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Genetic and Environmental Contributions to Systemic Sclerosis: Current Evidence and Future Directions in Precision Disease Profiling

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ABSTRACT

Systemic sclerosis (SSc) is a complex autoimmune disease characterized by connective tissue involvement and a diverse array of clinical manifestations. The pathophysiology of SSc, which encompasses systemic sclerosis and localized scleroderma, remains incompletely understood. This review provides an overview of the genetic and environmental factors implicated in the development of SSc, as well as the advancements in scientific methods utilized to study the disease.

Genetic factors, particularly human leukocyte antigen (HLA) genes within the major histocompatibility complex (MHC) region, have been extensively linked to susceptibility to SSc. Research has identified specific HLA alleles, including HLA-DPB1 and HLA-DRB1, to be associated with distinct clinical subsets and autoimmune responses in different ethnic populations. Additionally, non-HLA genes, such as IRF5, STAT4, IL12, IL12RB, CD247, PRDM1, TNFAIP3, TNIP1, CSK, and GSDMA, have been implicated in SSc susceptibility and pathogenesis.

Environmental factors, including food contaminants, silica dust, and certain drugs, are known to contribute to the onset of SSc. The interplay between genetic susceptibility and environmental influences emphasizes the multifactorial nature of SSc etiology.

Scientific methods, such as genome-wide association studies (GWAS) and genomic risk scores, have provided insights into the genetic basis of SSc and its subtypes. These methods have aided in identifying specific genetic variations associated with SSc development, helping to elucidate the complex interplay of genes involved in immune regulation and inflammatory responses.

In conclusion, a comprehensive understanding of the genetic and environmental factors, as well as the scientific methods used in SSc studies, is essential for advancing the diagnosis, prognosis, and treatment of SSc, ultimately leading to improved clinical outcomes for individuals affected by this debilitating autoimmune disease.

Keywords: scleroderma, systemic sclerosis, genetics, GWAS, risk factors, autoimmunity, inflammation

INTRODUCTION

Systemic sclerosis, or scleroderma, is a rare autoimmune disease that affects connective tissue. Its pathophysiology is complex and remains incompletely understood. There are 2 main forms of scleroderma - systemic sclerosis and localized scleroderma (which includes morphea, linear scleroderma, and scleroderma en coup de sabre). Depending on serological and clinical criteria, the former can then be divided into diffuse systemic sclerosis and limited systemic sclerosis (also known as CREST syndrome, which stands for Calcinosis, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia). Despite the notable progress in understanding the pathogenesis of the disease, scleroderma still displays considerable morbidity and mortality rates [1,2].

Localized scleroderma targets the skin and subcutaneous tissue, and as a result, patches of thickened skin are formed. The biopsy of the tissue shows dermal fibrosis that resembles the histopathological changes found in areas affected by systemic sclerosis. Regardless of the similarity, it is not linked to the Raynaud phenomenon, digital ischemic events, neither it is to internal organ involvement. Even though the antinuclear antibodies can be found in up to 50% of localized scleroderma cases, there is no anti-RNA polymerase III or more specific autoantibodies such as anti-centromere (ACA) and anti-Scl-70 [3]. (ATA) Localized scleroderma is not associated with increased mortality, while systemic sclerosis is, as it affects other parts of the body and internal organs; the classification of the latter depends on skin involvement [4,5].

Formerly known as CREST syndrome, limited cutaneous systemic sclerosis is recognized by the skin fibrosis of the areas distal to the elbows and/or knees and, in some cases, of the face and neck. It does not involve the trunk, unlike diffuse cutaneous systemic sclerosis, which also may target areas proximal to the elbows and/or knees. Positive autoantibodies and certain systemic manifestations are linked to both limited and diffuse cutaneous systemic sclerosis [6]. For systemic sclerosis, antinuclear antibodies make appearance in more than 90% of the cases, and at least one of the more specific autoantibodies (ACA, anti-Scl-70, and anti-RNA polymerase III) can be found in up 70% of the cases. Scleroderma most often targets the skin, but it can also affect skeletal muscles, pericardium and internal organs, such as gastrointestinal tract, lungs and kidneys. The symptoms of scleroderma may largely resemble other rheumatological or immunological diseases and their severity can alter with respect to the timing of the diagnosis [7,8].

GENETIC AND ENVIRONMENTAL FACTORS

Different studies on the Systemic Sclerosis (SSc) have revealed that several genes are responsible for the inflammation control and autoimmunity, and thus are connected to the disease progression and development. This was studied by analyzing human leucocyte antigen genes in twins at first, and more recently researched in bigger genome-wide association studies [9-11].

Moreover, it was also discovered that SSc and scleroderma-like conditions can be caused by certain environmental factors. Despite the fact that their exact influence mechanism is not yet understood, it is already known that various food contaminants, silica dust and drugs are among the constituents can increase the likelihood of the disease. According to the data, a combination of external factors and genetic susceptibility are directly involved in the initial disease induction [12,13].

SCIENTIFIC METHODS USED IN SSC STUDIES

Comparing the information contained in DNA fragments of a subject to that of a control group is one of the simplest ways to shed light on the influence of the genetic material in the given candidate. Despite the fact act that this method makes it easier to detect any alterations in single nucleotides, referred to as Single-Nucleotide-Polymorphisms (SNPs), it cannot show if a given SNP will lead to an actual change in the structure of the final protein [14]. This means that such studies do not provide any information on which of the spotted SNPs may result in clinical manifestation. Alternatively, candidate gene testing allows to avoid this issue as it examines genes that are already linked with a known disease, an important process, or any other known pathophysiological consequence [15,16].

The genome-wide association study (GWAS) investigates the entire genome of people with a disease and then compares it to the control group that shows no signs of it. Since GWAS typically focuses on the association between SNPs and a given trait, it not only allows to spot a SNP already in the context of a given disease, but also to locate genes that were not previously linked to it [17,18].

Genomic Risk Score is a newly created estimate of the likelihood of development of a certain disease, that was successfully tested in various diseases, including SSc [19].

The inception and development of SSc is evidently influenced by genetics, even though it is not the only contributing factor. Systemic Sclerosis is a representative of prototypical autoimmune inflammatory disorders that are significantly influenced by genetics. In cases like that, the genes that are responsible for the regulation of immune responses become a central point of interest. These genes can be divided in to 5 categories [20]:

I. Major Histocompatibility Complex Region (MHC) Human Leucocyte Antigene (HLA) genes;

II. Major Histocompatibility Complex Region (MHC) non-HLA genes;

III. Non-Major Histocompatibility Complex (non-MHC) Region genes;

IV. Genes involved in cytokine synthesis regulation;

V. Genes involved in immune signaling pathway regulation.

Table 1. Genetic Variants Associations with Systemic Sclerosis

Category	Gene/Environmental Factor	Alleles/Variants	Associated Findings	Implications
MHC Genes	HLA-B	HLA-B*44:03	Protective against limited cutaneous SSc (lcSSc); interacts with NK cell receptors	May reduce risk or severity of SSc in certain populations
	HLA-DPB1	HLA-DPB1*1301	Strongly linked to Anti-Topoisomerase I antibody; associated with diffuse cutaneous SSc (dcSSc)	Indicates heightened immune response contributing to disease pathology
	HLA-DRB1	HLA-DRB1*1101, HLA-DRB1*1104	Frequent in SSc patients; linked to anti-topo I autoantibodies	Suggests potential markers for disease stratification and prognosis
	HLA-DQA1	HLA-DQA1*02:01, HLA-DQA1*05:01	Exclusively linked to lcSSc and dcSSc respectively	Helps identify subtype-specific genetic risk factors
Non-HLA Genes	IRF5	rs2004640	Associated with susceptibility to SSc, particularly in fibrotic phenotypes	Highlights the role of immune signaling in SSc pathogenesis
	STAT4	rs7574865	Linked to increased risk of limited SSc and pulmonary fibrosis	Indicates the gene's involvement in T-cell differentiation and immune responses
	IL12RB2	rs3790567	Identified in association studies; functional implications unclear	Suggests further research needed on the IL-12 pathway's role in SSc
	CD247	rs2056626	Identified as a susceptibility locus; mixed findings in different studies	Indicates variability in genetic contributions across populations
	PRDM1	rs4134466	Significant association with SSc in Japanese and European populations	Important for understanding mechanisms of B-cell differentiation and immune function

MAJOR HISTOCOMPATIBILITY COMPLEX REGION HUMAN LEUCOCYTE ANTIGEN GENES

SSc, being an autoimmune inflammatory disease, is strongly connected with genetic association; specifically, a combination of MHC alleles. The band 6p21.3 at the short arm of chromosome 6 contains the largest cluster of the human genome that carries information about the MHC molecule. The locus can be divided into three regions, which are classified as class I, class II and class III genes [21-23].

The first two classes are both directly linked to the immune response, but are responsible for synthesis of different molecules. The gene products of the MHC are called Human Leukocyte Antigens (HLA), and the gene system itself is the most polymorphic one yet. Notably, the β chain of the class I molecule is encoded on chromosome 15 (outside of the HLA region), so only α polypeptide chain is contained in the class I genes [24,25]. Most somatic cells express class I genes, however, the level of expression differs with respect to the tissue. Even though there is a total of 20 class I genes in the HLA region, the main focus is on the class Ia genes (HLA-A, HLA-B and HLA-C), as these three exhibit the most significant contribution to immune response [26,27].

Class II of the MHC genes is associated with a different set of immunocompetent cells. The MHC II molecules are expressed on the surfaces antigen-presenting cells, lymphocytes, macrophages, dendritic and thymic epithelial cells. By binding the pathogen-derived antigens, MHC facilitates the recognition of antigens by the immune system. The MHC

molecules are quite efficient due to variability within each gene, and without them the antigens would not be recognized by the immune system [28]. This means that the chance of pathogens getting away is close to none, but on the other hand it leads to an elevated risk for mutations that could manifest into autoimmunity. For over half a century, the HLA region has been heavily linked to the autoimmune diseases, as it encodes the genes that are most essential for the immune response [29-31].

It has been proven by various GWAS that MHC is a susceptibility loci for SSc, along with twelve various gene loci. While MHC was identified to be the most significant, HLAB, HLAC and several HLA class II genes (DRA, DRB1, DRB5, DQA1, DQB1, DMB, DOA, DPA1, DPB1, DPB2) were also associated with development of the disease. A comprehensive study on diverse ethnic backgrounds has identified that HLA class II alleles linked to SSc are different across Caucasian, African and Hispanic Americans [32,33]. It also correlates with a different Korean study, which revealed a strong association between SSc and HLA-DPB1 and DPB2, especially in subjects that had the Anti-Topoisomerase I antibody (anti-topo I). Other studies demonstrate a direct connection between the synthesis of disease-specific antibodies and the alterations in the MHC-encoding genes; for example, one of the studies showed that Caucasian SSc patients with Anti-Topoisomerase Autoantibodies could be directly linked to HLA DPB1*1301 and HLA DRB1*1104. Another multi-ethnic research of SSc identified HLA-DRB1*08 to be the most common among African Americans with the condition, while HLA-DQB1*1301 was associated with both White and African American patients [34,35].

While researching the connection between certain class II genes (HLA-DRB1 and HLA-DQB1) and a selection of autoantibodies, it was discovered that anti-topo I autoantibody response was linked with HLA-DRB*11 across all three ethnic groups. In particular, compared to patients with SSc that had no anti-topo I, HLA-DRB*1101 was more frequently found in White and African Americans with the autoantibody [36,37]. Similarly, HLA-DRB1*1104 was more often found within the Hispanic SSc patients with ATA compared to the control group without it; moreover, the research also identified a connection between HLA-DQB1*0402 allele and anti-topo I within the Hispanic subgroup. The association between the specific HLA variations and diffuse (dcSSc) and limited (lcSSc) forms of the disease is still unclear, although indirect data were derived from the comparison of recurrences of Anti-Topoisomerase (ATA) and Anti-Centromere (ACA) autoantibodies [38]. Considering that ATAs and ACAs are more commonly associated with the dcSSc and lcSSc respectively, it is possible that haplotypes may be linked with the limited subtype. More specifically, it is suggested that HLA-DRB1*01, HLA-DRB1*04, HLA-DRB1*09, HLA-DQB1*0501, HLA-DDQB1*26 can be connected to lcSSc as they are associated with the presence of ACA antibodies [39,40].

One of the newer studies from Spain provided additional insight on the association between the HLA gene frequencies and SSc forms. Six different alleles were concluded to be independently linked to lcSSc, HLA-DQA1*02:01 being exclusively associated with the limited subphenotype [41]. Similarly, four alleles were associated with dcSSc, HLA-DQA1*05:01 being exclusive to this form. Moreover, the antibody profile can be affected by a selection of HLA alleles; HLA-DRB1*0404, HLA-DRB1*11 and HLA-DQB1*03 distinguishing patients with SSc and anti-RNA polymerase III seropositivity [42]. Another recent research from Thailand identified that all patients with SSc exhibited higher levels of HLA-DRBQ*15:02:01, HLA-DRB5*01:02:01, HLA-DQB1:05:01:24, HLA-HLA-DQA1*01:01:01 and DPB1*13:01:01, the latter being the most susceptible allele. The same could be said for SSc patients that had ATA, but not ACA (SSc/ATA+/ACA-) [43].

Conspicuously, several studies have shown that not all HLA genes add to the predisposition to the development of SSc. A Japanese study has discovered that DRB*13:02, DRB1*14:06, DQB1*03:01 and DPB*02:01 were contributing to the protection against the susceptibility to SSc [44]. Similarly, according to the Australian-American study, HLA-DRB1*07:01, HLA-DQA1*02:01, HLA-DQB1*02:02, HLA-DRB4*01:01 HLA-B*44:03, and HLA-C*16:01 have displayed a protective effect and were associated with lcSSc [45]. The same study identified HLA-DPB1*13:01 to have a strong connection to the increased disease risk in dcSSc.

The relation between SSc and MHC class I is relatively clear. According to recent findings, certain HLA class I allele can regulate the activity of Natural Killer (NK) cells by acting as ligands for killer Ig-like receptors (KIR). HLA-B*44:03 allele has exhibited protective properties against lcSSc. It is a part of HLA-Bw4 KIR ligands, interacting with the specific receptor KIR3DL [46,47]. Recent studies suggest a direct association between several HLA class I and the function of NK cells; fever-inducing KIR3DL1+ SSc patients express the HLA-Bw4 inhibitory ligand unlike the KIR3DL+ controls without SSc. Despite several studies that contradict this statement, it directly correlates with an elevated risk of SSc development [48].

NON-HLA COMPLEX GENES

The innate immune system is generally perceived as the initial barrier against pathogens and cell changes that could disrupt the body. Due to the fact that innate immune system does not distinguish between foreign (xeno) and self-antigens, it can

potentially lead to autoimmune responses. Different sources suggest that it is responsible for the pathophysiology and progression of SSc, as genes that are directly a part of innate responses would also affect the disease course [49].

IRF5

Interferon Regulatory Factor 5 (IRF5) regulates type I Interferon (IFN) signaling, IFN signatures and IFN-inducible genes.

A study in 2009 discovered an association between IRF5 intron 1 rs2004640T allele and SSc, exceptionally in the ATA(+) scSSc with fibrosing alveolitis (FA). This led to a suggestion that rs2004640 could affect the fibrotic phenotype via type I IFN activation. This was followed up by a genotype-phenotype-haplotype correlation analyses of IRF5 with the SNPs rs3757385, rs10954213 and rs2004640, which indicated that the "R" haplotype (C-T-A) granted susceptibility to SSc, especially its diffuse form, while the "P" haplotype (A-G-G) had a protective effect for both FA and dcSSc. The former leads to excessive binding of SP1 transcriptional factor by inferring the CGGGG insertion risk allele; it is also associated with Sjogren syndrome [50].

Another meta-analysis confirmed the association of IRF5 with SSc beyond populations, and a GWAS of SSc in 2010 also strongly affirmed a central role of IRF5 in SSc pathogenesis [51].

STAT4

Signal transducer activator transcriptional factor 4 (STAT4) is crucial for mediating interleukin-12 signaling. A member of a STAT protein family, it also takes part in differentiating helper T-cells and linking innate and adaptive immune responses via type I IFN-mediated IFN-γ production [52].

According to a Caucasian case-control study conducted in 2020, SNP rs7574865 (intron 3) T allele is correlated with STAT4 mRNA expression, thus associating STAT4 with SSc. While it is also known to be connected with other AIDs and susceptibility to limited SSc, it is not linked to the diffuse form of the disease [53]. Additionally, a dosage effect was observed showing individuals with rs7574865 TT genotype higher risk for lcSSc ($P = 1.02 \times 10^{-7}$). Considerable association was also found by two others Caucasian GWASs - however, it is notable that there might me a population overlap between one of the GWASs and the 2020's case-control study [54,55]. A different case-control study of Chinese population reported rs7574865 and rs10168266 to be strongly linked with the presence of ATA ($P = 0.0012$ and $P = 3.1 \times 10^{-4}$, respectively) Pulmonary Fibrosis (PF) ($P = 1.2 \times 10^{-4}$ and $P = 7.7 \times 10^{-4}$, respectively) and dcSSc ($P = 6.4 \times 10^{-4}$ and $P = 0.0015$, respectively). Unlike the Caucasian study, no significant association was found between the analyzed SNPs and ACA or lcSSc [56].

A considerable SSc susceptibility ($P<0.00001$) was associated with rs7574865T in a meta-analysis of six related studies. A similar finding was also discovered in another multiethnic meta-analysis of GWS [57].

Considering how rs7574865T affects SSc subtypes and autoantibody profiles within different ethnicities, it could be possible that rs7574865T is connected to ACA(+) SSc only in European populations. As for the Asian populations, the connection is not as distinctive due to two possible reasons: either the smaller sample size in the conducted research, or the likelihood that different ethnicities are affected by different SNPs [58].

One of the above-mentioned studies that linked IRF5 rs2004640 and susceptibility to SSc and SSc-related FA has also identified additive effects of STAT4 rs7574865, resulting into a 28% increased risk of SSc [59].

Finally, an animal study has showed that compared to the control group, STAT4-deficient mice were protected against bleomycin-induced dermal fibrosis and exhibited lower cytokine production. Although there are still some gaps that need to be filled in, several lines of evidence suggest that STAT4 polymorphisms play a significant role in SSc onset and progression [60,61].

IL12, IL12RB1, and IL12RB2

Type 1 helper T-cell differentiation and is facilitated by the p35 subunit of interleukin-12 (IL-12) encoded by IL12. On the other hand, it antagonizes cell differentiation for type 2 helper T-cells along with IFN-γ [62,63].

SNP rs77583790 was identified to have a strong connection to SSc both in general, and in the lcSSc and ACA(+) subgroup. It is located between SCHIP1, that encodes schwannomin interacting protein 1, and IL12A, a non-HLA loci, distinguished by ImmunoChip Study [64].

The two chains of the IL-12 receptor are encoded by IL12RB1 and IL12RB2. A Caucasian GWAS has suggested their relation to SSc, and follow-up research has identified a link between SSc and rs3790567, an intronic SNP of IL12RB2. Notably, the SNP could have an unknown functional significance or be a tagging another functional SNP [65].

A follow-up study on association signals of 1L12RB1 locus in the ImmunoChip study has identified four SNPs that could be linked with SSc susceptibility: rs8109496, rs2305743, rs11668601, and rs436857. The latter (situated in the IL12RB1 promoter region) was also considered as the possible casual variant. Its minor allele was locked in a cis-expression quantitative trait locus (cis-eQTL) and has displayed a protective effect against SSc by limiting IL12RB1 expression, and thus reducing the IL-12 response. Additionally, a common variant of a gene encoding Tyrosine kinase 2 (V362F of TYK2) involved in IL-12 pathway was associated with SSc susceptibility in the same study [9].

The combination of the above-mentioned data along with the studies on STAT4, suggests the significance of IL-12/STAT4 axis in the pathogenesis of SSc.

CD247

CD3ζ is encoded by CD247 and its expression is directly connected to the immune response. Alterations in the 3' untranslated region of CD247 resulted into lower expression of CD3ζ chain, thus increasing the risk of systemic autoimmunity [65].

A European Ancestry GWAS has distinguished rs2056626 of CD247 as a susceptibility locus for SSc. Similar findings were reported by a different study, additionally identifying minor allele rs2056656G to have a protective effect. Alternatively, non-European studies were unable to identify such relation, leaving the exact role of CD247 as a point of interest for the future studies [66].

PRDM1

A transcription factor PRDM1, also known as BLIMP1 (B-lymphocyte-induced maturation protein 1) is associated with the immune functionality. PRDM1 is important for epithelial and B-cell differentiation, cell proliferation and the immune system, thus also being connected to several AIDs [67,68].

A notable relation between PRDM1 rs4134466 and SSc susceptibility was discovered by a meta-GWAS analysis in Japanese and European populations. While the SNP was independent of rs9373839 in ATG5, also linked to SSc susceptibility, it had scored the highest in H3K4me3 in naïve CD4+ T among other variants. This implies that rs4134466 may have a functional manifestation [69].

TUMOR NECROSIS FACTOR-A-RELATED GENES

Tumor necrosis factor (TNF)-α induced protein (A20) is encoded by TNFAIP3, while TNIP1 encodes TNFAIP3-interacting protein. Both of them negatively affect the TNF-induced nuclear factor (NF)-κB signaling pathway. A20 also suppresses profibrotic signaling, relevant to SSc pathogenesis [70].

A close relation between rs4958881 of TNIP1 and SSc was indicated by a European GWAS. A significantly reduced expression of TNIP1 and TNFAIP3-interacting protein was observed in SSc patients, both in skin lesions and cultured dermal fibroblasts. An association between inflammation/immunity and fibrosis has also been researched as TNIP1 showed in vitro inhibitory effects on inflammatory cytokine-induced collagen production [71]. A replication study within the Caucasian populations had further affirmed the connection between SSc and rs4958881, rs2233287 and rs3792783 ($P= 3.26 \times 10^{-4}$, $P= 1.94 \times 10^{-4}$ and $P = 2.16 \times 10^{-4}$ respectively) [72].

The relation between susceptibility to SSc (and its subgroups) and polymorphisms of TNFAIP3 had been consistently reported across different studies with various ethnic backgrounds. Notably, only a single one had been associated with dcSSc. Due to the fact that TNIP1 and TNFAIP3 are closely associated it is worth contemplating the effects both these genes SNPs at the same time [64].

CSK

C-Src kinase (CSK) is a tyrosine-protein kinase that phosphorylates Src-family kinases, which are important for fibroblast activation, as well as the development of experimental fibrosis. By phosphorylating the Src-family kinases, C-Src negatively regulates lymphocyte activation. Inhibition of the Src kinase can prevent experimental dermal fibrosis by reducing the transcriptional activity of genes encoding collagen type 1 α1, α2 chains, and fibronectin 1 (COL1A1, COL1A2 and FN1 respectively) [73,74].

CSK, specifically rs1378942, was recently identified as a SSc genetic risk factor through GWAS follow-up. The functional implications of CSK-related SNP are still to be studied, however, if the rate of its regulation were to be less effective, it could lead to uncontrolled fibroblast activation [75].

GSDMA

GSDMA, encoding gasdermin A, was identified to be related to several AIDs, including RA and IBD. The rs3894194 was associated with SSc in general, and the limited form of the disease. Notably, the study has observed enhancing activity and enrichment of histone marks of rs3894194. Moreover, it strongly correlates with the expression of neighbouring genes that encode gasdermin B (GSDMB) and ORMDL sphingolipid biosynthesis regulator 3 (ORMDL3) thus making it a promising candidate for being the causative SNP [76]. Alternatively, rs3894194 was also reported to be involved in alteration of transcription signatures in SSc macrophages. There are several factors along Gasdermin A that are also connected to SSc, like the lack of GWS or replications, toll-like receptor (TLR) and NLR family porin domain (NLRP). All of them are involved the formation of the inflammasome and the induction of pyroptosis, making them highly relevant to the immune/inflammasome pathway underlying SSc pathogenesis [77].

CONCLUSION

The complexity of systemic sclerosis (SSc) demands a comprehensive understanding of the interplay between genetic and environmental factors and the ongoing advancements in scientific methodologies. The identification of specific genetic associations, particularly within the major histocompatibility complex (MHC) region, has provided crucial insights into the susceptibility to SSc, as well as the diverse clinical manifestations observed across different ethnic populations. Additionally, the involvement of non-HLA genes, such as IRF5, STAT4, IL12, IL12RB, CD247, PRDM1, TNFAIP3, TNIP1, CSK, and GSDMA, highlights the heterogeneous nature of SSc and the underlying immunopathogenic mechanisms.

Environmental factors, including food contaminants and silica dust, in conjunction with genetic susceptibility, underscore the multifactorial etiology of SSc. Understanding the intricate relationship between genetic predisposition and environmental triggers is essential for the development of targeted therapeutic interventions and prevention strategies.

Furthermore, the utilization of scientific methodologies, such as genome-wide association studies (GWAS) and genomic risk scores, has expanded our knowledge of the genetic basis of SSc. These approaches have uncovered specific genetic variations and provided valuable insights into the molecular pathways involved in immune regulation and inflammatory responses in SSc.

Moving forward, a multidisciplinary approach that integrates genetic, environmental, and methodological advancements will be instrumental in advancing the diagnosis, prognostication, and treatment of SSc. By gaining a deeper understanding of the intricate mechanisms underlying SSc, we can strive to develop personalized therapeutic strategies and improve clinical outcomes for individuals affected by this challenging autoimmune disease.

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