**Scleroderma autoantibodies in guiding monitoring and treatment decisions**

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**Abstract**

Purpose of review

One of the key clinical challenges of systemic sclerosis (SSc) is diversity in clinical presentation, organ involvement and disease progression. Antinuclear autoantibodies (ANA) are central to the diagnosis of SSc. ANA specificities associated with distinct clinical patterns of organ and skin involvement. Understanding of the molecular differences and pathogenesis of scleroderma has helped further inform clinical acumen. Here we provide an update on ANA on clinical profiling, management and future direction of SSc.

Recent findings

There has been further development in delineating clinical patterns in ANA, genetic susceptibility and antigen triggers predisposing to ANA subtypes. Sub-group analysis of recent clinical trials shows differing treatment responses to novel therapeutics.

Summary

ANA subtyping is likely to be firmly embedded into future classification systems. Beyond informing current management and monitoring of scleroderma patients, ANA subsets have implication on future research and clinical trial design.

Keywords: Systemic Sclerosis, connective tissue disease, Antinuclear autoantibodies,

## 1. Introduction

Systemic sclerosis (SSc) is an autoimmune condition with substantial clinical and serological heterogeneity. Antinuclear autoantibodies (ANA) are a spectrum of autoantibodies that react with various nucleolar and cytoplasmic components of normal human cells. They are integral to scleroderma the diagnosis, subtype classification, and prognostic evaluation. ANA are present in 90% of scleroderma patients [1].

The 'classical' ANA subtypes in SSc are the anticentromere antibodies (ACA), anti-topoisomerase-1 antibodies (ATA; Anti-Scl-70), anti-RNA polymerase III antibodies (ARA). Collectively, these antibodies are found in 50-80% of scleroderma patients [2,3]. ANA associated with SSc are mutually exclusive and specific for SSc. Antibodies associated with scleroderma overlap syndromes, such as anti-Pml/Scl and anti-Ku are less specific for scleroderma but remain mutually exclusive [3]. Patients do not switch ANA subset type throughout their disease duration.

Over the recent years advances in collaborative practice and genetic analysis has further improved our understanding of these distinct clinical patterns. This review focuses on the principal differences in ANA profiles, mechanisms of pathogenicity, and impact on management.

## 2. Clinical phenotype by ANA subtypes

The clinical phenotypes of antibody subtypes have been summarized in Table 1.

### 2.1 Anti-centromere Antibodies (ACA)

ACA, targeting centriole proteins are the most common autoantibodies found in SSc [1]. ACA seropositivity is a positive prognostic marker with an overall increased survival 5-20 years post diagnosis and reduced incidence of scleroderma renal crisis (SRC), cardiac scleroderma and scleroderma associated interstitial lung disease (SSc-ILD) [3,4]. ACA positivity is associated with calcinosis, digital ischemia with digital tip ulcerations and oesophageal dysmotility (80%) [3-5]. The most serious complication of ACA positivity is increased incidence of Pulmonary arterial hypertension (PAH) [3,6].

ACA is typically associated with limited cutaneous scleroderma (lcSSc). However, a small percentage of ACA positive patients (5-7%) are within the diffuse cutaneous subset (dcSSc) [7]. Comparing ACA positive dcSSc to ACA negative dcSSc, ACA positivity was associated with lower incidence of organ-based complications and improved survival, evidencing its protective effect on phenotype [7]

2.2 Anti-Topoisomerase Antibodies (ATA)

ATA are the second most common ANA and are associated with poor prognosis [3]. ATA has a propensity towards diffuse cutaneous involvement and higher incidence of significant SSc-ILD (80%) regardless of cutaneous subtype [3,8]. PAH incidence is decreased compared to overall scleroderma population [3,6]. In dcSSc, ATA positivity is a negative prognostic factor with dcSSc ATA-positive patients having the worst prognosis and lowest survival rate of all SSc patients. A large cohort study found that ATA positive lcSSc patients have the second highest survival rate behind ACA-positive patients [3]. Although, incidence rates of SRC are not as pronounced relative to ARA, ATA seropositivity is associated with higher mortality rates in SRC scleroderma [9].

2.3 Anti-RNA Polymerase 3 Antibodies (ARA)

ARA positivity occurs almost exclusively in the diffuse cutaneous subtype and associated with severe skin involvement and a ten-fold increase in SRC [3]. Modified Rodnan Skin Score (MRSS) peak occurs earlier and in higher values relative to ARA but is also associated with faster improvement [3,10]. ARA seropositivity is one of the strongest risk factors for Gastric antral vascular ectasia (GAVE) with a 4-5 greater fold risk of GAVE in ARA positive patients compared to overall SSc [11-12]. ARA positivity is associated with lower prevalence of cardiac scleroderma and SSc-ILD [3]. ARA positive patients have a 4-7-fold increased risk of developing cancer within 6 months to 5 years after SSc onset, the highest amongst all ANA subsets [13,14].

2.4 Anti-Fibrillarin (Anti-U3RNP)

Anti-U3RNP positivity is associated with the highest incidence of both PAH and cardiac involvement in SSc [3]. A distinct feature of Anti-U3RNP is non-inflammatory skeletal myopathy [15]. Anti-U3RNP is associated with poor prognosis mainly due to its association with early severe organ involvement [16]. In early scleroderma, this antibody is associated with very high mortality rates, however, long-term survival rates in Anti-U3RNP positive patients were higher compared with Anti-U3RNP negative SSc [3]. Anti-U3RNP is also strongly associated with severe GI involvement that includes gut malabsorption and pseudo-obstruction [16].

2.5 Anti-Th/To Antibodies

Anti Th/To antibodies are associated with limited cutaneous involvement and oesophageal dysmotility [8]. Diagnosis delay is usually reduced due to shorter duration between Raynaud's and first non-Raynaud's symptom onset [3]. Anti-Th/To is associated with significant SSc-ILD and PAH which occur early in disease course [8]. LcSSc patients with Anti-Th/To positivity have

higher pulmonary involvement compared to overall lcSSc [17-18]. A recent case-control study of Th/To SSc, the largest to date, showed a PAH incidence rate of 38% in Th/To positive SSc patients [18].

### 2.6 Anti-U11/U12RNP Antibodies

Anti-U11/U12RNP is associated with high incidence of PF (>80%) and severe gastrointestinal involvement [9,19]. SSc-ILD in Anti-U11/U12 positive patients is severe and rapidly progressive with a 2.25 fold greater risk of death or lung transplant in SSc-ILD patients [19]. Interestingly, overall survival rates are equivalent to anti-U11/U12 negative SSc patients [3,19]. Anti-U11/12 SSc patients have significantly increased rates of synchronous cancer diagnosis [13].

### 2.7 Anti-PM/Scl Antibodies

Anti-PM/Scl antibodies are associated with scleroderma-myositis overlap syndrome [20]. This antibody is associated with a good prognosis with low incidence rates of SRC, PAH, and cardiac scleroderma [3,20-22]. In contrast to other subsets the overall mortality rate of Anti-PM/Scl in early stages of SSc is low but starts to increase after 10-15 years from onset [3]. Pml/Scl antibodies are associated with increased incidence of ILD with good functional preservation [8]. The classical phenotype for Anti-Pm/Scl SSc includes mild muscle involvement ILD, calcinosis and cutaneous dermatomyositis [20-22]. Anti-PM/Scl SSc is usually associated with limited cutaneous involvement and may often present without any skin involvement [22,23]. Analysis of the EUSTAR database has shown presence of muscle involvement is associated with more severe scleroderma with higher incidence of cardiac involvement, SSc-ILD, GI involvement, joint contractures, and tendon friction rubs [20,21]. Although a recent single centre cohort suggested association of anti PM/Scl with increased sold organ malignancy and

SRC, reminiscent of some cases of ARA SSc, this association was not confirmed in the multi-centric EUSTAR analysis [20,21].

### 2.8 Anti-Ku Antibodies

Anti-Ku antibodies are also associated with scleroderma myositis overlap with a lower incidence compared to anti-Pm/Scl (<2% overall SSc) [24,25]. They present similar to Pm/SCl positive patients with strong associations with myositis, limited phenotype, dermatomyositis skin rashes, and inflammatory arthritis [23]. Anti-Pm/Scl, Anti-Ku is strongly associated with SSc-ILD with a good functional outcome, and they have a lower incidence of vascular manifestations (Raynaud's, telangiectasias, GAVE) [8,25]. Multiple case studies report Anti-Ku antibodies are associated with immune thrombocytopenic purpura and thrombocytopaenia may be a precursor to anti-Ku antibody-related scleroderma–polymyositis overlap syndrome [26]

### 2.9 Anti-U1RNP Antibodies

Anti-U1RNP phenotype is a mix of SSc, systemic lupus erythematosus (SLE) and polymyositis [8]. Patients with this antibody are usually classified as having mixed connective tissue disease (MCTD) but if a patient exhibits predominantly scleroderma symptoms than they are classified as scleroderma. Anti-U1RNP SSc Is associated with younger onset, limited cutaneous subset, inflammatory arthritis, myositis and ILD [9]. Anti-U1RNP-SSc patients who develop PAH have worse prognosis than Anti-U1RNP-SLE/MCTD patients [27]

### 2.10 ANA negative ENA negative Scleroderma (ANA-ENA-)

ANA-ENA- SSc patients expectedly have a heterogenous clinical phenotype. AN-ENA- SSc is associated with male gender, diffuse cutaneous subset, widespread pigmentation, and lower

incidence of: GI involvement, vasculopathy and SRC [28]. As diagnostic tests continue develop, newer antibodies within this group are being identified.

Anti-elF2B is a novel anti-cytoplasmic antibody found in ANA-ENA- SSc patient which is associated with diffuse cutaneous involvement and SSc-ILD [29,30]. The association with ILD is extremely high with two independent studies reporting a 100% ILD incidence rate with Anti-eIF2 [8,29,30]. Anti-RuvBL1/2 in ANA-ENA- SSc is associated with overlap myositis and diffuse cutaneous subset [31].

**3. Mechanisms Underlying mutual exclusivity**

Both genetic and environmental factors contribute to the risk of SSc. Genomic studies have shown clear genetic risk factors in scleroderma, however, familial occurrence of SSc is uncommon accounting for <2% of overall cases [32]. A recent case report detailed three cases of systemic sclerosis within one family all of whom had different ANA subtypes (ACA, ATA, ARA) [32]. This case reports feeds the upcoming hypothesis that the predisposition to SSc is genetic however the phenotype and ANA subtype is variable and more influenceable by environmental factors. However, it should also be noted that a larger cases series showed that the observed SSc-specific antibody concordance within each multicase SSc family was statistically more common than expected by chance alone [33]

A recent genomic risk score tool utilizing 33 alleles can accurately differentiate patients with SSc and healthy controls [34]. The genetic risk score was not able to differentiate between ANA subtypes once again displaying factors beyond genetics account for SSC phenotype/ANA subtype.

## 3.1 Genetics of SSc

Immune tolerance breakdown is key to scleroderma pathogenesis. In particular, the dendritic cell (DC)-T cell axis is integral to the development of autoantibodies in SSc.

Numerous studies have illustrated multiple HLA alleles that confer with increased risk of SSc, In particular within the HLA class II peptide binding groove [34,35,36]. Known HLA associations have been summarised in table 2.

The largest genome-wide-association study to date by Accosta-Herrera at al. (2021) found a novel association of increased scleroderma risk and HLA Class I locus HLA-B*08:01 which suggests novels mechanisms of pathogenesis involving CD8+T helper cells [35].

27 non-HLA GWAS level associations have been identified. 6 gene loci have been highlighted with SSc susceptibility (ARHGAP31, BLK, CD247, TNIP1, CSK, STAT4-a) [37]. The genes affected suggest that most non-HLA genetic variations are related to transcriptional regulatory mechanisms.

It is notable that genetic factors are likely to underlie some of the observed differences in autoantibody frequency across different racial groups. For example, varying prevalence of autoantibodies based on race. For example, anti-fibrillarin antibodies are the second most common SSc related antibody in African American patients, most probably due to high rate of HLA-DRB1*08:04 positivity in this population [38]. Recent analysis suggests that this may be explained by molecular mimicry [39].

## 3.2 Antigen Triggers

Human cytomegalovirus (CMV) infection is associated with increased incidence of SSc [40]. CMV associated antibodies Anti-UL83 and Anti-UL44 have been associated with ARA and ACA

seropositivity [41]. These two CMV associated antibodies have also been associated with higher incidence of anti-Ro52 antibodies, a supplemental SSc antibody associated with progressive ILD [42,43]. The process underlying CMV and SSc is likely molecular mimicry leading to generation of autoantibodies.

Several case studies link silicone breast implants with increased incidence of ARA positive scleroderma and silicone breast implant rupture has been implicated in induction of ARA positive SSc [44,45].

### 3.2 Molecular basis of pathogenic mechanisms of ANA

ANA subtypes have a direct role in altering gene expression through immune-complexes (IC) [10,40,46,47]. ANA-IC have been shown to modulate pro-inflammatory and pro-fibrotic pathways in healthy control fibroblasts and endothelial cells thought to be mediated via toll-like receptors [46]. Distinct differences in between ANA-IC subset and gene expression with ATA-ICs influencing Interferon mRNA signatures whilst ARA-IC activating Nuclear Factor-κB (NFKB) signaling [46].

The BIOPSY and GENISOS studies both showed differing gene expression patterns between ANA subtypes with differences noted in IL-6 signalling, adhesion cascade activation and angiogenesis [10,47]. The GENISOS study reported ACA enriched keratinocyte differentiation, ATA enriched cellular stress response pathways and ARA upregulated pathways of NFKB signalling and Tumour growth factor-beta signalling [47].

## 4. Management implications of ANA

### 4.1 Interstitial Lung Disease

ILD is the leading causes of death in scleroderma patients. 50-80% of SSc patients develop ILD during the disease [8,48,49]. Disease behavior is highly variable with <30% of SSc-ILD patients progressing to respiratory insufficiency [8].

Most SSc-ILD patients are diagnosed within the first 5 years after onset with a peak incidence at 2 years from SSc onset [3].

The current gold standard of diagnosis is high resolution computerised tomography (HRCT) however the use of this is limited due to its high radiation dose and access [48]. ANA status helps detect patients more at risk of developing SSc and, after diagnosis, risk of progression.

Diffuse cutaneous subset is strongly associated with higher incidence and severity of SSc-ILD [3,50]. ACA is protective against ILD whereas ATA antibodies are associated with the highest incidence of ILD independent of cutaneous subset [3]. In limited scleroderma, alongside ATA, ANAs that are associated with high incidence rates of SSc-ILD are Anti-Th/To and Anti-U11/U12RNP [8].

ATA seropositivity in multiple studies has been associated with faster and more severe progression [8]. A large cohort single-site study demonstrated patients ATA positivity was predictive of forced vital capacity (FVC) decline >70% within 5 years of onset in SSc-ILD [48].

Anti-U11/U12 RNP antibody in SSc-ILD patients is associated with increased risk of progress to end stage respiratory disease and death [19]. Conversely, Anti-PM/Scl and Anti-Ku antibodies are associated with non-severe ILD[8,20-26].

4.2 Pulmonary Hypertension

Second to SSc-ILD, PAH is one of the leading SSc-related causes of mortality [52,53]. The overall incidence of PAH is 5-10% and remains a serious clinical challenge [52,53]. Mortality

rates remain high in this cohort of patients with 3-year survival for SSc patients with PAH estimated at 56% compared with 94% in those without PAH [53].

Earlier detection of PAH has been found to improve clinical outcomes. Organ surveillance using echoes and pulmonary function tests at regular intervals help detect PAH. Gold standard of diagnosis remains through right heart catheter studies which can be costly and difficult to access [53]. The DETECT study devised a two-step risk stratification tool (named DETECT) to help diagnose PAH at earlier, milder stages. Of note this tool uses ACA status within its algorithm [53].

In contrast to SSc-ILD, Incidence is lowest in early stages of scleroderma and equivalent across dcSSc and lcSSc [3]. Incidence is low in the first 10 years (1-2%/year) after which incidence gradually increases [3]. ACA and Th/To are associated with higher incidence. U3RNP+ (Anti-fibrillarin) antibodies confer highest risk of PAH whilst ATA and Anti-PM/Scl have lowest risk [3].

4.3 Scleroderma Renal Crisis

SRC is a life-threatening complication of SSc characterized by malignant hypertension and acute renal failure. Despite the revolutionary impact of ACE-inhibitors on SRC survival, SRC is still associated with high mortality with a 5-year survival rate of 50-90% [54].

Early detection and management is integral to reducing mortality rates. ARA holds the highest risk of developing SRC with a 10-fold increased risk of SRC [10]. Other antibodies with increased risk are Anti-U1RNP and ATA [9].

A single-site Japanese study showed ATA seropositivity was associated with worst outcomes with significantly higher 1-year mortality risk 6 times greater than ATA-negative SRC patients [9].

For patients at high-risk it is recommended regular blood pressure checks, sparring use of prednisolone, regular monitoring of urine protein creatinine ratios at clinic appointments.

4.4 Malignancy

Malignancy is the most common cause of non-SSc-related mortality accounting for 38% of non-SSc-related deaths, and third leading cause of overall death in scleroderma patients overall [13]. Scleroderma is associated with a 41-75% increased risk of malignancy on observational studies compared to the general population [13].

ARA positive patients have been found to have a marked increase in incidence of cancer across multiple studies with a 4-7 fold increase in odds of cancer within 6 months to 5 years [13]. 9-18% of cancer diagnoses in ARA positive patients were synchronous (diagnosed between 6 months and 12 months after SSc onset) [13,55].

Other antibodies associated with increased risk of cancer are ATA and U1RNP with a 3-5 fold increase in cancer diagnosis within the first 2 years of SSc onset compared to general SSc population in both subtypes [13]. Cancers with generally increased incidence with scleroderma include lung, haematological, oesophageal and breast cancer [56].

There is no agreed guideline on cancer screening with scleroderma patients. In SSc patients with high-risk ANA cross-sectional imaging may be warranted.

4.5 Differential Therapeutic Response

Reviewing data from recent clinical trials shows ANA subtypes have different treatment responses to therapeutic agents.

Riociguat, soluble guanylate cyclase stimulator, was trialled in dSSc in the RISE-SSc study. Overall the study found no significant impact in reducing skin thickening compared to placebo. However, subgroup analysis showed a substantial decrease in skin fibrosis progression in ARA-positive patients but not ATA positive [57].

In contrast, the faSScinate study that explored the use of tocilizumab in dcSSc showed highly significant decrease in rates of lung function decline in ATA positive patients but not in ATA negative patients in phase 2 and 3 studies [58,58].

There is difficulty in retrospective subgroup analysis as clinical trial design is often underpowered to explore these relations. This is illustrated with the SENESCIS trial of nintedanib on SSc-ILD which showed a numerically greater preservation of lung function in ATA-negative SSc, but no significant differences [60,61].

## 5. Future considerations

### 5.1 Need for reclassification

Separation of SSc patients into limited and diffuse subsets based on their extent of skin involvement incompletely reflects the distinct clinical patterns within each group. Conversely, categorizing patients only based on their serological profile does not produce replicable clinical patterns [3,7].

Currently, most SSc experts use systems of subtyping SSc patients in their practice [59]. Enriching our classification system to include cutaneous subset with serological status provides a robust categorization. Hybrid classification system offers the best predictor of

clinical outcome and prognosis to help aid risk management and organ surveillance [3,52,63]. Efforts have been initiated to update the SSc classification system and are most likely to involve a hierarchical approach.

### 6.2 Standardizing ANA testing

A substantial limitation in focusing clinical acumen on autoantibodies is the lack of standardization in diagnostic lab techniques and interpretation [63]. In scleroderma, there are numerous commercial diagnostic assays that utilise different methodology. For the two most predominate ANA subtypes, ACA and ATA, there is high concordance of results across differing assays, commercial platforms and laboratories [63,64]. However, despite reported concordance for anti-Scl-70 testing among the different testing methods some concerns remain about the specificity of Scl-70 antibody testing based on multiplex methods [65,66]. Moreover, other ANA have high discordance rates, in particular, anti Pm/Scl, anti-fibrillarin, and Th/To [67]. Further work needs to be implemented to achieve greater harmonisation between centres.

### 6.3 Incorporating ANA into Clinical Trial Design

As aforementioned, ANA subgroups may respond differently to therapeutic agents. Despite this knowledge, majority of clinical trial designs do not account for ANA subset and broadly divide patients into lcSSc and dcSSc. This results in multiple potentially useful therapeutic agents being labelled as ineffective when they may have a significant impact if used on the correct ANA subtype.

Stratification strategies based on ANA and cutaneous subtype offer the opportunity of selecting and identifying the best candidates most likely to achieve the greatest magnitude of treatment benefit for each targeted therapy.

Limitations of subgrouping by ANA status includes the relatively small sample sizes of clinical trials due to the rarity of disease itself.

**7. Conclusion**

As in some other Immune-mediated inflammatory disease such as idiopathic inflammatory myopathies and ANCA-associated vasculitis, in scleroderma there are important and disease specific 'ANA-clinical phenotype links. These have important implications for management, including monitoring, risk stratifications and treatment decisions (especially targeted therapies) and because of this are also important for clinical trial design to optimise informative subject enrolment and minimise is across treatment arms in parallel group trials. Finally, the ANA associations are giving powerful insight into disease mechanism.

**Key points:**

- Antinuclear autoantibodies (ANA) used to diagnose systemic sclerosis are associated with distinct clinical phenotypes and outcome.
- Mutual exclusivity of ANA patterns in systemic sclerosis is related to HLA association and means that these reactivities may be used in risk stratification
- Clinically relevant associations include anti-RNA polymerase III and scleroderma renal crisis, anti-topoisomerase 1 and lung fibrosis and anti-centromere antibody with limited cutaneous subset.
- In assessing ANA subgroup it is important to consider the reliability of the assay platform used for determination.

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**Table 1 [Original] Clinical Phenotype of anti-nuclear antibodies associated with Systemic Sclerosis [References 3-33]**

| Antibody | ANA pattern | Intracellular Target | Prevalence in SSc patients [9,30] | Cutaneous Subtype Propensity | GI involvement | PAH | Lung Involvement | Oncology | Other |
|---|---|---|---|---|---|---|---|---|---|
| ACA | Speckled Centromere | Centromeric nucleoproteins | 28-37% | Limited (98%) | High prevalence of oesophageal dysmotility (80%) | Increased risk | Reduced incidence | - - | Associated with Calcinosis, DU |
| ATA | Nucleolar/ Speckled or homogenous | Type I topisomerase | 20-30 % | Diffuse Sustained skin fibrosis | - | Moderately decreased risk | 80% develop ILD of which up to 30-50% progress to severe ILD | 3-5 fold increased risk of synchronous cancer | DU in early stages |
| ARA | Nucleolar/ Homogenous | RNA Polymerase type 3 | 4-19% | Diffuse phenotype Severe Early skin progression followed by rapid improvement | Highest prevalence of GAVE | - | Lower risk of SSc-ILD | 4-7-fold increased risk of cancer | 10-fold increased risk of SRC Decreased rate to cardiac scleroderma |
| Antifibrillarin | Nucleolar/ homogenous | Fibrillarin | 1 -8% (16-19% in AA) | Diffuse | Severe GI involvement | High risk | - | - | High risk of cardiac scleroderma Increased risk of Myopathy |
| Anti Th/To | Nucleolar | nucleolar 7–2/8–2 RNA-protein complex | 2-5% | Limited | Oesophageal dysmotility | Increased risk | 50% develop of which 30% progress | Reduced risk | Less DU |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Anti-U11/U12 | Speckled | U11/U12 RNA Polymerase complex | 1-3% | Limited/Diffuse | Severe GI involvement | - | 80% develop<br>Often severe and rapidly progressive | 3-5 fold increased risk of synchronous cancer | - |
| Anti-PM/Scl | Nucleolar | Nucleolar PM/Scl macromolecular complex | 3-6% (25% of SSc-Myositis overlap) | Limited<br>Can present without skin involvement | - | Decreased risk | 35-87% develop<br>Good functional outcome | - | Decreased risk of cardiac scleroderma and SRC<br>Increased risk of Myositis, Inflammatory arthritis, calcinosis |
| Anti- Ku | Speckled | Ku complex (p70/p80 heterodimer) | 2% (15% of SSc-Myositis overlap) | Limited | Decreased risk of GAVE | - | Up to 76% develop<br>Good functional outcome | - | Lower incidence of Raynaud's , telangiectasia |
| Anti-U1RNP | Speckled | small nuclear ribonucleoproteins | 5-35 % (100% in Mixed CTD) | Limited | - | Increased risk | 35% develop<br>20% progress | - | Increased risk of Inflammatory arthritis, Myositis |
| AntiEIF2B | ANA negative Cytoplasmic staining | Eukaryotic initiation factor-2B | <1% | Diffuse | - | - | High incidence<br>Up to 100% develop | - | - |

*AA, Afro-American population; ACA, Anti-centromere antibodies ; ARA, Anti-RNA polymerase III, ATA, Anti-Topisomerase I; CTD, Connective tissue disease; DU, digital ulcer; GAVE, gastric antral vascular ectasia; GI, gastrointestinal; ILD, Interstitial Lung Disease; SRC, scleroderma renal crisis; SSc, Scleroderma.*

**Table 2 [Original ]Summary of HLA associations of Scleroderma**

| Gene | Variation | Association |
|---|---|---|
| HLA-B | 08*01 | Overall SSc |
| HLA-DPA1 | HLA-DPA1*02:01 | ATA positive SSc |
| HLA-DPB1 | HLA-DPB1*08:01 | ACA positive SSc |
| | HLA-DPB1*13:01 | Overall SSC (1.2 OR)<br>ATA positive SSc (4.3 OR) |
| HLA-DQA1 | HLA-DQA1*02 :01 | Limited SSc |
| | HLA-DQA1*04:01 | ACA positive SSc (2.7 OR) |
| | HLA-DQA1*05:01 | Exclusive for DcSSc<br>ATA positive SSc (2.1 OR) |
| HLA-DQB1 | HLA-DQB1*02:02 | Overall SSc |
| | HLA-DQB1*03:01 | ATA positive SSc |
| | HLA-DQB1*05:01 | ACA positive SSc (2.0 OR) |
| | HLA-DQB1*06:09 | Antifibrillan positive SSc (3.8 OR) |
| HLA- DRB1 | HLA- DRB1*07:01 | ACA positive SSc (0.1 OR) |
| | HLA- DRB1*08:04 | Overall SSc (3.2 OR)<br>AntiFibrillan SSs (7.4 OR) |
| | HLA- DRB1*11:02 | Overall SSc (2.2 OR) |
| | HLA- DRB1*11:04 | Overall Ssc<br>ARA positive [45]<br>ATA positive SSc (6.5 OR) [46] |

*ACA, Anti-centromere antibodies ; ARA, Anti-RNA polymerase III, ATA, Anti-Topisomerase I; HLA, human leukocyte antigens; OR, Odds Risk; SSc, Scleroderma,*