TABLE 382-2 SUBSETS OF SYSTEMIC SCLEROSIS (SSC): FEATURES OF LIMITED CUTANEOUS SSC VERSUS DIFFUSE CUTANEOUS SSC

Characteristic Feature	Limited Cutaneous SSc	Diffuse Cutaneous SSc
Skin involvement	Indolent onset. Limited to fingers, distal to elbows, face; slow progression	Rapid onset. Diffuse: fingers, extremities, face, trunk; rapid progression
Raynaud's phenomenon	Antedates skin involvement, sometimes by years; may be associated with critical ischemia in the digits	Onset coincident with skin involvement; critical ischemia less common
Musculoskeletal	Mild arthralgia	Severe arthralgia, carpal tunnel syndrome, tendon friction rubs
Interstitial lung disease	Slowly progressive, generally mild	Frequent, early onset and progression, can be severe
Pulmonary arterial hypertension	Frequent, late, may occur as an isolated complication	Often occurs in association with interstitial lung disease
Scleroderma renal crisis	Very rare	Occurs in 15%; generally early (<4 years from disease onset)
Calcinosis cutis	Frequent, prominent	Less common, mild
Characteristic autoantibodies	Anticentromere	Anti–topoisomerase I (Scl-70), anti-RNA polymerase III

grouped into diffuse cutaneous and limited cutaneous subsets defined by the pattern of skin involvement, as well as clinical and laboratory features (Table 382-2). Diffuse cutaneous SSc (dcSSc) is associated with extensive skin induration, starting in the fingers and ascending from distal to proximal limbs and the trunk. These patients often have early interstitial lung disease and acute renal involvement. In contrast, in patients with limited cutaneous SSc (lcSSc), Raynaud's phenomenon may precede other manifestations of SSc by years. In these patients, skin involvement remains limited to the fingers (sclerodactyly), distal limbs, and face, and the trunk is not affected. The constellation of calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia, seen in some lcSSc patients, is termed the *CREST syndrome*. Visceral organ involvement in lcSSc tends to show insidious progression, and pulmonary arterial hypertension (PAH), interstitial lung disease, hypothyroidism, and primary biliary cirrhosis may occur as late complications. In some patients, Raynaud's phenomenon and other characteristic features of SSc occur in the absence of skin thickening. This syndrome has been termed *SSc sine scleroderma*.

EPIDEMIOLOGY

SSc is an acquired sporadic disease with a worldwide distribution and affecting all races. In the United States, the incidence is estimated at 9–19 cases per million per year. The only community-based survey of SSc yielded a prevalence of 286 cases per million. There are an estimated 100,000 cases in the United States, although this number may be significantly higher if patients who do not meet strict classification criteria are also included. Rates of SSc in England, Australia, and Japan appear to be lower. Age, gender, and ethnicity are important in disease susceptibility. In common with other connective tissue diseases, SSc shows a strong female predominance (4.6:1), which is most pronounced in the childbearing years and declines after menopause. Although SSc can present at any age, the peak age of onset for both limited and diffuse cutaneous forms is 30–50 years. The incidence is higher in blacks than whites, and disease onset occurs at an earlier age. Furthermore, blacks with SSc are more likely to have diffuse cutaneous disease associated with interstitial lung involvement and a worse prognosis.

GENETIC CONSIDERATIONS

In general, SSc shows modest heritability, and the genetic associations identified to date make only a small contribution to disease susceptibility. Concordance rates for SSc are low (4.7%) in monozygotic twins, although concordance for antinuclear antibody (ANA) positivity is significantly higher. On the other hand, evidence for genetic contribution to disease susceptibility is provided by the observation that 1.6% of SSc patients have a first-degree relative with SSc, a prevalence rate markedly increased compared to the general population. The risk of Raynaud's phenomenon, interstitial lung disease, and other autoimmune diseases, including systemic lupus erythematosus (SLE) (Chap. 378), rheumatoid arthritis (Chap. 380), and autoimmune thyroiditis (Chap. 405), is also increased. Approaches to study the role of genetics in SSc use candidate gene single nucleotide polymorphism (SNP) analysis and genome-wide association studies (GWASs). Candidate gene studies in SSc have shown associations with multiple gene variants, many related to B and T lymphocyte activation and signaling (*BANK1*, *BLK*, *CD247*, *CSK*, *IRAK1*, *IL2RA*, *PTPN22*, and *TNIP1*). *IRAK1*, which codes for a gene involved in both innate and adaptive immunity, is the first X-linked gene associated with SSc and may contribute to female predominance. Other gene variants associated with SSc are involved in innate immunity and the interferon pathways (*IRF5*, *IRF7*, *STAT4*, *TNFAIP3*, and *TLR2*). In addition, candidate gene studies and GWAS both identified association with genes in the major histocompatibility complex (MHC), including *NOTCH4* and *PSORSC1*. In addition to disease susceptibility, some of these genetic loci are associated with particular SSc disease manifestations or serologic subsets, including interstitial lung disease (ILD) (*CTGF*, *CD226*), PAH (*TNIP1*), and scleroderma renal crisis (*HLA-DRB1**). Although the functional consequences of these gene variants are currently not well understood, they may result in altered immune function, leading to increased susceptibility to autoimmunity and inflammation. Of note, many of the genetic variants associated with SSc are also seen in other autoimmune disorders, including SLE, rheumatoid arthritis, and psoriasis, suggesting common pathways shared among these conditions. The genetic associations identified to date only explain a fraction of the heritability of SSc, and GWASs, fine mapping, and resequencing of DNA regions of interest to identify additional genetic susceptibility factors in SSc, particularly rare variants, are currently ongoing.

ENVIRONMENTAL AND OCCUPATIONAL RISK FACTORS

Given the relatively modest genetic contribution to disease susceptibility, environmental factors, such as infectious agents, intestinal microbiota, and occupational, dietary, and drug exposures, are likely to play a major role in causing SSc. Patients with SSc show evidence of chronic infection of lesional tissue with Epstein-Barr virus (EBV). They also have increased antibodies to human cytomegalovirus (hCMV), and anti–topoisomerase I (Scl-70) autoantibodies recognize hCMV-associated antigenic epitopes, suggesting molecular mimicry as a possible mechanistic link between hCMV infection and SSc. An epidemic of a novel syndrome with features suggestive of SSc occurred in Spain in the 1980s. The outbreak, termed *toxic oil syndrome*, was linked to contaminated rapeseed oils used for cooking. Another epidemic outbreak, termed *eosinophilia-myalgia syndrome* (EMS), occurred a decade later and was linked to the consumption of L-tryptophan-containing dietary supplements. Although both of these novel toxic-epidemic syndromes were characterized by scleroderma-like chronic skin changes and variable visceral organ involvement, they were associated with clinical, pathologic, and laboratory features distinguishing them from SSc. Occupational exposures tentatively linked with SSc include silica dust in miners, polyvinyl chloride, epoxy resins, and aromatic hydrocarbons including toluene and trichloroethylene. Drugs implicated in SSc-like illnesses include bleomycin, pentazocine, and cocaine, and appetite suppressants linked with pulmonary hypertension. Although case reports and series describing SSc in women with silicone breast implants had raised concern regarding a possible causal role of silicone