Genetics, Epigenetics, and Genomics of Systemic Sclerosis

Gloria Salazar, MD, Maureen D. Mayes, MD, MPH*

KEYWORDS

• Genetics • Epigenetics • Systemic sclerosis • Scleroderma • Gene expression • microRNA • miRNA • Splicing

KEY POINTS

- Multiple genes are associated with susceptibility to systemic sclerosis and can lead to alterations in innate and adaptive immunity, cell signaling, extracellular matrix, DNA or RNA degradation, and apoptosis or autophagy.
- There are several mechanisms (such as epigenetics and splicing mutations) that influence gene expression and are important for disease in addition to the genetic variants.
- Epigenetic mechanisms govern gene expression at different levels before translation. They are just being explored in systemic sclerosis and may help explain some of the missing heritability.

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease (AID) characterized by fibrosis of skin and internal organs as well as vasculopathy and immune dysregulation. SSc is a clinically heterogeneous disease and presents with 3 distinct subphenotypes: limited, diffuse, and "sine," based on the severity of skin involvement. This classification also reflects internal organ involvement, which can range from minimal to rapidly progressive disease resulting in premature death. Finally, SSc is characterized by the production of mutually exclusive antinuclear antibodies subtypes that are associated with different clinical manifestations, disease phenotypes, and prognosis.

SSc is a complex disease that entails abnormalities in several different pathways. Its pathogenesis is not well understood, but several studies have established that SSc occurs in a genetically susceptible host presumably after encountering environmental

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Division of Rheumatology and Clinical Immunogenetics, University of Texas Health Science Center at Houston, 6431 Fannin Street, MSB 5.270, Houston, TX 77030, USA
* Corresponding author.
E-mail address: Maureen.d.mayes@uth.tmc.edu

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exposures or other external triggers.[1–3] Genetic studies performed so far reveal that multiple genetic loci contribute to disease susceptibility in SSc.[4] The purpose of this review is to discuss the current knowledge of SSc genetics by exploring the observational evidence, the different genetic studies performed to date, as well as the most relevant genes discovered by these. Also, the article explores the concept of gene expression variation and the recently discovered field of epigenetics.

INITIAL EVIDENCE OF THE GENETIC INFLUENCE IN SYSTEMIC SCLEROSIS

SSc is not inherited in a Mendelian fashion and, although its pathogenesis is unclear, it is thought that gene variants influence not only disease susceptibility but also differences in clinical expression and progression.[2] Here some of the initial observational evidence that supported the role of genetics in SSc is discussed.

Ethnic Associations

Differences in prevalence and clinical manifestations among different ethnic groups are evident and support the role of genetics in SSc. Some ethnic groups or subpopulations have higher prevalence of SSc compared with the general population. For example, the Choctaw tribe in Oklahoma is a population with a high prevalence of SSc (2 times higher than the expected prevalence) and displays a more homogeneous clinical and immunologic phenotype than is seen in the general population.[3,5]

Shared Genetic Background in Autoimmune Diseases

Several studies have noted that AIDs cluster in families (familial aggregation) and that there is co-occurrence in the same individual of 2 or more AIDs (individual aggregation or overlap syndromes) supporting the concept of a shared autoimmune genetic background among AIDs. In a cross-sectional study including 719 SSc patients, 38% had at least one other overlapping AID. The most frequent overlapping AIDs were autoimmune thyroid disease (AITD) (38%), rheumatoid arthritis (RA) (21%), and Sjogren syndrome (18%). Regarding the familial clustering of autoimmunity, 36% of the first-degree relatives had at least one AID, of which the most frequent were RA (18%) and AITD (9%),[6] suggesting that AIDs and their manifestations share genetic risk factors and support the role of genetic influences in SSc.

GENETIC STUDY MODALITIES

The most frequent type of DNA variation consists of a change in an individual nucleotide, known as a single-nucleotide polymorphism (SNP). These differences in the DNA sequence may or may not produce functional changes because of modification in the gene expression or alteration in the resulting protein.[7] In general, 2 basic approaches are used to study genetic associations: the candidate gene approach (CGA) and the genome-wide association study (GWAS). Both methodologies rely on the identification of SNPs and determine the likelihood that the variant occurs more or less frequently in the cases than in the controls (communicated in the form of an odds ratio).[8]

To date, genetic studies have identified SSc susceptibility factors involved in the immune system as well as genes in pathways that play a role in vascular damage and fibrotic processes.[1,3]

Candidate Gene Approach

CGA studies aim to determine specific SNPs associated with disease. Candidate genes are chosen either because they have been associated with other AIDs or