JD, Fischbach M, McNearney T, *et al.*: **Systemic sclerosis in three U.S. ethnic groups: a comparison of clinical, sociodemographic, serologic and immunogenetic determinants.** *Semin Arthritis Rheum* 2001, **30:**332–346.

The baseline report of the GENISOS study demonstrating important sociodemographic, clinical, and serologic differences among a prospective multi-ethnic systemic sclerosis cohort.

18. Kuwana M, Inoko H, Kameda H, *et al.*: **Association of human leukocyte antigen class II genes with autoantibody profiles, but not with disease susceptibility in Japanese patients with systemic sclerosis.** *Intern Med* 1999, **38:**336–344.

19. Susol E, Pepper C, Harrick A, *et al.*: **Association of HLA class II genes with autoantibody production but not with disease susceptibility in UK Caucasian systemic sclerosis patients [abstract].** *Arthritis Rheum* 2000, **43:**S263.

20. Briggs D, Stephens C, Vaughan R, *et al.*: **A molecular and serologic analysis of the major histocompatibility complex and complement component C4 in systemic sclerosis.** *Arthritis Rheum* 1993, **36:**943–954.

21. Reveille JD, Brady J, MacLeod-St. Clair M, Durban E: **HLA-DPB1 alleles and autoantibody subsets in systemic lupus erythematosus, Sjögren's syndrome and progressive systemic sclerosis: a question of disease relevance.** *Tissue Antigens* 1992, **40:**45–48.

22. Tan FK, Stivers DN, Arnett FC, *et al.*: **HLA haplotypes and microsatellite polymorphisms in and around the major histocompatibility complex region in Native American population with a high prevalence of scleroderma (systemic sclerosis).** *Tissue Antigens* 1999, **53:**74–80.

23. Falkner D, Wilson J, Fertig N, *et al.*: **Studies of HLA-DR and DQ alleles in systemic sclerosis patients with autoantibodies to RNA polymerases and U3-RNP (fibrillarin).** *J Rheumatol* 2000, **27:**1196–1202.

24. Arnett FC, Reveille JD, Goldstein R, *et al.*: **Autoantibodies to fibrillarin in systemic sclerosis (scleroderma): an immunogenetic, serologic, and clinical analysis.** *Arthritis Rheum* 1996, **39:**1151–1160.

25. Falkner D, Wilson J, Medsger TA Jr, Morel PA: **HLA and clinical associations in systemic sclerosis patients with anti-Th/To antibodies.** *Arthritis Rheum* 1998, **41:**74–80.

26. Nelson JL, Furst DE, Maloney S, *et al.*: **Microchimerism and HLA-compatible relationships of pregnancy in scleroderma.** *Lancet* 1998, **351:**559–562.

27. Artlett CM, Smith JB, Jimenez SA: **Identification of fetal DNA and cells in skin lesions from women with systemic sclerosis.** *N Engl J Med* 1998, **338:**1186–1191.

28. Maloney S, Smith A, Furst DE, *et al.*: **Microchimerism of maternal origin persists into adult life.** *J Clin Invest* 1999, **104:**41–47.

29. Lambert NC, Bianchi DW, Johnson K, *et al.*: **Microchimerism in systemic sclerosis [abstract].** *Arthritis Rheum* 2000, **43:**S315.

30. Lambert NC, Evans PC, Hashizumi TL, *et al.*: **Persistent fetal microchimerism in T lymphocytes is associated with HLA-DQA1*0501: implications in autoimmunity.** *J Immunol* 2000, **164:**5545–5548.

31. Bornstein P, Sage H: **Regulation of collagen gene expression.** *Prog Nucleic Acid Res Mol Biol* 1989, **37:**67–106.

32. Hitraya EG, Varga J, Artlett CM, Jimenez SA: **Identification of elements in the promoter region of the α1(I) procollagen gene involved in its up-regulated expression in systemic sclerosis.** *Arthritis Rheum* 1998, **41:**2048–2058.

33. Saitta B, Gaidarova S, Cicchillitti L, Jimenez SA: **CCAAT binding transcription factor binds and regulates human COL1A1 promoter activity in human dermal fibroblasts.** *Arthritis Rheum* 2000, **43:**2219–2229.

34. Denton CP, Zheng B, Shiwen X, *et al.*: **Activation of a fibroblast-specific enhancer of the Proα2(I) collagen gene in tight-skin mice.** *Arthritis Rheum* 2001, **44:**712–722.

35. Ihn H, Tamaki K: **Increased phosphorylation of transcription factor Sp1 in scleroderma fibroblasts.** *Arthritis Rheum* 2000, **43:**2240–2247.

36. Artlett CM, Chen SJ, Varga J, Jimenez SA: **Modulation of basal expression of the human alpha1(I) procollagen gene (COL1A1) by tandem NF-1/Sp1 promoter elements in normal human dermal fibroblasts.** *Matrix Biol* 1998, **17:**425–434.

37. Hata RI, Akai J, Kimura A, *et al.*: **Association of functional microsatellites in the human type I collagen α2 chain (COL1A2) gene with systemic sclerosis.** *Biochem Biophys Res Com* 2000, **272:**36–40.

38. Johnson RW, Reveille JD, McNearney T, *et al.*: **Lack of association of a functionally relevant single nucleotide polymorphism of matrix metalloproteinase-1 promoter with systemic sclerosis (scleroderma).** *Genes Immun* 2001, **2:**273–275.

39. Kielty CM, Raghunath M, Siracusa LD, *et al.*: **The *tight skin* mouse: demonstration of mutant fibrillin-1 production and assembly into abnormal microfibrils.** *J Cell Biol* 1998, **140:**1159–1166.

40.•• Tan FK, Stivers DN, Foster MW, *et al.*: **Association of microsatellite markers near the fibrillin 1 gene on human chromosome 15q with scleroderma in a Native American population.** *Arthritis Rheum* 1998, **41:**1729–1737.

This important study demonstrated genetic linkage between FBN1, the mouse homologue that is abnormal in the tight skin mouse model of systemic sclerosis (SSc), and human SSc.

41. Tan FK, Wang N, Kuwana M, *et al.*: **Association of fibrillin 1 single nucleotide polymorphism haplotypes with systemic sclerosis in Choctaw and Japanese populations.** *Arthritis Rheum* 2001, **44:**893–901.

42. Saito S, Nishimura H, Brumeanu T-D, *et al.*: **Characterization of mutated protein encoded by partially duplicated fibrillin-1 gene in tight skin (tsk) mice.** *Mol Immunol* 1999, **36:**169–176.

43. Wallis DD, Tan FK, Kielty CM, *et al.*: **Abnormalities in fibrillin-1-containing microfibrils in dermal fibroblast cultures from patients with systemic sclerosis (scleroderma).** *Arthritis Rheum* 2001, **44:**1855–1864.

44. Murai C, Saito S, Kasturi KN, Bona CA: **Spontaneous occurrence of anti-fibrillin-1 autoantibodies in tight skin mice.** *Autoimmunity* 1998, **28:**151–155.

45. Tan FK, Arnett FC, Antohi S, *et al.*: **Autoantibodies to the extracellular matrix microfibrillar protein, fibrillin-1, in patients with scleroderma and other connective tissue diseases.** *J Immunol* 1999, **163:**1066–1072.

46.• Tan FK, Arnett FC, Reveille JD, *et al.*: **Autoantibodies to fibrillin 1 in systemic sclerosis: ethnic differences in antigen recognition and lack of correlation with specific clinical features or HLA alleles.** *Arthritis Rheum* 2000, **43:**2464–2471.

This study demonstrates the specificity of antifibrillin-1 antibodies for systemic sclerosis and investigates the ethnically determined variations in recognized epitopes.

47. Arnett FC, Tan FK, Uziel Y, *et al.*: **Autoantibodies to the extracellular matrix microfibrillar protein, fibrillin 1, in patients with localized scleroderma.** *Arthritis Rheum* 1999, **42:**2656–2659.

48. Phelps RG, Daian C, Shibata S, *et al.*: **Induction of skin fibrosis and autoantibodies by infusion of immunocompetent cells from tight skin mice into C57BL/6 pa/pa mice.** *J Autoimmun* 1993, **6:**710–718.

49. McGaha T, Saito S, Phelps RG, *et al.*: **Lack of skin fibrosis in tight skin (TSK) mice with targeted mutation in the interleukin-4Rα and transforming growth factor-β genes.** *J Invest Dermatol* 2001, **116:**136–143.
50. Siracusa LD, McGrath R, Fisher JK, Jimenez SA: **The mouse tight skin (tsk) phenotype is not dependent on the presence of mature T and B lymphocytes.** *Mamm Genome* 1998, **9:**907–909.
51. Dodig TD, Mack KT, Cassarino DF, Clark SH: **Development of the tight-skin phenotype in immune-deficient mice.** *Arthritis Rheum* 2001, **44:**723–727.
52. Rennard SI, Hunninghake GW, Bitterman PB, Crystal RG: **Production of fibronectin by the human alveolar macrophage: mechanism for the recruitment of fibroblasts to sites of tissue injury in interstitial lung disease.** *Proc Natl Acad Sci USA* 1981, **78:**7147–7151.
53. Avila JJ, Lympany PA, Pantelidis P, Welsh KI, *et al.*: **Fibronectin gene polymorphisms associated with fibrosing alveolitis in systemic sclerosis.** *Am J Respir Cell Mol Biol* 1999, **20:**106–112.
54. Zhou XD, Stivers DN, Tan FK, Arnett FC: **Secreted protein, acidic, cysteine-rich (SPARC) or osteonectin in systemic sclerosis (scleroderma): altered gene expression in dermal fibroblasts and associated microsatellite markers [abstract].** *Arthritis Rheum* 1999, **42:**S169.
55. McCormick LL, Zhang Y, Tootell, Gilliam AC: **Anti-TGF-β treatment prevents skin and lung fibrosis in murine scleroderma-tous graft-versus-host disease: a model for human scleroderma.** *J Immunol* 1999, **163:**5693–5699.
56. Shi-wen X, Pennington D, Holmes A, *et al.*: **Autocrine overexpression of CTGF maintains fibrosis: RDA analysis of fibrosis genes in systemic sclerosis.** *Exp Cell Res* 2000, **259:**213–224.
57. Zhou X, Tan FK, Stivers DN, Arnett FK: **Microsatellites and intragenic polymorphisms of transforming growth factor β and platelet-derived growth factor and their receptor genes in Native Americans with systemic sclerosis (scleroderma).** *Arthritis Rheum* 2000, **43:**1068–1073.
58. Susol E, Rands AL, Herrick A, *et al.*: **Association of markers for *TGFβ* 3, *TGFβ* 3 and *TIMP1* with systemic sclerosis.** *Rheumatology (Oxford)* 2000, **39:**1332–1336.
59. Awad MR, El-Gamel A, Hasleton P, *et al.*: **Genotypic variation in the transforming growth factor β1 gene: association with transforming growth factor-beta1 production, fibrotic lung disease, and graft fibrosis after lung transplantation.** *Transplantation* 1998, **66:**1014–1020.
60. Crilly A, Hamilton J, Clarke C, *et al.*: **Analysis of TGFβ1 gene polymorphisms in patients with limited and diffuse scleroderma [abstract].** *Arthritis Rheum* 2000, **43:**S168.
61. Kawakami T, Ihn H, Xu W, *et al.*: **Increased expression of TGF-β receptors by scleroderma fibroblasts: evidence for contribution of autocrine TGF-β signaling to scleroderma phenotype.** *J Invest Dermatol* 1998, **110:**47–51.
62. Serpier H, Gillery P, Salmon-Her V, *et al.*: **Antagonistic effects of interferon-γ and interleukin-4 on fibroblast cultures.** *J Invest Dermatol* 1997, **109:**158–162.
63. Machado RD, Pauciulo MW, Thomson JR, *et al.*: ***BMPR2* haploinsufficiency as the inherited molecular mechanism for primary pulmonary hypertension.** *Am J Hum Genet* 2001, **68:**92–102.
64. Deng Z, Morse JH, Slager SL, *et al.*: **Familial primary pulmonary hypertension (Gene PPH1) is caused by mutations in the bone morphogenetic protein receptor-II gene.** *Am J Hum Genet* 2000, **67:**737–744.
65.•• The International PPH Consortium: **Heterozygous germline mutations in *BMPR2*, encoding a TGF-β receptor, cause familial primary pulmonary hypertension.** *Nature Genet* 2000, **26:**81–84.

These three articles report the linkage of familial primary pulmonary hypertension to mutations in *BMPR2*, which codes for a tumor growth factor-beta (TGFβ) receptor. This may represent a model for the influence of genetics on TGFβ-related phenomena in systemic sclerosis.

66. Atamas SP, Yurovsky VV, Wise R, *et al.*: **Production of type 2 cytokines by CD8+ lung cells is associated with greater decline in pulmonary function in patients with systemic sclerosis.** *Arthritis Rheum* 1999, **42:**1168–1178.
67. Ong C, Wong C, Roberts CR, *et al.*: **Anti-IL-4 treatment prevents dermal collagen deposition in the tight-skin mouse model of scleroderma.** *Eur J Immunol* 1998, **28:**2619–2629.
68. Sakkas LI, Tourtellotte C, Berney S, *et al.*: **Increased levels of alternatively spliced interleukin 4 (IL-4delta2) transcripts in peripheral blood mononuclear cells from patients with systemic sclerosis.** *Clin Diagn Lab Immunol* 1999, **6:**660–664.
69. Youn J, Hwang S-H, Cho C-S, *et al.*: **Association of the interleukin-4 receptor α variant *Q576R* with Th1/Th2 imbalance in connective tissue disease.** *Immunogenetics* 2000, **51:**743–746.
70. Bolster MB, Ludwicka A, Sutherland SE, *et al.*: **Cytokine concentrations in bronchoalveolar lavage fluid of patients with systemic sclerosis.** *Arthritis Rheum* 1997, **40:**743–751.
71. Renzoni E, Lympany P, Sestini P, *et al.*: **Distribution of novel polymorphisms of the interleukin-8 and CXC receptor 1 and 2 genes in systemic sclerosis and cryptogenic fibrosing alveolitis.** *Arthritis Rheum* 2000, **43:**1633–1640.
72. Hasegawa M, Fujimoto M, Kikuchi K, Takahara K: **Elevated serum tumor necrosis factor-α levels in patients with systemic sclerosis: association with pulmonary fibrosis.** *J Rheumatol* 1997, **24:**663–665.
73. Abraham DJ, Shiwen X, Black CM, *et al.*: **Tumor necrosis factor α suppresses the induction of connective tissue growth factor by transforming growth factor-β in normal and scleroderma fibroblasts.** *J Biol Chem* 2000, **275:**15220–15225.
74. Pandey JP, Takeuchi F: **TNF-α and TNF-β gene polymorphisms in systemic sclerosis.** *Hum Immunol* 1999, **60:**1128–1130.
75. Pociot F, Briant L, Jongeneel CV, *et al.*: **Association of tumor necrosis factor (TNF) and class II major histocompatibility complex alleles with the secretion of TNF-α and TNF-β by human mononuclear cells: a possible link to insulin-dependent diabetes mellitus.** *Eur J Immunol* 1993, **23:**224–231.
76. Takeuchi F, Nabeta H, Fussel M, *et al.*: **Association of the TNFa13 microsatellite with systemic sclerosis in Japanese patients.** *Ann Rheum Dis* 2000, **59:**293–296.
77. Povey A, Guppy MJ, Wood M, *et al.*: **Cytochrome P2 polymorphisms and susceptibility to scleroderma following exposure to organic solvents.** *Arthritis Rheum* 2001, **44:**662–665.
78. Tew MB, Reveille JD, Arnett FC, *et al.*: **Glutathione S-transferase genotypes in systemic sclerosis and their association with clinical manifestations in early disease.** *Genes Immun* 2001, **2:**236–238.
79. Becker KG, Simon RM, Bailey-Wilson JE, *et al.*: **Clustering of non-major histocompatibility complex susceptibility candidate loci in human autoimmune diseases.** *Proc Natl Acad Sci USA* 1998, **95:**9979–9984.
80. Gaffney PM, Ortmann WA, Selby SA, *et al.*: **Genome screening in human systemic lupus erythematosus: results from a second Minnesota cohort and combined analyses of 187 sib-pair families.** *Am J Hum Genet* 2000, **66:**547–556.
81.• Jawaheer D, Seldin MF, Amos CI, *et al.*: **A genomewide screen in multiplex rheumatoid arthritis families suggests genetic overlap with other autoimmune diseases.** *Am J Hum Genet* 2001, **68:**927–936.

This article is representative of a number of genomewide studies published recently concerning autoimmune disorders. It highlights the interesting linkage similarities reported between rheumatoid arthritis and other prototypic autoimmune diseases.