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The genetics of scleroderma: looking into the postgenomic era

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Abstract

Purpose of review—The last decade has seen enormous progress in understanding genetic associations of systemic sclerosis to explain the observed heritability. This review highlights the most recent findings and places them in the context of proposed functional roles.

Recent findings—Over 30 genes and gene regions have now been identified as scleroderma susceptibility loci. These include both human leukocyte antigen (HLA) and non-HLA genes, most of which involve immune-related pathways and modifiers of immune function. Many of these associations have also been reported in other systemic autoimmune diseases and suggest that there are multiple autoimmunity genes resulting in disease occurrence.

Summary—In spite of these advances, only a small proportion of the heritability of systemic sclerosis has been explained. Ongoing studies include fine mapping and sequencing studies to identify causal variants, whereas other studies focus on functional consequences of these variants in order to identify the link between these genetic variants and disease susceptibility. Such knowledge should lead to more targeted and effective treatment in this disease.

Keywords

genetic variants; genome-wide association studies; scleroderma; single nucleotide polymorphisms; systemic sclerosis

INTRODUCTION

The last decade, and particularly the past year, has been one of enormous progress in the identification of genetic loci that contribute to systemic sclerosis (SSc) susceptibility.

Multiple genetic association studies have been conducted to address the following key questions related to SSc: What are the susceptibility loci associated with SSc? Are there different genetic variants that influence the development of the different clinical subphenotypes of SSc? How does the presence of these variants result in clinical disease?

In general, two approaches are used to study genetic associations, namely, a candidate gene approach and a genome-wide association study (GWAS). Both methods rely on the identification of genetic variants called single nucleotide polymorphisms (SNPs) and determine an odds ratio (OR), that is, the likelihood that the variant occurs more or less

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Conflicts of interest

There are no conflicts of interest.

frequently in the cases than in the controls. An OR greater than 1 indicates that the SNP of interest (allele) is more frequently found in cases than controls and is considered to be a risk locus. Conversely, an OR less than 1 indicates that the SNP is less frequently seen in cases than controls, and thus is considered protective.

Candidate gene studies

In this approach, one or more SNPs occurring in suspected disease-related genes are tested in a case-control comparison. Candidate genes are chosen either because they make biological sense or because they have been reported as associated with other autoimmune diseases.

Genome-wide association study approach

GWAS, on the other hand, makes no *a priori* assumptions about what loci are likely to be involved, but scan across the entire genome with tag SNPs that identify gene regions.

The major advantage of the candidate gene approach is that one can test for a particular SNP with known functional consequences, whereas the advantage to the GWAS approach is that it is unbiased and can identify novel genes that were not previously suspected to be disease-associated. For both approaches (candidate gene and GWAS), association is first tested in a discovery cohort and then repeated in a nonoverlapping group of cases and controls.

ANALYSIS BY SUBPHENOTYPES

From a clinical point of view, SSc is a heterogeneous disease with a broad spectrum of disease severity. The SSc clinical subphenotypes of diffuse or limited cutaneous involvement are helpful but still imprecise. Classifying the disease according to mutually exclusive autoantibody subsets provides objective and more homogeneous categories but excludes that proportion of cases who lack these antibodies thus decreasing statistical power. Also, data on anti-RNA polymerase III antibody status (accounting for almost 20% of SSc) is lacking in many patients, precluding analysis in this subset. Analysis by organ involvement, particularly interstitial lung disease (ILD, fibrosing alveolitis) or pulmonary arterial hypertension (PAH) also provides an opportunity to detect genetic influences on specific disease manifestations but again limits the number of cases available for analysis.

MAJOR ASSOCIATION SIGNALS IN SYSTEMIC SCLEROSIS

Table 1 [1–7,8■,9,10■,11–16,17■,18–22,23■,24,25■, 26■,27–40] lists selected nonmajor histocompatibility complex (MHC) genetic loci that have been associated with SSc. Although the precise role that these gene variants play in disease pathogenesis remains unclear, they can be grouped into several broad categories.

Gene variants related to lymphocyte activation and signaling

The gene *BANK1* codes for B-cell scaffold protein with ankyrin repeats-1 and has been studied in two independent candidate gene studies [1,2], both of which showed a statistically significant association but in opposite directions in terms of protection or risk. The study by Dieudé *et al.* [1] reported that the minor allele of the SNP rs10516487 was protective (less frequent in cases than in controls), whereas Rueda *et al.* [2] found that this same allele was a risk factor for the disease (more frequent in cases than in controls). These contradictory findings remain to be resolved and are, in fact, the exception as most other studies of gene variants in SSc have provided concordant results. The Rueda study also analyzed subsets of SSc cases and reported that the risk association was seen most strongly in those with diffuse cutaneous SSc and in those with the antitopoisomerase antibody (ATA). The role of the

BANK1 variant in SSc susceptibility is unclear but presumably is related to changes in B-cell signaling threshold. Future studies and combined or meta-analysis will have to be done to resolve this controversy.

The gene *BLK* codes for B-lymphocyte kinase and has been reported as a risk factor for SSc in those of European [3,4] as well as Japanese ancestry [5]. In the meta-analysis [4], an association was seen in the anticentromere antibody (ACA) positive subgroup, but not in the ATA-positive group. The proposed mechanism is a disrupted gene expression in B cells especially via the nuclear factor kappa B (NF- κ B) signaling pathway.

CD247 codes for the zeta chain of the T-cell receptor (TCR) and was first identified through a GWAS approach [6], confirmed in a subsequent candidate gene study [7] and then replicated in a separate GWAS study [8]. In all three populations, the minor allele was found to be protective, that is, it was less frequently present in cases than in controls (OR significantly less than 1.0). Variants in this gene may contribute to dysregulation of T-cell activation through the T-cell receptor.

CSK codes for c-Src tyrosine kinase and was found to be associated with SSc in a GWAS follow-up study [9]. The gene product of CSK is a major inhibitor of an enzyme (Src kinase) that promotes myofibroblast differentiation *in vitro* and fibrosis *in vivo* in experimental mouse models [41]. At least theoretically, a less potent inhibitor of this profibrotic pathway could contribute to fibrosis in SSc.

IRAK1 codes for interleukin (IL) 1 receptor-associated kinase-1 and is the only example of a sex chromosome gene reported to influence SSc susceptibility [10]. The gene product regulates NF- κ B through T-cell receptor signaling and Toll-like receptor (TLR) activation as well as the induction of interferons (IFNs) α and gamma [42]. This study found that a recessive model of inheritance was the best fit to the data, that is, the highest risk was found in those who were homozygous for the minor allele. In addition, the homozygous genotype was more frequent among diffuse cutaneous SSc (dcSSc) compared with limited disease and among ATA-positive cases than ACA-positive cases, suggesting that it is a risk factor for disease severity as well as for susceptibility. Although this finding has yet to be replicated by others, the fact that the association involves the X chromosome is particularly intriguing in this female-predominant disease.

PTPN22 codes for protein tyrosine phosphatase nonreceptor-22 and was investigated in SSc after it was established as a risk allele for rheumatoid arthritis (RA), SLE and other autoimmune diseases. Although early studies of small numbers [11,12] did not find an association with SSc, larger studies clearly demonstrated an increased risk in both US cohorts (Americans of European and African ancestry) [13] and European cohorts [14,15]. This gene variant results in an amino acid change in the catalytic domain of the enzyme that is thought to promote autoimmunity by reducing the threshold for TCR signaling [43].

TNFAIP3 codes for tumor necrosis factor α -induced protein-3 and has been identified as a risk factor in SSc [9,16] particularly with dcSSc, ILD (fibrosing alveolitis) and PAH as well as in individuals with SSc and other autoimmune diseases [17]. The gene product regulates ubiquitination (the addition or removal of ubiquitin) that is a common means of regulating immune signaling pathways.

TNFSF4 codes for tumor necrosis factor ligand superfamily member-4 (also known as OX40 ligand) and has been associated with SSc in two studies [18,19] with divergent results. A recently reported meta-analysis, however, [20] has helped to clarify the association noting a risk for all SSc but most strongly in the limited form (limited cutaneous SSc) and in ACA-positive cases.

TNIP1 codes for TNFAIP3-interacting protein-1 that negatively regulates NF- κ B activity. A recent GWAS demonstrated that a variant in this gene increased the risk for SSc [8]. Studies of gene expression in lesional skin biopsies and in cultured fibroblasts suggested that the TNIP1 protein was decreased. The authors speculated that reduced inhibition of NF- κ B could favor inflammatory immune responses leading to fibrosis.

Gene variants related to innate immunity: interferon pathway-associated genes

The type I IFNs are a family of related proteins that were originally defined by their ability to interfere with viral replication in cell cultures [44,45]. The type I IFN system includes the IFN regulatory factors 5, 7 and 8 coded by *IRF5*, *IRF7* and *IRF8*. Variants in these genes have been associated with SSc either with the disease overall or with particular subsets in both European ancestry and Japanese populations [21,22,23,24,25].

TLRs are part of the pattern-recognition receptors that are key to innate immunity. A gene variant in the *TLR2* gene that codes for TLR2 (but not variants in other TLRs) has been associated with an increased risk for dcSSc, particularly antitopoisomerase-positive cases and those with PAH [26].

Gene variants related to transcription factors

Candidate gene studies in European ancestry and Japanese cohorts [27–29] and both SSc GWAS studies [6,8] have validated the association of SSc with variants in the gene *STAT4* (coding for signal transducer and activator of transcription protein-4) that plays a key role in both the innate as well as the adaptive immune systems particularly in the development of T helper type-1 (Th1) cells from naive CD4⁺ T cells.

STAT4 can be considered an autoimmunity locus as it has now been firmly associated with SLE, RA, primary biliary cirrhosis as well as SSc (for review see [46]). It is not clear whether the variants that predispose to SSc are the same as those that confer susceptibility to these other autoimmune diseases.

Gene variants related to cytokines and cytokine receptors

Variants in genes that code for several cytokines and cytokine receptors have been reported to be associated with SSc as summarized in Table 1. SSc genetic studies have thus far identified a relatively small number of genes in this category. These include the genes *IL2RA* that codes for IL-2 receptor α , a marker of regulatory T cells [31]; *IL12RB2* coding for IL-12 receptor β 2 that plays a role in Th1 cell differentiation [32] and *MIF* which codes for macrophage migration inhibitory factor and which induces adhesion molecules on endothelial cells possibly contributing to SSc vasculopathy [33,34].

Other genetic associations

In addition to the gene variants noted above, several additional but less well established associations deserve mentioning. *CAV1*, the gene that codes for Caveolin-1, is of interest because mice lacking CAV1 develop skin and lung tissue fibrosis as well as PAH [47]. An allele in this gene was identified as being protective for SSc, particularly for the limited cutaneous subset and individuals with this allele were noted to have increased CAV1 protein expression [35]. This is one of the few genes reported to be associated with SSc that has a direct role in tissue fibrosis.

CD226, which codes for DNA accessory molecule-1 and which is involved in the adhesion and costimulation of T cells, has been reported to be associated with risk for SSc particularly in those with ILD [36,37].

An analysis of copy number variations in the gene *FCGR3B*, which codes for the low-affinity Fc gamma receptor 3B, has found that risk for SSc is greater in those with a deletion at this locus or with a single copy number, that is, those with a copy number of 1 versus those with 2 or more [38].

Finally, there is conflicting data regarding the association of a SNP in the gene *ITGAM* which codes for integrin α M precursor. One group has reported an increased risk [39], whereas another group failed to find an association [40].

THE MAJOR HISTOCOMPATIBILITY COMPLEX

No discussion of SSc susceptibility loci can be complete without a discussion of the MHC region. Multiple studies, using genotyping techniques based on sequencing [48–51] as well as GWAS studies based on SNP analysis [6,8], have reproducibly identified several human leukocyte antigen (HLA) class II associations with SSc, both with the overall disease and with individual autoantibody subsets in populations of many different ancestries. This review will focus on two recent additions to our knowledge in this area, particularly the association of variants in *NOTCH4* in the HLA class III region [25] and *PSORS1A1* near the class II HLA-DRB locus [8]. Because of the high degree of linkage disequilibrium in this region, it has been difficult to separate independent signals of non-HLA genes from the nearby strongly associated HLA loci.

NOTCH4 codes for a transmembrane protein receptor (neurogenic locus notch homolog protein-4) that has effects on angiogenesis and vascular remodeling. The *NOTCH4* gene product is preferentially expressed on endothelial cells, making it an attractive candidate for a scleroderma susceptibility locus. Somewhat surprisingly, the associated allele was found to be a risk factor for those with ATA-positive disease but was found to be protective for ACA-positive disease [25]. It is unusual among genetic studies for there to be a statistically significant association in two mutually exclusive subgroups that are in opposite directions. It is not clear what functional consequences result from these variants.

PSORS1C1 is a gene close to the DRB1 gene complex in the HLA class II region that has been associated with psoriasis. A recent study [8] suggests that this locus represents an independent risk for SSc that is distinct from the HLA–DRB association. Again, the functional role of this variant is not clear.

CONCLUSION

In spite of these multiple successes, many of which have been identified or validated in the last year, only a small proportion of the heritability of SSc has been explained. Efforts are ongoing to identify the source of the ‘missing heritability’ including the identification of rare variants that may have larger effects on disease susceptibility and analysis of gene–gene interactions that may have effects greater than simply additive ones.

Although no longer in its infancy, the study of the genetics of SSc susceptibility is at best in adolescence. With our current knowledge from these genetic association studies, we can now begin to address the question that prompted this work to begin with: what are the functional consequences of these gene variants? How do they result in clinical disease? Or simply put, what story do they tell?

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KEY POINTS

- Multiple genes have been firmly associated as SSc susceptibility loci.
- Many of these gene regions are shared between SSc and systemic lupus erythematosus (SLE), suggesting common pathways involved in clinical autoimmunity.
- A gene on the X chromosome, *IRAK1*, which codes for a protein that is important in both innate and adaptive immune system pathways, is the first X-linked gene to be identified in SSc and may contribute to the female predominance in this disease.
- The human leukocyte antigen (HLA) region is also firmly established as conferring risk for SSc, but these regions are different from those reported for SLE and rheumatoid arthritis (RA).
- In spite of this large body of data, there is still 'missing heritability' in SSc, that is, genetic associations not yet identified.

Table 1

Selected major nonmajor histocompatibility complex association signals in systemic sclerosis

Gene	Location	Approach	Population	SSc phenotype	Effect: risk or protective	Proposed mechanism	Author, (Reference number)
<i>BANK1</i> (codes for B-cell scaffold protein with ankryrin repeats 1)	4q24	Candidate Gene	European ancestry	dcSSc All SSc dcSSc ATA positive	Protective Risk	Changes in B-cell activation threshold	Dieudé <i>et al.</i> [1] Rueda <i>et al.</i> [2]
<i>BLK</i> (codes for B-lymphocyte kinase)	8p23	Candidate Gene Meta-analysis	European ancestry Japanese European/Japanese	All SSc lcSSc ACA positive All SSc dcSSc lcSSc ACA positive	Risk Risk Risk	Disruption of NF- κ B signaling pathway in B cells.	Gourh <i>et al.</i> [3] Coustet <i>et al.</i> [4] Ito <i>et al.</i> [5]
<i>CD247</i> (codes for the zeta chain of the T-cell receptor)	1q22	GWAS candidate gene	European ancestry	All SSc	Protective	Dysregulation of T-cell activation through the T-cell receptor	Radstake <i>et al.</i> [6] Dieudé <i>et al.</i> [7] Allanore <i>et al.</i> [8■]
<i>CSK</i> (codes for c-src tyrosine kinase)	15q24	GWAS	European ancestry	All SSc	Risk	Inhibition of profibrotic pathways	Martin <i>et al.</i> [9]
<i>IRAK1</i> (codes for IL-1 receptor-associated kinase 1)	X q28	Candidate gene	European ancestry (women)	All SSc dcSSc > lcSSc ATA positive > ACA positive	Risk	X chromosome regulator of NF- κ B, influences T-cell receptor signaling, TLR activation and induction of IFNs α and γ	Dieudé <i>et al.</i> [10■]
<i>PTPN22</i> (codes for protein tyrosine phosphatase nonreceptor-22)	1p13	Candidate gene	European-Americans African-Americans European ancestry	All SSc	Risk	Modulation of T-cell receptor signaling	Balada <i>et al.</i> [11] Wipff <i>et al.</i> [12] Gourh <i>et al.</i> [13] Dieude <i>et al.</i> [14] Diaz-Gallo <i>et al.</i> [15]
<i>TNFAIP3</i> (codes for TNF α -induced protein 3)	6q23	Candidate gene confirmed in GWAS	European ancestry	All SSc dcSSc ATA positive ILD PAH	Risk	Regulation of NF- κ B signaling	Dieudé <i>et al.</i> [16] Martin <i>et al.</i> [9] Koumakis <i>et al.</i> [17■]
<i>TNFSF4</i> (codes for TNF ligand)	1q25	Candidate gene	European ancestry	All SSc lcSSc ACA positive	Risk	Enhancement of B-cell proliferation and differentiation and increases	Gourh <i>et al.</i> [18]

Gene	Location	Approach	Population	SSc phenotype	Effect: risk or protective	Proposed mechanism	Author, (Reference number)
superfamily member-4)						proliferation and survival of T cells	Bossini-Castillo <i>et al.</i> [19] Coustet <i>et al.</i> [20]
<i>TNIP1</i> (codes for TNFAIP3-interacting protein-1)	5q32	GWAS	European ancestry	All SSc	Risk	Negatively regulates NF-κB activity	Allanore <i>et al.</i> [8■]
<i>IRF5</i> (codes for IFN regulatory factor-5)	7q32	Candidate gene Confirmed in GWAS	European ancestry Japanese	All SSc dcSSc ILD dcSSc ATA positive	Risk	Regulates the expression of IFN-dependent genes and inflammatory cytokines	Dieudé <i>et al.</i> [21] Ito <i>et al.</i> [22] Dieudé <i>et al.</i> [23■]
<i>IRF7</i> (codes for IFN regulatory factor-7)	11p15	Candidate gene	European ancestry	ACA positive	Protective	Regulates the expression of IFN-dependent genes and inflammatory cytokines	Carmona <i>et al.</i> [24]
<i>IRF8</i> (codes for IFN regulatory factor-8)	16q24	GWAS	European ancestry	lcSSc	Protective	Regulates the expression of IFN-dependent genes and inflammatory cytokines	Gorlova <i>et al.</i> [25■]
<i>TLR2</i> (codes for TLR-2)	4q32	Candidate Gene*	European ancestry	dcSSc ATA positive SSc-PAH	Risk	Rare variant that may increase IL-6 and TNF α responses of monocyte-derived dendritic cells to TLR ligands	Broen <i>et al.</i> [26■]
<i>STAT4</i> (codes for signal transducer and activator of transcription-4)	2q32	Candidate gene Confirmed in GWAS	European ancestry Japanese	All SSc lcSSc	Risk	Regulation of multiple cytokine signals, including IL-12	Rueda <i>et al.</i> [27] Dieudé <i>et al.</i> [28] Tsuchiya <i>et al.</i> [29] Gourh <i>et al.</i> [30] Radstake <i>et al.</i> [6] Allanore <i>et al.</i> [8■]
<i>IL2RA</i> (codes for IL-2 receptor α)	10p15	Candidate gene	European ancestry	ACA positive	Risk	Marker of Regulatory T cells	Martin <i>et al.</i> [31]
<i>IL12RB2</i> (codes for IL-12 receptor β 2 subunit)	1p31	GWAS	European Ancestry	All SSc	Risk	Induces IFNγ and plays a role in Th1 cell differentiation	Bossini-Castillo <i>et al.</i> [32]
<i>MIF</i> (codes for macrophage	22q11	Candidate gene	European ancestry	dcSSc	Risk	Induces adhesion molecules on endothelial cells possibly contributing to vasculopathy	Wu <i>et al.</i> [33]

Gene	Location	Approach	Population	SSc phenotype	Effect: risk or protective	Proposed mechanism	Author, (Reference number)
migration inhibitory factor)							Bossini-Castillo [34]
<i>CAV1</i> (codes for caveolin-1)	7q31	Candidate gene	European ancestry	All SSc, lcSSc	Protective	Inhibitor of tissue fibrosis	Manetti <i>et al.</i> [35]
<i>CD226</i> (codes for DNA accessory molecule-1)	18q22	Candidate gene	European ancestry	All SSc, dcSSc, ATA positive, ILD ILD	Risk	Involved in the adhesion and costimulation of T cells	Dieudé <i>et al.</i> [36]
					Risk for haplotype		Bossini-Castillo [37]
<i>FCGR3B</i> (codes for low-affinity Fc gamma receptor 3B)	1q23	Candidate gene – copy number variation analysis	European ancestry	All SSc	Risk for copy number 1 compared with 2	Impaired immune complex clearance arising from relative deficiency of	McKinney <i>et al.</i> [38]
<i>ITGAM</i> (codes for integrin α M precursor)	16p11	Candidate gene	European ancestry	All SSc	Risk	Involved in immune complex clearance and leukocyte adhesion	Carmona <i>et al.</i> [39] Coustet <i>et al.</i> [40]

ACA+, anticomplement antibody positive; ATA+, antitopoisomerase antibody positive; dcSSc, diffuse cutaneous Systemic Sclerosis; GWAS, genome-wide association study; IL, interleukin; ILD, interstitial lung disease; IFN, interferon; lcSSc, limited cutaneous Systemic Sclerosis; NF- κ B, nuclear factor kappa B; PAH, pulmonary arterial hypertension; SSc, Systemic Sclerosis; Th1, T helper type-1; TLR, Toll-like receptor; TNF, tumor necrosis factor.