Review

The genetics of systemic sclerosis: an update

E. Romano¹, M. Manetti¹,², S. Guiducci¹, C. Ceccarelli¹, Y. Allanore³, M. Matucci-Cerinic¹

¹Department of Biomedicine, Division of Rheumatology, University of Florence, AOUC, DENOthe Centre, Florence, Italy; ²Department of Anatomy, Histology and Forensic Medicine, University of Florence, Florence, Italy; ³Université Paris Descartes, INSERM U1016, and Service de Rhumatologie A, Hôpital Cochin, Paris, France.

ABSTRACT

Systemic sclerosis (SSc) is a complex systemic disease characterised by fibrosis of the skin and internal organs, vasculopathy, and activation of the immune system. The complex pathophysiology of SSc implies the potential involvement of ‘culprit’ genes, either individually or, more likely, together, in driving the disease process. Most of the studies that have provided evidence for the contribution of various genes/loci in SSc pathogenesis are based on a candidate gene approach, on the basis of a shared autoimmune genetic background with other autoimmune diseases, such as systemic lupus erythematosus. In fact, autoimmune genes seem to play a pivotal role in SSc pathogenesis, while less is known about the genetic involvement in vasculopathy and fibrosis. Recently, the availability of genome-wide association studies, which make it possible to screen single-nucleotide polymorphisms across the entire genome without previous knowledge of candidate regions or genes, has yielded a wealth of new genetic susceptibility loci leading to the identification of new pathogenetic mechanisms of complex genetic disorders. In this article, we aim to provide a comprehensive review of recent studies on the genetics of SSc, including genes associated with autoimmunity, fibrosis, and vascular disease. We also discuss the most relevant data obtained in genetic association studies of large populations that included a replication strategy, or studies for which independent replication was available.

Introduction

Systemic sclerosis (SSc, scleroderma) is a chronic, multisystem connective tissue disorder affecting the skin and internal organs characterised by widespread microangiopathy, fibrosis, and autoimmunity. The precise etiology of SSc has not been established, but epidemiologic and genetic studies reflect a complex genetic component, along with a largely unknown and presumably variable environmental contribution (1). A study of familial clustering of SSc in three North American cohorts showed a significant increase in the prevalence of SSc compared to the general population (2.6% vs. 0.026%, respectively) (2). In twin studies, concordance rate for the presence of antinuclear antibodies was found to be significantly higher in the monozygotic twins (90%) than in the dizygotic twins (40%), suggesting that the genetic component may selectively contribute to susceptibility to the SSc-related autoimmune processes (3). In the last few years, many progresses have been made in the field of SSc genetics. The complex pathophysiology of SSc implies the potential involvement of ‘culprit’ genes, either singly or, more likely, together, in driving the disease process. Many of these genes have been found to be associated with other autoimmune diseases, such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA), which suggests a shared genetic pathway for autoimmunity. Increasing evidence indicates that autoimmunity associated genes may play a pivotal role in the pathogenesis of SSc, while less is known about the contribution of genes involved in the vasculopathy and fibrotic processes. This review summarises recent advances on the complex genetic component of SSc, including studies on genes implicated in the three major areas of disease expression: autoimmune response, vascular disease and fibrosis.

SSc susceptibility genes

Immune response

Major histocompatibility complex (MHC)-Human leucocyte antigen (HLA) region: The association be-
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tween HLA class II genotype and autoantibody profile in SSc has been reported in many studies (4-8). HLA-DRB1*01-DQB1*0501 haplotypes are more common in anticientromere antibody (ACA)-positive SSc patients, while HLA-DRB1*11-DQB1*0301 haplotypes have been associated with anti-topoisomerase I (anti-topo I) antibody-positivity (9). In the first reported genome-wide association study (GWAS) (10), 137 SSc Korean patients were compared with 564 healthy controls. The study was then replicated in North Americans. Five single-nucleotide polymorphisms (SNPs) located at the HLA-DPB1 and HLA-DPB2 locus formed a distinctive peak with log p-values for association with SSc susceptibility (p=8.16x10^-13). Fine mapping analysis of this genetic region confirmed that rs3128930, rs7763822 and rs7764491 were the SNPs accounting for the observed association, which was particularly strong in anti-topo I-positive SSc patients. In the replicate step (1.107 SSc patients and 2,300 controls of North American Caucasian origin), the genotyping of these five SNPs revealed that rs7763822 and rs7764491 were significantly associated with anti-topo I-positive SSc patients (10). Furthermore, a recent large case-control association study analysed HLA-class II (DRB1, DQB1, DQA1, and DPB1) alleles, haplotypes and shared epitopes in a large multi-ethnic American cohort (9). The strongest positive class II associations with SSc observed in white and Hispanic populations were the DRB1*1104,DQA1*0501,DQB1*0301 haplotype, and DQB1 alleles encoding a non-leucine residue at position 26 (DQB126*epi). Instead, DRB1*0701, DQA1*0201, DQB1*0202 haplotype and DRB1*1501 haplotype were negatively correlated and possibly protective in dominant and recessive models, respectively (9). In the very recent, much larger GWAS (11), a strong association with SSc susceptibility was found for a cluster of SNPs in an extended region of the 6p21 locus within the HCM region. In particular, the rs6457617 SNP located in the HLA-DQB1 gene region gave the highest p-value (p=2.31x10^-18) (11). No details about the sub-types and autoantibody status of SSc patients have yet been reported from this study. Further large GWAS studies will be necessary to investigate whether SNPs located in the MHC region may be associated with specific SSc phenotypes, such as the autoantibody pattern, disease subset and organ involvement. **STAT4**: The protein encoded by **STAT4** gene is a member of the STAT family of transcription factors. In response to cytokines and growth factors, STAT family members are phosphorylated by the receptor associated kinases, and then form homo- or heterodimers that translocate into the cell nucleus where they act as transcription activators (12). STAT4 protein is essential for mediating responses to interleukin-12 (IL-12) in lymphocytes, and regulates the differentiation of T helper cells. In particular, STAT4 appears to critically regulate the Th1/Th2 balance, which is known to be dysregulated in SSc (12). Independent studies have analysed the possible role of **STAT4** gene in the genetic predisposition to SSc. In the first study, the intronic rs7574865 polymorphism has been analysed in a case-control study of Spanish Caucasian ancestry with five independent cohorts of European Caucasian ancestry (12). The rs7574865-T allele was significantly associated with susceptibility to limited cutaneous SSc (lcSSc) in the Spanish population (p=1.9x10^-5; odds ratio [OR] 1.61; 95% confidence interval [CI] [1.29–1.99]) and the association was validated in all the replication cohorts with different effect sizes (OR ranging between 1.15 and 1.86). In all the cohorts, no association was found between **STAT4** and T-cell cutaneous SSc (dcSSc) subset. A meta-analysis to test the overall effect of the rs7574865 polymorphism further showed a strong risk effect of the T allele for lcSSc susceptibility (pooled OR 1.54; 95% CI [1.36–1.74]; p=0.0001) (12). The second study, performed in a Japanese population, confirmed the association between **STAT4** rs7574865 polymorphism and lcSSc (13). Another study, performed in 1,855 individuals of French Caucasian origin, showed a significant association between the rs7574865 polymorphism and SSc, without restriction to a particular phenotype (14). This study also revealed an additive effect between **STAT4** and **IRF5** genes, in particular in terms of susceptibility to SSc-related fibrosing alveolitis (14). Another **STAT4** gene SNP, the rs11889341 variant, was recently investigated in 1,039 SSc patients and 3,322 controls of North American Caucasian background. These investigators found that the rs11889341-A allele increased the susceptibility (p=2.4x10^-5) to SSc in a dominant pattern (15). The role of **STAT4** as SSc genetic risk locus has been confirmed in the recently published GWAS, which identified an association with rs3821236 (11). Finally, the role of **STAT4** gene in tissue fibrosis has been demonstrated in a recent translational study using different animal models of SSc (16).

**TBX21**: **TBX21** is another critical transcription factor that regulates the Th1/Th2 balance. Multiple SNPs in **TBX21** gene were found to be associated with SSc in a Caucasian American population of 902 SSc patients and 4,745 controls (15). The rs11650354-T allele showed a recessive pattern for disease susceptibility (p=1.4x10^-15; OR 3.37; 95% CI [2.4–4.6]). Furthermore, the authors identified gene-gene interaction among the **TBX21** rs11650354 and **STAT4** rs11889341 variants. In particular, the **STAT4** genotype increased the risk of SSc only in the **TBX21** rs11650354-CC genotype group. SSc patients carrying the **TBX21** CC genotype had higher IL-6 and tumour necrosis factor alpha (Th1 cytokines) levels, while those with the TT genotype had elevated IL-2, IL-5, IL-4, and IL-13 (Th2 cytokines) levels, compared with controls. Moreover, whole blood expression profiles revealed dysregulation of type I interferon pathways in the CC group and T-cell pathways in the TT group of the **TBX21** SNP, respectively. Collectively, these data indicate that **TBX21** and **STAT4** genes contribute interactively to SSc susceptibility, and may have a role in the altered Th1/Th2 cytokine balance and immune dysregulation (15).

**Interferon regulatory factor 5 (IRF5)**: Type I interferon (IFN) is a central mediator of innate immunity. IFN regulatory factors coordinate the expression
of type I IFNs, which are believed to play a pivotal role in the pathophysiology of connective tissue disorders such as SLE, Sjögren’s syndrome (SS), and SSc. Recently, the IRF5 gene, a member of the IFN regulatory factors, was identified as a susceptibility gene for both SLE and SS (17, 18). A first case-control study showed that there was a significant association between the IRF5 rs2004640 G/T functional polymorphism and SSc (19). The IRF5 rs2004640-T allele creates a donor splice site in intron 1 of the gene resulting in transcription of the alternative exon 1B (19). This polymorphism has been genotyped in 1,641 subjects of French European Caucasian origin split into discovery and replication cohorts. In both the discovery set and the replication set, the TT genotype was significantly more common in SSc patients than in controls (OR 1.58; 95% CI [1.18–2.11] in combined cohorts). Analyses of the whole SSc population showed a significant association between homozgyosity for the T allele and the presence of antinuclear antibodies and fibrosing alveolitis (OR 2.07; 95% CI [1.38–3.11]) (19). The association of IRF5 rs2004640 polymorphism and SSc has also been replicated in a Japanese population (20). In particular, an association was preferentially observed with dcSSc and anti-topo I antibody-positive SSc (20). Recently, additional functional IRF5 variants have been identified as autoimmune susceptibility factors. IRF5 rs377385, rs2004640, and rs10954213 were genotyped in 1,623 individuals of French European Caucasian origin (21). In this report, the authors found that a risk haplotype defined by the rs377385-C, rs2004640-T, and rs10954213-A SNPs (C-T-A) confers susceptibility to SSc, and defines subsets of patients with dcSSc and lung fibrosis (21). The role of IRF5 gene as SSc genetic risk factor has also been confirmed in the recently published large GWAS of SSc (11).

Protein tyrosine phosphatase, non-receptor type 22 (lymphoid) (PTPN22): The PTPN22 gene encodes a protein tyrosine phosphatase which is expressed primarily in lymphoid tissues. It is involved in the suppression of T cell activation, and thereby in T cell-dependent antibody production, potentially contributing to the pathogenesis of autoimmune diseases. The minor allele of the R620W missense SNP (C1858T, rs2476601) in the PTPN22 gene was firstly analysed in a French (22) and in a Spanish cohort (23) in two independent studies. No association was found between rs2476601 and SSc in both studies. Subsequently, the first evidence of association was found in a large cohort of 1,120 patients belonging to 4 ethnic groups in the US (white, black, Hispanic, and Choctaw Indian individuals). In particular, the PTPN22 R620W polymorphism was associated with both ACA-positive and anti-topo I antibody-positive subsets of SSc (24). A first meta-analysis of studies on this polymorphism in SSc provided evidence that the PTPN22 1858T allele is involved in the genetic susceptibility to SSc in European Caucasian (p=8.39x10^-8; OR 1.08; 95% CI [1.02–1.15]) and mixed (p=3.11x10^-3; OR 1.09; 95% CI [1.04–1.16]) populations, particularly in the anti-topo I-positive subset (25). Recently, an additional meta-analysis of seven Caucasian cohorts from Spain, Belgium, England, Germany, Italy, the Netherlands, and Sweden, and including the findings from two previous studies on US and French Caucasian populations (24, 25), showed evidence for an association of the 1858T allele restricted to the ACA-positive SSc subset (p=0.02 pooled, OR=1.22, 95% CI [1.05–1.42]) (26). Instead, no association was found between SSc and the rs33996649 (R263Q) PTPN22 polymorphism (26). Collectively, these findings highlight the importance of meta-analyses to solve contradictory results from previously published independent case-control studies.

B cell scaffold protein with ankyrin repeats 1 (BANK1): BANK1 is a B cell-specific scaffold protein that functions in B cell receptor-induced calcium mobilisation from intracellular stores. Two BANK1 gene missense variants (rs10516487 and rs3733197) were studied in 874 SSc patients and 955 controls of a French cohort and 421 SSc patients and 182 controls of a German cohort (27). The rs3733197-A rare allele and the rs10516487-T rare allele were found to be associated with dcSSc in both cohorts. The G-C haplotype was shown to be a risk factor (p=0.008; OR 1.25; 95% CI [1.06–1.47]), while the A-T haplotype was reduced among dcSSc patients, indicating a protective effect (p=3.39x10^-4; OR 0.70; 95% CI [0.57–0.86]) (27). The association between rs10516487-G (C) and rs3733197-G polymorphic alleles with dcSSc was then confirmed in a large multicentre case-control study from six independent cohorts of Caucasian ancestry (28). The association was not restricted to dcSSc, but was also found to be linked to the anti-topo I antibody-positive subset. In particular, a significant association of the rs10516487-G and rs17266594-T alleles with SSc susceptibility was observed (pooled OR=1.12; 95% CI [1.03–1.22], p=0.01 and pooled OR=1.14, 95% CI [1.05–1.25], p=0.003, respectively) (28). Taken together, the association of BANK1 gene with the SSc phenotype found in independent studies suggests an important role of B cells in the diffuse cutaneous subset of SSc patients. In this context, recent preclinical and clinical studies lend support to the notion that B cell depletion may be a promising therapeutic target in patients with dcSSc (29).
The genetics of SSc /  
ζ) subunit, (for a total of 6,149 individuals) was  
SSc patients and 1,012 controls), and a  
meta-analysis of all the available data (for a total of 6,149 individuals) was also performed (32). Minor allele frequencies for rs13277113 revealed an association restricted to the dcSSc subtype (p=0.012, OR 1.29) in the French sample. Meta-analysis of combined Caucasian populations showed association with both SSc (p=0.0013, OR 1.16 [1.06–0.26]) and dcSSc (p=0.0012, OR 1.23 [1.08–1.39]). Inclusion of the Japanese population (31) confirmed the overall association with the disease, with the strongest association for dcSSc (p=3.27×10⁻⁵, OR 1.27). An additional analysis in the French sample revealed additive effects between C8orf13/BLK and BANK1, mainly for dcSSc susceptibility (32). Taken together, these findings extend the evidence for a genetic association of SSc with B cell-specific genes (BANK1 and BLK).

**T cell surface glycoprotein CD3 zeta chain or T cell receptor T3 zeta chain (CD247):** CD247 gene encodes the T cell receptor zeta (CD3ζ) subunit, a component of the T cell receptor (TCR)-CD3 complex. The CD3ζ chain plays an important role in the assembly of the TCR-CD3 complex and its transport to the cell surface, and is crucial to receptor signalling function. The expression of the CD3ζ chain is altered in chronic autoimmune and inflammatory disorders and its low expression results in impaired immune response. The first large GWAS, including a total of 2,296 individuals with SSc and 5,171 controls of European Caucasian ancestry, identified a new susceptibility locus, previously found in SLE, at CD247 (1q22–23, rs2056626, p=3.39×10⁻⁶) (11). Recently, the rs2056626 SNP has been genotyped in a French Caucasian population consisting of 1,031 SSc patients and 1,014 controls (33). This study confirmed the association of CD247 rs2056626-G allele with SSc susceptibility under a dominant model of inheritance (p=7.22×10⁻⁵; OR 0.69; 95% CI [0.58–0.83]) (33).

**Tumour necrosis factor alpha-induced protein 3 (TNFAIP3):** TNFAIP3 gene encodes the ubiquitin-modifying enzyme, a key regulator of inflammatory signalling pathways. Polymorphisms in TNFAIP3 have been associated with multiple autoimmune diseases (34). In a recent study, three SNPs, two intergenic (rs10499194 and rs6920220) and one located in intron 2 (rs5029939), were genotyped in a set of 1,018 SSc patients and 1,012 controls of French European Caucasian ancestry (34). TNFAIP3 rs5029939 was found associated with SSc in the French population, and then the association was replicated in a second set of 465 SSc patients and 182 controls from Germany and 184 SSc patients and 124 controls from Italy. In the combined populations, the rs5029939-G allele was found to be significantly associated with SSc susceptibility (pooled OR=2.08; 95% CI [1.94–2.22]; p=1.16×10⁻⁵) and in particular with dcSSc (pooled OR=2.71; CI [1.61–3.17], p=5.25×10⁻⁵), SSc-related fibrosing alveolitis (pooled OR=2.26; CI [1.61–3.17], p=2.5×10⁻⁵) and pulmonary arterial hypertension (PAH) (pooled OR=3.11; CI [1.86–5.17], p=1.3×10⁻³). No association was found for the rs10499194 and rs6920220 variants (34). These results suggest that TNFAIP3 may contribute to the autoimmune component of SSc pathogenesis.

**CD226:** CD226 gene encodes DNAX accessory molecule 1, which is involved in T cell co-stimulation pathways. The non-synonymous rs763361 polymorphism in the CD226 gene has recently been identified as a genetic risk factor for different autoimmune disorders. The rs763361 SNP has been genotyped in 3,632 European Caucasian individuals, consisting of a discovery sample (991 SSc patients and 1,008 controls) and a replication sample (999 SSc patients and 634 controls) (35). The CD226 rs763361-T allele was found to be associated with SSc in both the discovery and the replication samples, reaching an OR of 1.22 (95% CI [1.10–1.34], p=5.69×10⁻⁵) in the combined population. The most remarkable associations of the CD226 TT risk genotype were observed with the dcSSc subtype (OR 1.86, 95% CI [1.42–2.43], p=5.15×10⁻⁴), the anti-topo I antibody-positive (OR 1.82, 95% CI [1.38–2.40], p=2.16×10⁻³), and SSc-related fibrosing alveolitis subsets (OR 1.61, 95% CI [1.25–2.08], p=2.73×10⁻³) (35). These results suggest that co-stimulation pathways may be involved in the immune abnormalities of SSc. However, postgenomic functional studies on peripheral blood mononuclear cells did not reveal any correlation between CD226 rs763361 genotypes and CD226 expression in all the T cell subtypes investigated (35). Therefore, further studies will be necessary to define the causal variant at the CD226 locus as well as the functional consequences.

**FAS:** FAS antigen (Apo-1/CD95) is a key molecule involved in the apoptosis of a wide variety of cell types, including activated immune cells and fibroblasts. A SNP in the enhancer region of the FAS gene promoter, FAS-670GA SNP (rs1800682), has been described (36). SSc is characterized by sustained activation and clonal expansion of B and T lymphocytes, and different subsets of circulating T cells from SSc patients have been shown to be resistant to FAS-mediated apoptosis (37). In a large cohort of Italian Caucasian patients, an association between the FAS-670GA polymorphism and SSc was described (38). Moreover, FAS-670 genotype was found to be correlated with serum levels of antiapoptotic soluble FAS, which competes with membrane-bound FAS for the binding to FAS-ligand (38). In another study, the role of FAS-670GA polymorphism has been analysed in 9 distinct ethnic cohorts, 6 of European Caucasian ancestry and 3 distinct ethnic cohorts from the US (white, black and hispanic) (39). A meta-analysis comprising all 9 cohorts revealed an association of both the FAS-670G allele (OR 1.10) and the FAS-670GG genotype (OR 1.13) with the lcSSc phenotype. In addition, the -670GG genotype was associated with ACA-positive lcSSc (39). Dysregulation of the FAS-mediated proapoptotic signalling might play a role in SSc pathogenesis through the genetic control of apoptosis resistance.
in different cell types, such as activated lymphocytes and fibroblasts. Interleukin-23 receptor (IL23R): Multiple studies suggest a role for mediators of Th17 pathway, such as IL-17 and IL-23, in different autoimmune diseases, including SSc. In particular IL-23 is essential for the amplification and/or stabilisation of Th17 phenotype, and IL-23 protein levels have been found to be increased in patients with SSc. IL-23 activity is mediated by binding to the IL-23 receptor complex, which is composed of an IL-12Rβ1 and a unique cytokine receptor subunit termed IL23R. Recent results pointed toward the important role of IL23R gene as a genetic marker for autoimmunity (40). In particular, a non-synonymous polymorphism (rs11209026, Arg381Gln) has been associated with susceptibility to different autoimmune conditions such as inflammatory bowel disease, ankylosing spondylitis or psoriasis. Seven SNPs spanning the IL23R gene, including rs11209026, were genotype in two cohorts of European Caucasian patients, but no association was found between any IL23R genetic variant and SSc susceptibility and clinical phenotypes (40). In a recent study on 1,402 SSc cases and 1,038 controls of Caucasian, African American and Hispanic ethnicity from US, the IL23R rs11209026-GG and rs11465804-CT genotypes were found to be associated with anti-topo I antibody-positive SSc (p=0.001, and p=0.0001 respectively) (41). Moreover, the rs11465804-CT genotype was significantly associated with anti-topo I antibody-positivity in the dcSSc subset (p=0.0026). Wild-type genotype at both rs11209026 and rs11465804 showed significant protection against the development of PAH (p=3x10^-5, p=1x10^-5, respectively) (41).

Allograft inflammatory factor-1 (AIF-1): AIF-1 is involved in the immune response and proliferative vasculopathy that occurs during allograft rejection. It is encoded within the HLA class III genomic region on chromosome 6p21. AIF-1 expression was found increased in affected blood vessels of the lung and skin of SSc patients (42). A non-synonymous polymorphism (rs2269475) located in exon 3 and causing a tryptophan to arginine amino acid substitution has been identified in the AIF1 gene. The rs2269475 SNP has been investigated in two large independent cohorts of SSc patients of Caucasian, African American and Hispanic origin (43). T and CT/TT rs2269475 frequencies were significantly increased in ACA-positive Caucasian SSc patients, and in all ACA-positive SSc patients (the three ethnic groups combined), when compared with both ACA-negative SSc patients and healthy controls. In another study, the rs2269475 SNP was significantly associated with SSc (p=0.0009), and in particular with the dcSSc subset (p=0.002) in a Caucasian cohort (44). The discrepancies between these two studies indicate that further investigations and meta-analyses will be necessary to determine the exact role that AIF1 gene may play in the genetic susceptibility to SSc phenotype.

FCG receptor (FCGR): FCGRs recognise the Fc portion of IgG and are important in determining the response of leucocytes to deposited immune complexes. FCGRs also provide positive and negative regulation of immune cell responses (45). The FCGR2A 519A>G and FCGR3A 559A>C functional variants have been recently analysed in 6 independent European Caucasian cohorts (for a total of 1,566 SSc patients and 2,271 controls). Neither FCGR2A 519A>G nor FCGR3A 559A>C was significantly associated with susceptibility to SSc, and no association was found with specific disease phenotypes, limited or diffuse cutaneous in nature, lung, or scleroderma renal crisis (46). In a second study, four genetic variants of TNFSF4 gene promoter (rs1234314, rs844644, and rs12039904) were analysed in a total of 8 European populations of Caucasian ancestry (3,014 SSc patients and 3,125 healthy controls) (47). A pooled analysis found a significant association of rs1234314 and rs12039904 polymorphisms with SSc. All four tested variants were found to be significantly associated with lcSSc subset. In addition, rs1234314, rs844644 and rs12039904 minor alleles were associated with ACA-positive SSc (47). Collectively, these data confirm the influence of TNFSF4 gene in SSc susceptibility (46,47). However, the two studies highlight some discrepancies concerning the specific SSc subsets associated with different TNFSF4 SNPs. Therefore, additional meta-analytic studies will be required. Table I summarises the confirmed associations with SSc found in some of the genes involved in immune regulation.
Table I. Immune genes associated with SSc susceptibility and phenotypes.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
<th>Population</th>
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<th>Study</th>
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<td>lcSSc</td>
<td>Rueda et al. (12)</td>
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<td></td>
<td>US Caucasian</td>
<td>SSc</td>
<td>Gourh et al. (15)</td>
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<td></td>
<td></td>
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<td>SSc</td>
<td>Radstake et al. (11)</td>
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<td>IRF5</td>
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<td>SSc</td>
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<td>lcSSc, ACA</td>
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Fibrosis

Fibrosis is the most pathological hallmark of SSc. Progressive replacement of tissue architecture by collagen-rich extracellular matrix (ECM) results in functional impairment of affected organs. The ECM consists of a cellular compartment of resident and infiltrating cells, and a connective tissue compartment composed of collagens, proteoglycans, fibrillins and adhesion molecules. The ECM also functions as a reservoir for transforming growth factor β (TGFβ), connective tissue growth factor (CTGF), other growth factors and matricellular proteins that, together with the connective tissue compartment, control mesenchymal cell differentiation, function and survival (48). Excessive connective tissue accumulation in fibrotic disorders is due to overproduction by activated fibroblasts, myofibroblasts and related interactions. Impaired ECM degradation and turnover, and expansion of the pool of mesenchymal cells in lesional tissues further contribute to ECM accumulation (48). Genes involved in the fibrotic process encode proteins that make up or regulate the ECM composition, cytokines and growth factors.

Connective tissue growth factor (CTGF): CTGF (also known as CCN2) has a critical role in the development and maintenance of fibrosis (49-51). The expression of CTGF gene has been found to be up-regulated in gene-expression-profiling studies of skin-biopsy specimens and of fibroblasts cultured from SSc skin (49, 50). Moreover, CTGF has been associated with key biologic functions, including fibroblast proliferation, the production of ECM, and the formation of granulation tissue, which are all processes relevant in the field of SSc (49-51). A polymorphism (G→945C) (rs96918698) in the promoter of the CTGF gene was found to be associated with SSc in a UK population (52) and in a Japanese population (53). The homozygosity for the G allele was significantly associated with SSc, anti-topo I antibody-positivity and SSc-related fibrosing alveolitis (52). Functional studies demonstrated that the rs96918698-C allele had higher affinity for the transcriptional regulator Sp3 resulting in reduced transcriptional activity of the CTGF gene (52). However, this association was not replicated in two large studies in American and European Caucasian populations (54, 55). Recently, an association between another SNP in CTGF gene (rs9399005 C/T) and both deSSc and lcSSc has been found in a French European Caucasian population (56). These authors also provided evidence that the rs9399005 SNP may affect the structure of CTGF messenger RNA (56).

Serotonin 5-HT2A receptor: Platelet aggregation may contribute to the pathogenesis of SSc. Indeed, following activation, platelets release significant amounts of serotonin which promotes vasoconstriction and fibrosis. The C+1354T polymorphism in the exonice region of the serotonin 5-HT2A receptor gene, which determines a His452Tyr substitution, was associated with blunted intracellular responses after serotonin stimulation, and may have a role in susceptibility to SSc. In an Italian study, this polymorphism resulted associated with a three-fold reduction in the

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risk for SSc (57), but this was not replicated in a successive population-based replication study in a German Caucasian SSc cohort (58). Another study on serotonin transporter gene (SLC6A4) polymorphisms (rs1042173, rs2066713 and a long/short 44 base pair insertion within the promoter region), performed in a large cohort of European Caucasian SSc patients, showed no association between these polymorphisms and SSc or with SSc-related PAH and/or digital ulcerations (59).

Interleukin-1 alpha (IL1-α) and Interleukin-1 beta (IL1-β): IL1-α and IL1-β have been implicated in the fibrogenic phenotype of SSc fibroblasts. Three IL1-α gene SNPs (-889C/T, +4845G/T, and +4729T/C) were associated with SSc-related pulmonary fibrosis in a Japanese population (60). However, the association between IL1-α-889T polymorphism and SSc resulted controversial in subsequent studies (61-64). Three polymorphisms in the IL1-β gene (C-511T; C-31T; C+3962T) have been studied in Italian Caucasian SSc patients (62). The two polymorphic alleles IL1-β -511-T and IL1-β -31-C were significantly more frequent in SSc patients compared to a control population from the same geographic area (62), while the IL1-β C+3962T SNP resulted associated with the presence of severe restrictive pulmonary function in other studies (64,65). The important role of IL1-β in SSc has been confirmed in a recent study on NLRP1 gene which codifies a molecule that provides a scaffold for inflammasome assembly, promoting pro-IL1-β processing and maturation (66). In this study, performed in two large sets of European Caucasian individuals, the NLRP1 rs8182352 variant was found to be associated with both anti-topo I-positive SSc and SSc-related fibroblastic alveolitis subsets (p=0.0042 and p=0.0065 respectively) (66). Furthermore, NLRP1 rs8182352, IRF5 rs2046460 and STAT4 rs7574865 risk alleles showed an additive effect on SSc-related fibroblastic alveolitis (66). These findings provide new insights into the pathogenesis of SSc, underlining the potential role of innate immunity in particular in the fibroblastic alveolitis-positive SSc phenotype, which represents one of the most severe subsets of the disease.

Matrix metalloproteinase (MMP): ECM remodelling involves the complex interplay between ECM component synthesis, deposition, and degradation. MMPs are enzymes able to degrade ECM participating in physiologic and pathologic processes. In an Italian case-control study performed on 513 Caucasian subjects, the rs2276109 A/G functional polymorphism in the MMP12 gene promoter region was found to contribute to SSc susceptibility (67). The rs2276109-A allele has a higher affinity for AP-1 transcription factors, resulting in increased MMP12 gene expression. The MMP12 rs2276109-A allele was found to be significantly associated with dcSSc subset, anti-topo I antibody-positivity and SSc-related pulmonary fibrosis under a recessive model of inheritance (67). Studies performed on MMP1, MMP2, MMP9 and MMP14 gene polymorphisms revealed no association with SSc susceptibility or clinical phenotypes (68-70).

Vascular disease

Vascular damage is a primary event in the pathogenesis of SSc. The progressive vascular injury includes persistent endothelial cell activation/damage and apoptosis, intimal thickening, delamination, vessel narrowing and obliteration. These changes lead to vascular tone dysfunction and reduced capillary blood flow, with consequent tissue ischaemia and severe clinical manifestations, such as digital ulceration or amputation, pulmonary arterial hypertension, and scleroderma renal crisis (71). Nevertheless, in SSc patients there is no evidence of significant angiogenesis and the disease evolves towards chronic tissue ischaemia, with progressive and irreversible structural changes in multiple vascular beds culminating in the loss of capillaries (71). PAH is the main pulmonary vascular complication of SSc; it occurs in about 10% of patients and leads to major excess mortality (72). Many mediators that modulate arterial tone and remodelling are involved in the genesis of PAH, and all the genes encoding these mediators are potential candidate genes.

Endoglin (ENG): Among the factors that maintain vascular integrity, endoglin (CD105) is a component of the TGF-β receptor complex and is predominantly expressed on the cell surface of endothelial cells. A 6-base insertion in intron 7 (6bINS) of ENG gene has been reported to be associated with microvascular disturbance (73). In a multicentric cohort of European Caucasian SSc patients, the 6bINS allele resulted associated with a decreased risk of PAH (74). However, these results need independent replication in other populations.

Stromal cell-derived factor 1 (SDF-1/CXCL12): The chemokine SDF-1 and its receptor CXCR4 regulate specific steps in new vessel formation and play a role in CD34+ endothelial progenitor cells mobilisation into peripheral blood and homing to ischaemic tissues (75, 76). The SDF1 gene, located on chromosome 10q11, is polymorphic, with a G-to-A transition at position 801 in the 3'-untranslated region of cDNA encoding SDF-1β, one of the two isoforms of SDF-1 protein, referred as SDF1-3' polymorphism (rs1801157). This SNP has been correlated with the mobilisation of bone marrow CD34+ endothelial progenitor cells and the levels of SDF-1 transcript (77). In an Italian cohort, the SDF1-3' A allele was found to influence the predisposition to SSc-related PAH (OR=2.52, 95% CI [1.11–5.69], p=0.02) and skin ulcers (OR=2.31, 95% CI [1.18–4.52], p=0.01). After adjustment for age and gender, the SDF1-3’A allele remained a susceptibility factor for the SSc-related vascular manifestations (PAH: OR=2.37, 95% CI [1.04–5.42], p=0.04; ulcers: OR=2.33, 95% CI [1.78–4.62], p=0.01) (77). Further studies will be required to confirm these associations in independent cohorts of SSc patients.

Hypoxia-inducible factor 1A (HIF1A): HIF1A is a transcription factor that plays an essential role in cellular and systemic responses to hypoxia, and is involved in the ischaemia-induced angiogenic response. Three SNPs in the HIF1A gene (rs12434438 A/G, rs1957757 C/T and rs11549465 C/T) have been studied in a large French Caucasian population. The heterozygous
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rs12434438-AG genotype was significantly associated with SSc susceptibility, lcSSc and ACA-positive subsets, suggesting a role for HIF1 gene in SSc phenotype (78).

Urokinase-type plasminogen activator receptor (uPAR): uPAR (also known as CD87) is a glycosylphosphatidylinositol-anchored 3-extracellular domain receptor that has been implicated in SSc-related microvascular abnormalities and impaired angiogenesis, as well as in the fibrotic process (71, 79-83). Two uPAR (PLAUR) gene promoter polymorphisms (rs344781 and rs4251805) were investigated in two European Caucasian populations: an Italian discovery cohort and a French replication cohort. The combined analysis of the pooled samples (732 SSc patients and 607 controls) showed a strong association of the rs344781-G allele and -GG genotype with SSc-related ulcers (OR 1.96; 95%CI [1.01–3.85]; p=0.04) and lcSSc (allele OR 2.40; 95%CI [1.38–4.19]; p=0.004), SSc-related PAH (allele OR 1.65; 95%CI [1.17–2.32]; p=0.004; genotype OR 3.16; 95%CI [1.58–6.32]; p=0.0006), ACA-positive SSc (allele OR 1.47; 95%CI [1.15–1.89]; p=0.002; genotype OR 2.40; 95%CI [1.38–4.19]; p=0.001) and lcSSc (allele OR 1.34; 95%CI [1.09–1.64]; p=0.004; genotype OR 1.77; 95%CI [1.08–2.91]; p=0.02). Furthermore, in a multivariable logistic regression analysis model including the above associated phenotypes of SSc patients, the rs344781-GG genotype remained an independent risk factor for SSc-related ulcers (OR 1.96; 95%CI [1.01–3.85]; p=0.04) and SSc-PAH (OR 2.68; 95%CI [1.25–5.75]; p=0.01). Further functional studies are necessary to elucidate the exact molecular mechanisms by which the uPAR rs344781 SNP may be implicated in different aspects of SSc vascular phenotype, such as the lack of angiogenesis and proliferative vasculopathy (83).

Potassium voltage-gated channel, shaker related subfamily, member 5 (KCNA5): Functional KCNA5 SNPs have been reported to be associated with idiopathic PAH, including SNPs located in exons or the promoter region that may underlie the altered function and/or expression of voltage-gated K+ channel 1.5 (Kv1.5) channels observed in pulmonary arteriolar smooth muscle cells from patients with idiopathic PAH (84). Four KCNA5 SNPs (rs107444676, rs1860420, rs3741930, and rs2284136) were genotyped in a discovery set of 638 SSc patients and 469 controls of French Caucasian ancestry. In the same study, the rs107444676 was further genotyped in an independent replication sample (938 SSc patients and 564 controls) of German and Italian Caucasian ancestry, as well as in a cohort of 168 patients with different PAH subtypes (85). The rs107444676 SNP showed an association with SSc-PAH in the French population, and this finding was replicated in the second set. The other KCNA5 SNPs tested were not associated with any SSc subset. In the independent cohort of patients with different PAH subtypes, only the rs107444676 SNP showed an association with SSc-related PAH (85). This work suggests that KCNA5 gene may contribute to the development of proliferative vasculopathy in SSc.

Vascular endothelial growth factor (VEGF): VEGF is an endothelial cell-specific mitogen glycoprotein that promotes angiogenesis. Previous studies have implicated VEGF and VEGF receptors (VEGFRs) in the microvascular abnormalities and impaired angiogenesis that characterise SSc (71). In a multinational study involving European Caucasian individuals, three functional VEGF gene polymorphisms were studied (634 C/T, 936 C/G, and insertion/deletion of 18 base pairs at -2549 position in the promoter) (86). Moreover, in another case-control study on 1,170 European Caucasian subjects, eight SNPs covering the entire VEGFR1 gene and five SNPs in the VEGFR2 gene were analysed (87). Neither VEGF nor VEGFR1 and VEGFR2 polymorphisms were significantly associated with susceptibility to SSc or with specific disease phenotypes (86, 87). However, independent replication should be performed to definitively rule out the possible influence of VEGF, VEGFR1 and VEGFR2 genes in SSc phenotype.

Angiotensin-converting enzyme (ACE): The renin angiotensin system (RAS) is closely implicated in vascular disease. ACE, a key enzyme in the RAS, is encoded by the ACE gene, mapping to the 17q23 region. An insertion/deletion (I/D) polymorphism in intron 16 of the ACE gene correlates with high circulating levels of ACE enzyme in the general population. However, studies of its possible role in SSc susceptibility produced conflicting results: an association between the D allele of ACE I/D and SSc was firstly detected in an Italian cohort (88), but this finding was not replicated in North American (89), Greek (90), Korean (91) and French populations (92). These discrepancies may be explained by low statistical power or population stratification because of the heterogeneous genetic background.

Endothelial nitric oxide synthase (eNOS/NOS3) and inducible NOS (iNOS/NOS2): Endothelium derived nitric oxide (NO) plays a key role in the regulation of vascular tone and has vasoprotective effects by scavenging superoxide radicals and suppressing platelet aggregation, leucocyte adhesion and smooth muscle cell proliferation. The relative underproduction of the vasodilator NO, by eNOS, could contribute to the vascular damage typical of SSc. In an Italian cohort of SSc patients, the eNOS 894G>T polymorphism was more common in patients than in controls (88). In a successive study, the same group showed a role of eNOS -786>T>C and 894G>T polymorphisms in influencing the hemorheologic behavior in SSc (93). Subsequent studies failed to confirm the association between eNOS 894G>T polymorphism and SSc (89, 94). In a recent Turkish study, three eNOS gene polymorphisms (tandem 27-bp repeats (VNTR) in intron 4, -786T>C in promoter region and 894G>T in exon 7) were investigated (95). Genotype distribution was significantly different between SSc patients and controls for intron 4aa (alleles for four repeats), genotype frequency being 3.4% and 17.1% respectively. The -786CC genotype of the promoter was significantly higher in frequency in the SSc patients (16.9%) compared to controls (7.3%) (95). Another study investigated two SNPs in the promoter region (-1.026 and -277) and a pen-
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tanucleotide repeat (CCTTT) at -2.5 kilobases of the NOS2 gene (96). The -1,026 and -277 SNPs were found to be associated with SSc-related PAH. The CCTTT repeat was significantly shorter in SSc patients with PAH than in those without PAH or healthy controls. Functional studies demonstrated that a short allele of the CCTTT repeat determined a lower transcriptional activity of NOS2 gene (96).

Endothelin (ET-1) and receptors: ET-1 plays a crucial role in vascular damage, both directly through its potent vasoconstrictive effect and indirectly through the induction of genes implicated in vascular dysfunction and inflammatory response. ET-1 can also promote tissue remodeling and fibrosis by induction of fibroblast activation (97). The two endothelin receptors, ETRA and ETRB, belong to the superfamily of G protein-coupled receptors. Polymorphisms within the genes encoding ET-1 (EDN1 at 6p24), and its receptors (EDNRA at 4q31, and EDNRB at 13q22) have been analysed (97). No significant differences between the SSc group and control subjects were observed for any of the investigated polymorphisms. However, the presence of anti-RNA polymerase autoantibodies was associated with the EDNRA +69 C/T and +105 A/G SNPs in exon 6, while EDNRB -2446 C/A (exon 3), +2841 G/A (exon 2), and -2547 A/G (exon 3) SNPs were associated with dcSSc (97). These findings and their functional significance need to be confirmed and investigated in future studies.

Fibrinogen: Fibrinogen is a key protein involved in blood clotting. It increases blood viscosity, erythrocyte aggregation, vasoactivity and endothelial permeability, thereby promoting intra-vascular and parietal thrombosis in individuals with an underlying vascular injury, as occurs in SSc patients. The -455G>A polymorphism in the proximal promoter region of the β-fibrinogen gene has been reported to be an independent risk factor for thrombosis in both homo-(AA) and heterozygosity (GA) and to increase plasma fibrinogen levels (98). A preliminary study performed on 47 Italian SSc patients and 66 controls showed that the β-fibrinogen -455A allele was more frequent in SSc patients with digital lesions (pitting scars/ulcers) than in those with uncomplicated Raynaud’s phenomenon (13/17 vs. 6/30) (OR=13.000; 95% CI [3.098–54.557]; p=0.0002). Moreover, SSc patients carrying the β-fibrinogen -455GA genotype showed an increase in fibrinogen plasma levels (98). These preliminary data suggest an association between the β-fibrinogen -455A allele and peripheral vascular damage in SSc patients, and need to be extended and replicated in larger studies.

Conclusions and future perspectives

To date, most of the studies that have provided evidence for the contribution of various genes or gene regions to SSc pathogenesis are based on a candidate gene approach, on the basis of a shared autoimmune genetic background with other autoimmune diseases, notably SLE. Recently, the availability of GWAS, which makes it possible to screen SNPs across the entire genome without previous knowledge of candidate regions or genes, has yielded a wealth of new genetic susceptibility loci leading to the identification of complex genetic disorders, including SSc. Collectively, a major role of autoimmunity in SSc pathogenesis is supported by the recent identification of multiple genetic markers related to the innate and adaptive immune regulation, such as HLA class II gene region, STAT4, IRF5, BANK1, BLK, TNFSF4 and CD247 genes, which have been firmly established as SSc susceptibility genes through replication in independent studies. Recent meta-analytic studies have also proved to be useful tools in solving previously reported conflicting data on the association of immune genes with specific clinical and immunologocal subsets of the disease. Moreover, increasing evidence suggests that multiple immune genes may show an additive effect on SSc susceptibility and phenotypes. However, SSc is an heterogeneous disease likely regulated by complex mechanisms that are mostly unknown, but probably unique, and that involve a cross-talk among immune, vascular and fibrotic pathways.

Controversial results have been reported for genes involved in the development of fibrosis and vascular disease. However, those studies were often limited by small sample sizes and clinical heterogeneity of patients. Therefore, larger studies based on a candidate gene or GWAS approach, will be necessary to clarify the role of genes involved in vascular and fibrotic pathways in SSc genetic susceptibility. Future studies should also investigate whether gene-gene interactions between multiple common immune, vascular and fibrotic risk variants, as well as gene-environmental interactions, may influence the susceptibility to SSc and its clinical manifestations. Finally, postgenomic functional studies are now required to unravel the exact cellular and molecular mechanisms by which the multiple risk genetic components to date identified may participate in the pathogenesis of SSc.

References

5. GILCHRIST FC, BUNN C, FOLEY PI et al.: Class II HLA associations with autoantibodies in scleroderma: a highly significant role for HLA- DP. Genes Immun 2001; 2: 76-81.
6. UEKI A, ISOZAKI Y, TOMOKUNI A et al.: Different distribution of HLA class II alleles in anti-topoisomerase I autoantibody responders between silicosis and systemic sclerosis patients, with a common distinct sequence in the HLA-DQβ1 domain. Immunobiology 2001; 204: 458-65.
8. GREGersen PK, OLSSON LM: Recent ad-


27. DIADETE Pé et al.: BANK1 is a genetic risk factor for diffuse cutaneous systemic sclerosis and has additive effects with IRF5 and STAT4. Arthritis Rheum 2009; 60: 3447-54.


32. COUSTET B, DIEUDE P, GUEUD M et al.: C8orf 13/BLK is a genetic risk locus for systemic sclerosis and has additive effect with BANK1: Results from a large French cohort and meta-analysis. Arthritis Rheum 2011 Apr 7 [Epub ahead of print].


45. ALIZADEH BZ, BROEN J, RUEDA B et al.: Functional variants of Fc gamma receptor (FCGR2A) and FCGR3A are not associated with susceptibility to systemic sclerosis in a large European Study (EUSTAR). J Rheumatol 2010; 37: 1673-9.


