Human Immunology 78 (2017) 153–165

Contents lists available at ScienceDirect

journal homepage: www.elsevier.com/locate/humimm

Review

# Genomic and genetic studies of systemic sclerosis: A systematic review

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ARTICLE INFO

*Article history:*
Received 5 September 2016
Revised 27 October 2016
Accepted 27 October 2016
Available online 29 October 2016

*Keywords:*
Scleroderma
Systemic sclerosis
Autoimmune disease
Genetics
Systematic review

ABSTRACT

Systemic sclerosis is an autoimmune rheumatic disease characterised by fibrosis, vasculopathy and inflammation. The exact aetiology of SSc remains unknown but evidences show that various genetic factors may be involved. This review aimed to assess HLA alleles/non-HLA polymorphisms, microsatellites and chromosomal abnormalities that have thus far been associated with SSc. PubMed, Embase and Scopus databases were searched up to July 29, 2015 using a combination of search-terms. Articles retrieved were evaluated based on set exclusion and inclusion criteria. A total of 150 publications passed the filters. HLA and non-HLA studies showed that particular alleles in the *HLA-DRB1*, *HLA-DQB1*, *HLA-DQA1*, *HLA-DPB1* genes and variants in *STAT4*, *IRF5* and *CD247* are frequently associated with SSc. Non-HLA genes analysis was performed using the PANTHER and STRING$_{10}$ databases. PANTHER classification revealed that inflammation mediated by chemokine and cytokine, interleukin and integrin signalling pathways are among the common extracted pathways associated with SSc. STRING$_{10}$ analysis showed that *NFKB1*, *CSF3R*, *STAT4*, *IFNG*, *PRL* and *ILs* are the main "hubs" of interaction network of the non-HLA genes associated with SSc. This study gathers data of valid genetic factors associated with SSc and discusses the possible interactions of implicated molecules.


**Contents**



*Abbreviations:* ACA, anti-centromere antibody; AID, autoimmune disease; ARA, anti-RNA polymerase III antibody; ATA, anti-topoisomerase I antibody; SSc, systemic sclerosis; dcSSc, diffused cutaneous SSc; lcSSc, limited cutaneous SSc; GWAS, Genome Wide Association Study; HLA, human leukocyte antigen; MHC, major histocompatibility complex; PAH, pulmonary arterial hypertension; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; VNTRs, variable number tandem repeats.

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http://dx.doi.org/10.1016/j.humimm.2016.10.017
0198-8859/

## 1. Introduction

Systemic sclerosis (SSc) refers to a systemic connective-tissue disease generally classified as an autoimmune rheumatic disease [1,2]. It is characterised by excessive deposition of collagen in many tissues throughout the body, especially in the skin, causing hardening and thickening (fibrosis); vasculopathy; and inflammation associated with immune system abnormalities [1,3]. SSc is a heterogeneous disease, as many organs of the body may be affected with variable manifestations among individuals and populations [4].

The disease is subdivided into limited cutaneous SSc (lcSSc) and diffused cutaneous SSc (dcSSc) based on clinical criteria. LcSSc tends to be less severe as skin thickening is limited to the upper neck, face and distal extremities [4,5]. It is also known as CREST syndrome, due to the five common features; Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly and Telangectasias [4]. In contrast, dcSSc is more severe than lcSSc as internal organs (eg. heart, lung and kidney) are mainly affected and the condition progresses faster [4]. Internal organ complications include interstitial lung fibrosis, congestive heart failure, pulmonary arterial hypertension (PAH) and renal crisis [6–8]. Different types of autoantibodies are associated with each subgroup [9]. The presence of anti-centromere antibody (ACA) is mainly associated with lcSSc, whereas anti-RNA-polymerase family (anti-RNAP) and anti-topoisomerase antibody (ATA) (anti-Scl-70) autoantibodies are associated with dcSSc [10].

SSc does not occur randomly in the populations and is more common in women than men with a ratio of 3:1–6:1, according to the geographical region [11,12]. Up to date, there is no clear aetiology for SSc, however evidences reveal that genetic factors may play an important role in triggering the disease [5]. Many Major Histocompatibility Complex (MHC)[1] and non-MHC genetic variations have thus far been associated with predisposition to disease [13]. Identification of the genetic variants based on the SSc heritability promises the discovery of genetic biomarkers. Genetic biomarkers can be defined as characteristics of DNA, RNA and protein that indicate normal/pathological processes and response to therapeutic interventions [14–16]. Therefore, genetic biomarkers are candidates for better classification, prognosis, diagnosis and therapeutic response of the disease.

During the recent years, several narrative and systematic reviews were published on SSc. Narrative reviews give a general background of the disease and discuss several topics e.g. genetics and epigenetics, therapies, biomarkers, pathogenesis and clinical manifestations of SSc without a structured methodological plan [9,17–19]. On the other hand, systematic reviews are carried out using a specific methodological approach, thus all the relevant studies are included in the review and bias is minimised. Up to date, a small number of systematic reviews were performed on SSc, eg. mortality and survival in SSc and proteomic biomarkers of SSc [15,20]. Although, a number of genetic variants and abnormalities have been identified through genetic and genomic studies, and the most common variants/abnormalities have been mentioned in narrative reviews, to our knowledge, this is the first systematic review of the literature that explores these variations and abnormalities. This systematic review, aims at the assessment and comparison of HLA and non-HLA polymorphisms, microsatellites and chromosomal abnormalities associated with SSc thus facilitating a more accurate diagnosis, prognosis and therapeutic targeting.

[1] The MHC; also known as Human Leukocyte Antigen (HLA) in human is a set of genes located on the short arm (p) of chromosome 6 at position 21.3.

## 2. Methods

### 2.1. Literature search methodology

To complete this review, three electronic databases were used. PubMed (*http://www.ncbi.nlm.nih.gov/pubmed/*), Embase (*https://www.elsevier.com/solutions/embase-biomedical-research*) and Scopus (*http://www.scopus.com/*) databases were searched for all peer-reviewed articles. Searching was performed on 29th of July 2015 in PubMed (1965-29th of July 2015), Embase (1947-29th of July 2015) and Scopus (1976-29th of July 2015), using the following combination of search-terms: ("systemic sclerosis" **OR** "scleroderma" **OR** "systemic sclerosis" [MeSH] **OR** "scleroderma" [MeSH]) **AND** ("genomics" **OR** "genome" **OR** "genetic" **OR** "chromosome" **OR** "mutation" **OR** "polymorphism" **OR** "SNP" **OR** "genomics" [MeSH] **OR** "genome" [MeSH] **OR** "genetic" [MeSH] **OR** "chromosome" [MeSH] **OR** "mutation" [MeSH] **OR** "polymorphism" [MeSH] **OR** "SNP" [MeSH]). Medical Subject Headings (MeSH) were not used in Embase and Scopus databases, as they do not explode MeSH. Retrieved articles were imported in EndNote version X5 and duplicates were removed. Reviews, case reports, letters, author replies, news, editorials, conference abstracts, erratums, book chapters, notes, short surveys, conference reviews, invited articles, reports and posters were excluded (Supplementary Fig. 1). Articles not written in the English language were also excluded. The remaining articles were manually assessed by screening title and abstract, and only case-control studies involving human participants, directly referring to SSc and genetics, with statistically significant data were included for full-text evaluation. Articles without an abstract and full-text were excluded. Full-text papers were further assessed for their eligibility. Studies have been included only if they provide sufficient details about the number of patients, number of controls, type of controls, ethnicity and p-values. Chromosomal and family studies were not assessed for their eligibility. Additional publications were selected manually by searching the reference list of recent reviews associated with SSc [5,21–23]. This work was carried out by three independent reviewers, using the PRISMA guidelines [24].

### 2.2. HLA nomenclature

HLA genes and alleles were reported with the current HLA nomenclature system following the principles established by the Nomenclature Update 2010 [25].

### 2.3. Genes classification and analysis

#### 2.3.1. PANTHER

Non-HLA genes extracted from the reviewed studies were classified, using the Protein Analysis Through Evolutionary