Current Rheumatology Reports (2019) 21: 44
https://doi.org/10.1007/s11926-019-0845-6

SCLERODERMA (J VARGA, SECTION EDITOR)

Towards a Better Classification and Novel Therapies Based on the Genetics of Systemic Sclerosis

Marialbert Acosta-Herrera[1] · Elena López-Isac[1] · Javier Martín[1]

Published online: 15 July 2019

Abstract

Purpose of the Review Nowadays, important advances have occurred in our understanding of the pathogenesis of systemic sclerosis (SSc), which is a rare immune-mediated inflammatory disease (IMID) characterized by vascular damage, immune imbalance, and fibrosis. Its etiology remains unknown; nevertheless, both environmental and genetic factors play a major role in the disease. This review will focus on the main advances made in the field of genetics of SSc.

Recent Findings The assessment of how interindividual genetic variability affects disease onset and progression has enhanced our knowledge of disease biology, and this will eventually translate in the development of new diagnostic and therapeutic tools, which is the final goal of personalized medicine.

Summary We will provide an overview of the most relevant achievements in the genetics of SSc, its shared genetics among IMIDs with special attention on drug repurposing, current challenges for the functional characterization of risk variants, and future directions.

Keywords Scleroderma · Genomic medicine · Genetic risk factors · Susceptibility *loci* · Drug reposition

Introduction

Systemic sclerosis (SSc) is a rare immune-mediated inflammatory disease (IMID) of the connective tissue with a complex etiology that involves the deregulation of the immune system, vascular damage, and extensive collagen deposition, which eventually leads to the appearance of fibrosis in the skin and different internal organs [1–3]. This complex etiology refers to several environmental and genetic factors involved in disease onset and progression [2]. Pregnancy-related events, infectious agents, and exposure to chemical compounds are environmental factors that have been associated with the development of the disease [2]. Regarding genetic factors, the first evidences came from studies assessing familial disease co-occurrence, highlighting that a familial history of SSc is the major risk factor with a relative risk ranging from 10 to 27-fold higher than in the general population [4]. Moreover, twin studies have described a high concordance rate of autoantibody production [5, 6], and there is interesting evidence pointing out to different prevalence among different populations [7]. Current genetic studies account for ~20% of the estimated heritability and is expected that additional *loci* remain undiscovered [8]. Therefore, it is clear that the full understanding of genetic predisposition has the potential to impact disease management.

SSc patients are usually classified into two main clinical subgroups attending to the extent of the fibrosis: limited cutaneous SSc (lcSSc, where the fibrosis is restricted to the skin of the hands, arms, and face) and diffuse SSc (dcSSc, a more aggressive phenotype that affects the skin of all body and one or more visceral organs) [1–3]. Additionally, the immunological dysregulation leads to the production of autoantibodies and aberrant cytokine release. The most frequent autoantibodies are anticentromere (ACA), antitopoisomerase (ATA), and anti-RNA polymerase III autoantibodies (ARA) [1, 2]. This heterogeneity on disease presentation and outcomes represents a challenge for handling these patients and providing proper medical care. Therefore, genetic studies may

This article is part of the Topical Collection on *Scleroderma*

✉ Marialbert Acosta-Herrera
m.acostaherrera@ipb.csic.es

✉ Javier Martín
javiermartin@ipb.csic.es

[1] Cellular Biology and Immunology, Institute of Parasitology and Biomedicine López-Neyra (IPBLN), CSIC, PTS Granada , Av. del Conocimiento 17, 18016 Armilla, Granada, Spain

assist in addressing this heterogeneity through a better patient classification, based on the molecular mechanisms driving the disease. Patient stratification into a more homogeneous subtype of disease will improve therapeutic management by providing therapies to those patients more likely to respond. In addition, genetic studies bring the opportunity to improve our knowledge of the genes and pathways implicated in a disease process, allowing the repositioning of therapies that target the same pathways in other diseases [9].

In the modern era of genetic research, a developing field termed personalized medicine has revealed how genomic variations are responsible for differences in health outcomes. Traditionally, genetic studies were focused on assessing the association of single-nucleotide polymorphisms (SNPs) in candidate genes, and these genes were selected based on the biological plausibility on disease pathogenesis. Nowadays, our awareness of the genetic landscape of SSc has significantly improved, mainly due to the development of large-scale genetic studies, including genome-wide association studies (GWAS) and fine-mapping studies, such as the Immunochip [10]. Their main advantages come from the agnostic assessment of disease pathogenesis by interrogating the entire genome, and the generation of a new hypothesis, as the new associations may identify novel pathways never anticipated with the disease. In detriment, stringent statistical thresholds are necessary to account for multiple comparisons and therefore these studies require larger sample sizes to overcome this restriction.

The identification of genes and molecular pathways deregulated in SSc is essential to improve our understanding of this disorder and in the development of more effective therapeutic approaches. In this sense, recent data indicates that the pharmaceutical pipeline backed by genetic evidence doubles its chance to deliver a new drug than those without it, highlighting the importance of genetic information related to drug mechanisms [11]. This review aims to provide an update of the main genetic studies in SSc, such as firm candidate genes, GWAS, fine-mapping, trans-ethnic, and cross-disease meta-analyses. We discuss how they have enhanced our understanding of its pathogenesis and the potential in the development of new therapeutic targets for this orphan condition.

Systemic Sclerosis and its Genetic Component

GWAS in SSc

The low prevalence of SSc challenges the recruitment of large sample sizes required to reach proper statistical power in genomic studies to effectively detect association signals and this may be the reason for having such a small number of GWAS in SSc conducted to date in comparison with other IMIDs like rheumatoid arthritis (RA). In 2010, our group led the first GWAS published in SSc in the Caucasian population [12] (Fig. 1). This work included 2,296 cases and 5,171 controls and identified *CD247* gene as a novel susceptibility *loci* associated with the disease. This gene encodes a subunit of the T cell receptor (TCR)-CD3 complex and plays a major role in the receptor signaling function. Interestingly, these findings were independently replicated by Dieudé et al. [13]. In addition, previous associations in the Human Leukocyte Antigen (HLA) region, signal transducer, and activator of transcription 4 (*STAT4*) and interferon regulatory factor 5 (*IRF5*) were confirmed, as they were previously associated in candidate gene association studies [8].

In 2011, a second GWAS in the Caucasian population was published by Allanore et al. [14] identifying *TNIP1*, *RHOB*, and *PSORS1C1* as novel susceptibility *loci*. Altogether, their results were consistent with a reduced inhibition of NF-kappa B favoring inflammatory/immune responses and contributing to the overproduction of extracellular matrix. Nevertheless, a replication study in independent samples only confirmed the association of *TNIP1* as a genetic risk factor for SSc [15]. In addition, one SSc GWAS has been performed in a Korean population [16], identifying the genes *HLA-DPB1* and *HLA-DPB2* as risk factors for SSc.

Given the difficulties in recruiting sufficient sample sizes to reach the established significance threshold, a distinctive characteristic of GWAS, in general, is the assessment of the so-called gray zone, where SNPs with suggestive associations (p values between 5×10^{-8} and 5×10^{-3}) are analyzed in independent study samples. This data mining in GWAS has been very useful in SSc for the identification of newly associated *loci* since some of them were missed because of a lack of statistical power in previous GWAS. In this line, Bossini-Castillo et al. performed a follow-up study focusing on *IL12RB2* gene variants. This *locus* showed a suggestive association in the first SSc GWAS, confirming its involvement with disease susceptibility [17]. Furthermore, Martin et al. carried out a large follow-up of the same GWAS that included 768 SNPs and identified *CSK* as a genetic risk factor for SSc, confirming previously reported associations [18]. Additionally, Lopez-Isac et al. [19] performed a follow-up of the GWAS by Allanore et al. and confirmed the association of *PPARG* [19] with SSc susceptibility.

Fine-Mapping Studies in SSc

According to several results from GWAS in different IMIDs and the extent of their genetic overlap, a cost-effective and common genotyping array was developed; this is the case of the Immunochip [10]. This custom platform included 196,524

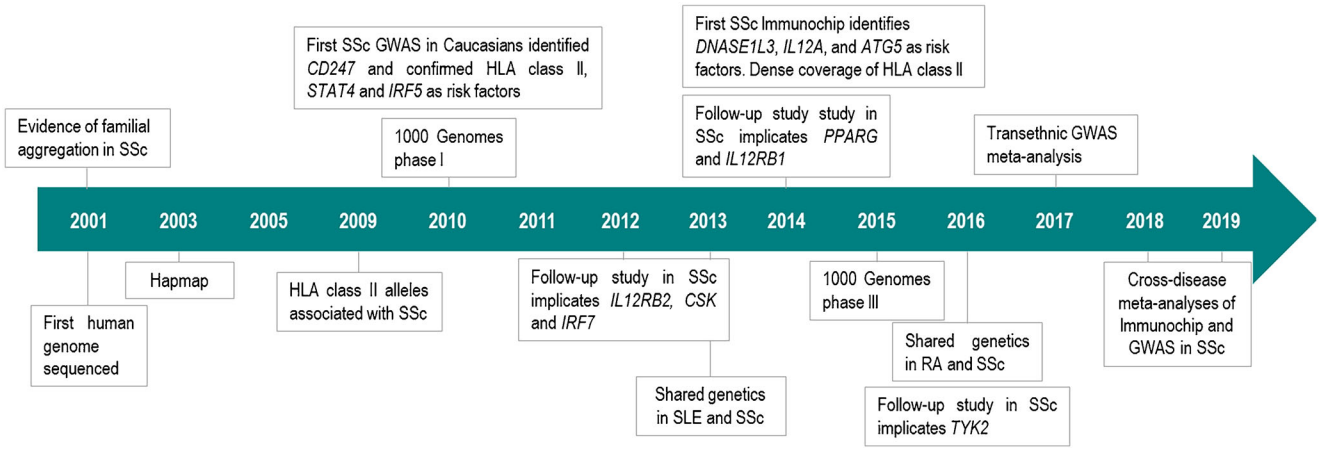

Fig. 1 Timeline of the major advances made in the field of genetics of systemic sclerosis. MHC, major histocompatibility complex; GWAS, genome wide association study; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; SSc, systemic sclerosis

variants on non-well covered regions from classic genotyping arrays with rarer variants, for fine-mapping 186 autoimmunity *loci*, and dense coverage of the HLA region.

In the case of SSc, our group led the first Immunochip study identifying several new susceptibility *loci* outside the HLA region, such as *DNASE1IL3*, *IL12A*, and *ATG5*, which implicated new biological mechanisms like apoptosis and autophagy with the disease [20]. Regarding the HLA region, this study showed that it is the strongest genetic association reported to date, specifically in HLA class II genes, as previously confirmed in several candidate gene association studies [8]. The dense coverage of the HLA on this genotyping platform along with novel imputation methods of classical HLA alleles and polymorphic amino acid positions from genetic data allowed the authors to describe a comprehensive model that explained all the observed associations in the region in European descent population, which included six polymorphic amino acid positions in HLA-DRB1, HLA-DQA1, and HLA-DPB1, and seven SNPs independently associated.

Moreover, this analysis confirmed the involvement of differential HLA allele associations between ACA-positive and ATA-positive serological subgroups. In the case of the ACA-positive subgroup, the model included two amino acid associations in HLA-DRB1 and HLA-DQA1, along with 5 SNPs. The ATA-positive subgroup comprises four amino acid associations in the HLA-DRB1 and in HLA-DPB1, along with two SNPs. Finally, Mayes et al. described cis-expression Quantitative Trait Loci (eQTLs) for most of the associated variants in the region, which correlated them with changes in gene expression [20].

A second SSc Immunochip performed in an Australian population including 486 cases and 4,458 controls, with a replication study using 833 cases and 1,938 controls, confirmed some of the previously reported associations with SSc susceptibility [21].

GWAS Meta-analyses

Meta-analyses are statistical methods that combine the results of large collections of individual studies, in order to integrate, synthesize, and summarize research findings [22]. In the case of GWAS, meta-analyses constitute powerful tools to vastly increase sample size, which largely improves the statistical power to detect disease-associated variants. In addition, large-scale meta-analyses among samples collected through international collaborations allow the confident associations of genetic variants, as their results are consistently replicated in independent study samples.

In spite of the great advances provided by these studies to improve our understanding of the genetics of complex traits, the vast majority has been performed in European descent populations [23••], and much of their heritability is still unexplained. The current availability of GWAS data from diverse populations offers a thrilling opportunity to identify novel associated *loci* by taking advantage of the differences in local linkage disequilibrium patterns among ethnic groups. In this line, in SSc, the first trans-ethnic meta-analysis in Japanese and European populations was published by Terao et al. [24•]. The authors were able to identify the association of *GSDMA* and *PRDM1* as novel risk *loci* involved in SSc susceptibility. In addition, they conducted a two-stage replication study validating their results, and functional enrichment analysis suggested the relevance of CD4-naïve primary T cell in the disease pathogenesis.

Additionally, the study of diverse populations in SSc has led to the confirmation of several susceptibility *loci* in the disease. For instance, Gonzalez-Serna et al. [25•] published the first meta-analysis in Turkish and Iranian population, leveraging the unique genetic structure in a Turkish population and the genetic overlap with other populations from the Middle East. In this study, the HLA class II was the highest association peak observed in the meta-analysis and two suggestive associations in the *IRF5-TNPO3* and *NFKB1* were described. These results confirm their involvement in SSc susceptibility as they have been consistently validated in different studies [12, 14, 20, 21, 26]. Moreover, an extensive analysis of the HLA region was performed and the authors observed that the HLA-DRB1*11:04 classical allele showed the most significant associations in both populations and that this effect might be driven by the amino acid Glu-58, reinforcing its role in SSc susceptibility, as it has been described in different populations including Caucasians [27–29], African-Americans [28], and Mexicans [30].

At the present time, our group is leading the largest meta-analysis in SSc, including 26,679 individuals from different European descent populations. This strategy will allow us to identify novel associations for SSc susceptibility and confirm previously reported risk *loci*; increasing considerably our understanding of the genetic basis of this complex disorder (Lopez-Isac et al. personal communication).

Shared Genetics In IMIDs and New Opportunities for Drug Development

Nowadays, it is widely accepted that several IMIDs share clinical manifestations, comorbidities, and familial aggregation. Moreover, shared risk genes and molecular pathways influencing their development have been undeniably recognized among autoimmune diseases [31, 32]. In this sense, SSc is not an exception as a large number of susceptibility *loci* described for the disease are common to different IMIDs. The study of the genetic component of different diseases into a single phenotype has proven to be useful for the identification of pathways involved in these diseases in a systematic fashion. Given the success in the pharmacological pipeline backed by genetic evidence and the assessment of this shared genetic architecture among IMIDs, new avenues might be explored for drug repurposing, e.g., reutilization of indicated drugs in orphan-related diseases.

Specifically, in SSc, this fact was first explored by Martin et al. [33] in 2013. The authors conducted a pan-meta-GWAS among two archetypical autoimmune diseases, SSc and systemic lupus erythematosus (SLE) being able to identify shared susceptibility genes among these conditions. For this, they combined two GWAS data from the diseases, altogether with a replication stage identifying *KIAA0319L* as novel shared susceptibility *loci*. Furthermore, this gene was overexpressed in peripheral blood cells of SSc and SLE patients compared with healthy controls. In addition, previously reported *loci* associated with SLE were also associated with SSc.

In 2016, Lopez-Isac et al. [34] described *IRF4* as new susceptibility *loci* shared between SSc and RA. The authors pooled GWAS data from the diseases and followed-up the top hits in independent SSc and RA samples, assessing a total of 8,830 patients with SSc, 16,870 patients with RA, and 43,393 healthy controls. They were able to pinpoint the type I interferon and interleukin-12 signaling pathways as the main common etiologic factors among SSc and RA.

Until then, this common genetic assessment was performed in a two by two fashion. However, by this time Li et al. [35] was able to combine GWAS data from ten pediatric autoimmune diseases that exposed new shared *loci* among them with immunoregulatory functions. Furthermore, Ellinghaus et al. [36] found shared genetic *loci* in seronegative conditions after combining Immunochip data. The first of these assessments including SSc was performed by Marquez et al. [37••], which pooled Immunochip data from seropositive autoimmune diseases: celiac disease (CeD), type 1 diabetes (T1D), RA, and SSc. They were able to identify new pleiotropic *loci* that may act by deregulating gene expression in different subsets of T cells, especially Th17 and regulatory T cells. Interestingly, based on these results, the authors identified potentially repositionable drugs, most of them indicated for RA that would be worth exploring for CeD, SSc, and/or T1D.

More recently, Acosta-Herrera et al. [38••] performed a systematic assessment among four systemic seropositive rheumatologic IMIDs like idiopathic inflammatory myopathies (IIM), SLE, RA, and SSc by joining GWAS data from these related conditions. The authors were able to identify newly associated shared *loci* related with immune processes with functional relevance, including shared eQTLs. Moreover, our results were significantly enriched in drugs that are being tested for the treatment of the diseases under study, highlighting the potential of drug repositioning among rheumatic IMIDs (Fig. 2). Altogether, these assessments endorse a line of thinking showing that genetic overlap between diseases suggests common mechanisms and hence common therapeutic management. This is particularly relevant in the path for personalized medicine in uncommon diseases like SSc, where there are no specific available treatments.

From Genetic Findings to Their Functional Implications and Clinical Applications in SSc

Genetic studies offer great potential for understanding the molecular mechanisms involved in SSc as described in this review. However, assigning them a functional effect is still a challenging task, mainly due to the difficulty of identifying

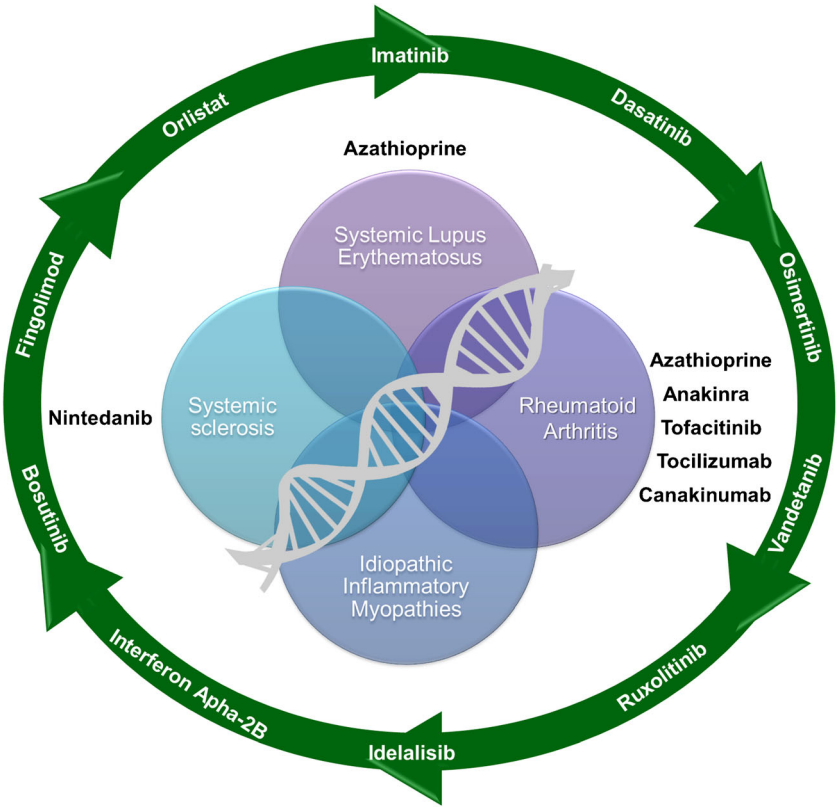

Fig. 2 Shared genetics in systemic seropositive immune-mediated inflammatory diseases and its implication for drug repurposing. Depicted in black boldface are the drugs indicated for each disease. The outer circle shows the drugs currently indicated for non-immune-mediated diseases. All of them could be repurposed in genetically related orphan conditions such as systemic sclerosis

causal variants, and because many of the disease-associated variants lie in non-coding regions of the genome. Consequently, great efforts are needed to understand the functional implications of genetic associations. In this line, complementary approaches including transcriptomic and epigenomics studies are of great value to deepen our knowledge of the molecular pathways involved in disease pathogenesis and to translate this knowledge into new therapeutic approaches [39••]. Interestingly, Van der Kroef et al. [40•] evaluated epigenomics changes at the level of histone modifications in monocyte cells from SSc patients by chromatin immunoprecipitation followed by sequencing (ChIPseq) assay. In addition, RNA sequencing was performed to correlate altered gene expression with the levels of histone methylations and acetylations. The authors were able to identify altered chromatin marks correlated with IFN signature in monocytes. In addition, enzymes that are able to modulate these epigenetic marks may constitute potential therapeutic targets to restore monocyte homeostasis in SSc. It is worth mentioning that interferon regulatory factors (IRFs) constitute a family of transcription factors consistently associated with SSc, namely *IRF4*, *IRF5*, *IRF7*, and *IRF8* [8].

In addition, in order to link the functional consequence of a specific association to a causal gene, its correlation with gene expression or gene methylation could be evaluated, i.e., if they are an expression or methylation quantitative trait loci (eQTLs and meQTLs). Moreover, until now, the results from GWAS have been assigned to the closest or most compelling local gene; however, these results are known to be enriched in cell-type-specific enhancer regions [8, 41]. These enhancers can modulate gene expression by physical interactions with their target genes and these can occur over large genetic distances due to the three-dimensional disposition of the chromatin [42]. Recent advances in nuclear dynamic technologies allow the design of experiments to unravel the functional consequences of associated *loci*. Chromosome conformation capture (Capture Hi-C) has been successfully used to detect these long-distance interactions in other autoimmune diseases like RA, T1D, psoriatic arthritis (PsA), and juvenile idiopathic arthritis (JIA) [43], and therefore an effective approach to associate non-coding genetic variation with target genes, an important challenge in the genomic landscape of complex diseases like SSc [44••,45•,46].

As mentioned before, genetic studies will shed light in our understanding of the molecular pathways involved in SSc; based on these results, we will be able to predict the susceptibility of each individual to develop the disease and stratify patients at risk based on polygenic risk scores (PRS) [47••,48–50]. These analyses have been conducted for other phenotypes with remarkable findings in the clinical arena

[51•]. Moreover, parallel PRS calculation on related diseases, such as IMIDs, could reflect shared and opposite mechanisms among them.

Conclusion

In spite of the great advances that have been achieved in the genetics of SSc, larger population studies are essential, which will require great collaborative efforts among research groups in the field. In addition, the integration of multi-omics will improve our knowledge of disease pathophysiology. At present, we might be on the way of influencing the treatment of patients through the identification of new drugs or by drug repurposing, which will eventually lead to personalized medicine in SSc.

Funding This work was supported by the Cooperative Research Thematic Network (RETICS) program (RD16/0012/0013) (RIER) from the Health Institute Carlos III (ISCIII) and (SAF2015–66761-P) Spanish Ministry of Economy, Industry and Competitiveness.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. N Engl J Med. 2009;360(19):1989–2003.
2. Katsumoto TR, Whitfield ML, Connolly MK. The pathogenesis of systemic sclerosis. Annu Rev Pathol. 2011;6:509–37.
3. Denton CP, Khanna D. Systemic sclerosis. Lancet. 2017;390(10103):1685–99.
4. Arnett FC, Cho M, Chatterjee S, Aguilar MB, Reveille JD, Mayes MD. Familial occurrence frequencies and relative risks for systemic sclerosis (scleroderma) in three United States cohorts. Arthritis Rheum. 2001;44(6):1359–62.
5. Feghali-Bostwick C, Medsger TA Jr, Wright TM. Analysis of systemic sclerosis in twins reveals low concordance for disease and high concordance for the presence of antinuclear antibodies. Arthritis Rheum. 2003;48(7):1956–63.
6. Assassi S, Arnett FC, Reveille JD, Gourh P, Mayes MD. Clinical, immunologic, and genetic features of familial systemic sclerosis. Arthritis Rheum. 2007;56(6):2031–7.
7. Gorlova OY, Li Y, Gorlov I, Ying J, Chen WV, Assassi S, et al. Gene-level association analysis of systemic sclerosis: a comparison of African-Americans and White populations. PLoS One. 2018;13(1):e0189498.
8. Bossini-Castillo L, Lopez-Isac E, Martin J. Immunogenetics of systemic sclerosis: defining heritability, functional variants and shared-autoimmunity pathways. J Autoimmun. 2015;64:53–65.
9. Eyre S, Orozco G, Worthington J. The genetics revolution in rheumatology: large scale genomic arrays and genetic mapping. Nat Rev Rheumatol. 2017;13(7):421–32.
10. Cortes A, Brown MA. Promise and pitfalls of the Immunochip. Arthritis Res Ther. 2011;13(1):101.
11. Nelson MR, Tipney H, Painter JL, Shen J, Nicoletti P, Shen Y, et al. The support of human genetic evidence for approved drug indications. Nat Genet. 2015;47(8):856–60.
12. Radstake TR, et al. Genome-wide association study of systemic sclerosis identifies CD247 as a new susceptibility locus. Nat Genet. 2010;42(5):426–9.
13. Dieude P, Boileau C, Guedj M, Avouac J, Ruiz B, Hachulla E, et al. Independent replication establishes the CD247 gene as a genetic systemic sclerosis susceptibility factor. Ann Rheum Dis. 2011;70(9):1695–6.
14. Allanore Y, Saad M, Dieudé P, Avouac J, Distler JHW, Amouyel P, et al. Genome-wide scan identifies TNIP1, PSORS1C1, and RHOB as novel risk loci for systemic sclerosis. PLoS Genet. 2011;7(7):e1002091.
15. Bossini-Castillo L, Martin JE, Broen J, Simeon CP, Beretta L, Gorlova OY, et al. Confirmation of TNIP1 but not RHOB and PSORS1C1 as systemic sclerosis risk factors in a large independent replication study. Ann Rheum Dis. 2013;72(4):602–7.
16. Zhou X, Lee JE, Arnett FC, Xiong M, Park MY, Yoo YK, et al. HLA-DPB1 and DPB2 are genetic loci for systemic sclerosis: a genome-wide association study in Koreans with replication in North Americans. Arthritis Rheum. 2009;60(12):3807–14.
17. Bossini-Castillo L, Martin JE, Broen J, Gorlova O, Simeón CP, Beretta L, et al. A GWAS follow-up study reveals the association of the IL1e2RB2 gene with systemic sclerosis in Caucasian populations. Hum Mol Genet. 2012;21(4):926–33.
18. Martin JE, Broen JC, Carmona FD, Teruel M, Simeon CP, Vonk MC, et al. Identification of CSK as a systemic sclerosis genetic risk factor through genome wide association study follow-up. Hum Mol Genet. 2012;21(12):2825–35.
19. Lopez-Isac E, et al. A genome-wide association study follow-up suggests a possible role for PPARG in systemic sclerosis susceptibility. Arthritis Res Ther. 2014;16(1):R6.
20. Mayes MD, Bossini-Castillo L, Gorlova O, Martin JE, Zhou X, Chen WV, et al. Immunochip analysis identifies multiple susceptibility loci for systemic sclerosis. Am J Hum Genet. 2014;94(1):47–61.
21. Zochling J, Newell F, Charlesworth JC, Leo P, Stankovich J, Cortes A, et al. An Immunochip-based interrogation of scleroderma susceptibility variants identifies a novel association at DNASE1L3. Arthritis Res Ther. 2014;16(5):438.
22. Cheung MW, Vijayakumar R. A guide to conducting a meta-analysis. Neuropsychol Rev. 2016;26(2):121–8.
23.•• *Genetics for all.* Nat Genet, 2019. 51(4): p. 579. **This editorial shows how most of the genetic studies haven been carried out in European populations and how this will bias their impact on health in genetically diverse populations.**
24.• Terao C, Kawaguchi T, Dieude P, Varga J, Kuwana M, Hudson M, et al. Transethnic meta-analysis identifies GSDMA and PRDM1 as susceptibility genes to systemic sclerosis. Ann Rheum Dis. 2017;76(6):1150–8 **This study represents the first transethnic meta-analysis in SSc among European and Asian population, highlighting the potential of studying other populations to find new genetic risk factors in complex diseases**.
25.• Gonzalez-Serna D, et al. Analysis of the genetic component of systemic sclerosis in Iranian and Turkish populations through a

genome-wide association study. Rheumatology (Oxford). 2019;58(2):289–98 **This paper confirms the association of the classical allele HLA-DRB1*11:04 with SSc in several populations.**

26. Gorlova O, Martin JE, Rueda B, Koeleman BPC, Ying J, Teruel M, et al. Identification of novel genetic markers associated with clinical phenotypes of systemic sclerosis through a genome-wide association strategy. PLoS Genet. 2011;7(7):e1002178.
27. Simeon CP, et al. Association of HLA class II genes with systemic sclerosis in Spanish patients. J Rheumatol. 2009;36(12):2733–6.
28. Arnett FC, Gourh P, Shete S, Ahn CW, Honey RE, Agarwal SK, et al. Major histocompatibility complex (MHC) class II alleles, haplotypes and epitopes which confer susceptibility or protection in systemic sclerosis: analyses in 1300 Caucasian, African-American and Hispanic cases and 1000 controls. Ann Rheum Dis. 2010;69(5):822–7.
29. Beretta L, Rueda B, Marchini M, Santaniello A, Simeon CP, Fonollosa V, et al. Analysis of class II human leucocyte antigens in Italian and Spanish systemic sclerosis. Rheumatology (Oxford). 2012;51(1):52–9.
30. Rodriguez-Reyna TS, Mercado-Velázquez P, Yu N, Alosco S, Ohashi M, Lebedeva T, et al. HLA class I and II blocks are associated to susceptibility, clinical subtypes and autoantibodies in Mexican systemic sclerosis (SSc) patients. PLoS One. 2015;10(5):e0126727.
31. Parkes M, Cortes A, van Heel DA, Brown MA. Genetic insights into common pathways and complex relationships among immune-mediated diseases. Nat Rev Genet. 2013;14(9):661–73.
32. Zhernakova A, Withoff S, Wijmenga C. Clinical implications of shared genetics and pathogenesis in autoimmune diseases. Nat Rev Endocrinol. 2013;9(11):646–59.
33. Martin JE, Assassi S, Diaz-Gallo LM, Broen JC, Simeon CP, Castellvi I, et al. A systemic sclerosis and systemic lupus erythematosus pan-meta-GWAS reveals new shared susceptibility loci. Hum Mol Genet. 2013;22(19):4021–9.
34. Lopez-Isac E, et al. Brief report: IRF4 newly identified as a common susceptibility locus for systemic sclerosis and rheumatoid arthritis in a cross-disease meta-analysis of genome-wide association studies. Arthritis Rheumatol. 2016;68(9):2338–44.
35. Li YR, Li J, Zhao SD, Bradfield JP, Mentch FD, Maggadottir SM, et al. Meta-analysis of shared genetic architecture across ten pediatric autoimmune diseases. Nat Med. 2015;21(9):1018–27.
36. Ellinghaus D, et al. Analysis of five chronic inflammatory diseases identifies 27 new associations and highlights disease-specific patterns at shared loci. Nat Genet. 2016;48(5):510–8.
37.•• Marquez A, et al. Meta-analysis of Immunochip data of four autoimmune diseases reveals novel single-disease and cross-phenotype associations. Genome Med. 2018;10(1):97 **This study shows the common genetic architecture of SSc with other autoimmune diseases and its potential on drug repositioning.**
38.•• Acosta-Herrera M, et al. Genome-wide meta-analysis reveals shared new loci in systemic seropositive rheumatic diseases. Ann Rheum Dis. 2019;78(3):311–9 **This paper identifies shared genetics across systemic seropositive rheumatic diseases with functional value and significantly enriched in drug targets, calling our attention on their potential for drug repurposing.**
39.•• Angiolilli C, et al. New insights into the genetics and epigenetics of systemic sclerosis. Nat Rev Rheumatol. 2018;14(11):657–73 **This review shows how different epigenetic studies in SSc might impact on the treatment of the disease.**
40.• van der Kroef M, et al. Histone modifications underlie monocyte dysregulation in patients with systemic sclerosis, underlining the treatment potential of epigenetic targeting. Ann Rheum Dis. 2019;78(4):529–38 **This study is an example of how epigenetic modifications can be targeted for the development of new therapies in SSc.**
41. Roadmap Epigenomics C, et al. Integrative analysis of 111 reference human epigenomes. Nature. 2015;518(7539):317–30.
42. Schoenfelder S, Clay I, Fraser P. The transcriptional interactome: gene expression in 3D. Curr Opin Genet Dev. 2010;20(2):127–33.
43. Martin P, McGovern A, Orozco G, Duffus K, Yarwood A, Schoenfelder S, et al. Capture Hi-C reveals novel candidate genes and complex long-range interactions with related autoimmune risk loci. Nat Commun. 2015;6(6):10069.
44.•• Schoenfelder, S., et al., Long-range enhancer-promoter contacts in gene expression control. Nat Rev Genet, 2019. In press. **This review goes over the enhancer-promoter interactions in the genome and their impact on development and disease.**
45.• Martin, P., et al., Chromatin interactions reveal novel gene targets for drug repositioning in rheumatic diseases. Ann Rheum Dis, 2019. In press. **This paper is an example of how functional genomics is an effective tool to identify new treatments and drug repurposing in related diseases.**
46. McGovern A, et al. Capture Hi-C identifies a novel causal gene, IL20RA, in the pan-autoimmune genetic susceptibility region 6q23. Genome Biol. 2016;17(1):212.
47.•• Torkamani A, et al. The personal and clinical utility of polygenic risk scores. Nat Rev Genet. 2018;19(9):581–90 **This study reviews the clinical utility of polygenic risk scores.**
48. GWAS to the people. Nat Med. 2018;24(10):1483.
49. Schork AJ, Schork MA, Schork NJ. Genetic risks and clinical rewards. Nat Genet. 2018;50(9):1210–1.
50. Hunter DJ, Drazen JM. Has the genome granted our wish yet? N Engl J Med. 2019;380(25):2391–3.
51.• Khera AV, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat Genet. 2018;50(9):1219–24 **This paper highlights the impact of stratifying patients at risk based on polygenic risk scores to enable early disease detection and intervention. The authors discuss how genetic prediction should be included into medical care.**