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Advancing drug development for SSc by prioritising findings from human genetic association studies

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Protocol status: Working

We use this protocol and it's working



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Keywords: Systemic sclerosis, Scleroderma, druggable targets for systemic sclerosis, drug development for ssc, systemic sclerosis, human genetic association study, findings from human genetic association study, advancing drug development, evidence synthesis on drug repurposing opportunity, support from human genetics, available evidence with bioinformatics source, human genetics, drug repurposing opportunity, genetics, bioinformatics source, druggable target

Abstract

This protocol describes in the detail the processes for an evidence synthesis on drug repurposing opportunities and potentially druggable targets for systemic sclerosis (SSc) with support from human genetics, by integrating the available evidence with bioinformatics sources.

- 1 **Review title**
Advancing drug development for SSc by prioritising findings from human genetic association studies
- 2 **Short title**
DRESS: Drug Repurposing for Systemic Sclerosis
- 2.1 **Original language title**
Not applicable
- 3 **Anticipated or actual start date**
27th December 2024
- 4 **Anticipated completion date**
4th August 2025
- 5 **Stage of review at the time of this submission.**
The study team are reviewing/registering the protocol.
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- 10 **Organisational affiliation of the review**
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- 12 **Funding sources/sponsors**

None

13 Conflicts of interest

None.

14 Collaborators

Not applicable.

15 Review question

Can we identify drug repurposing opportunities and potentially druggable targets for SSc with support from human genetics, by integrating the available evidence with bioinformatics sources?

16 Searches

These will be performed in three stages:

(i) search for genetic hits for SSc and related traits using the NHGRI-EBI Catalog of human genome-wide association studies (GWAS Catalog) and Ensembl EMBL-EBI.

(ii)

Genes derived from these platforms will be cross-referenced with the OpenTargets platform for drug interactions.

(iii)

Confirmation/validation will be obtained through structured searches and review of evidence on MEDLINE and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) for each drug and its association with SSc. A PRISMA 2020 flow diagram will be created.

17 URL to the search strategy

Not applicable.

18 Participants/population For stage iii, there will be two populations of interest:

a)

Patients with SSc

b)

Patients at risk of progression of SSc including major organ involvement and/or death

19 Intervention(s), exposure(s)

Drugs of interest identified in stage ii

20 Comparator(s)/control

Any active comparator, or placebo, or standard treatment, or no comparator

21 Types of study to be included

For stage i: Genome wide association studies (GWAS), as well as studies that employing whole genome sequencing (WGS) or copy number variant CNV) association analyses

identifying variants associated with either SSc or SSc-related traits (e.g., internal organ complications). These SSc-related traits are related to the disease pathology and therefore including such studies may identify further genes related to the disease process or replicate those found in SSc association analyses. Papers that were supplementary to original GWAS publications, in that they included expression Quantitative Trait Loci (eQTL) analyses, additional exome wide (ExWAS) or rare variant analyses (RVAS), will also be included.

For stage iii: we will include: published randomized controlled trials (RCTs) or RCT protocols available on WHO's ICTRP; observational studies (case-control, drug safety registries); lab studies Systematic reviews, randomized clinical trials (RCTs), RCT protocols available on WHO's ICTRP, and controlled studies in humans comparing the drug vs placebo or an active control were considered eligible for the evidence synthesis tables. Drug safety registries and lab studies will also be considered if no higher quality evidence is available. For each of the identified drugs we will search internal networks (ACR, EULAR, UKSSG, etc) for any existing guideline indication for the treatment of SSc. If the drug was not available/approved in America or Europe, then we will use the local SSc guideline.

22 **Context**

Systemic sclerosis (often referred to as 'scleroderma') is a complex, rare autoimmune rheumatological disease characterised by widespread tissue fibrosis and vascular damage (1–3).

Environmental factors in a genetically susceptible are strongly implicated (4), and with a key role for epigenetic modifications identified (5).

It has the highest mortality of the rheumatic diseases. Major internal organ involvement (e.g., lung, kidney, heart, GI) is associated with significant disease-related mortality (2,6).

Despite advancements in the modern pharmacological management of SSc, treatment options are still limited, and often reserved for those with end-organ damage or high-risk of progression. The disease is associated with a significant burden of non-lethal morbidity including (but not limited to) calcinosis, cutaneous telangiectasia and psychological burden. There is also a significant gender/sex inequity with females being more commonly involved (7), but with males often experiencing a more severe disease course (8).

With the advent of low-cost sequencing platforms and the maturation of statistical tools to generate inferences from genomic data,⁷ vast knowledge has been accumulated on the genetic associations of a multitude of common diseases. This includes many genetic studies (including candidate gene analysis and genome-wide association studies), which have identified that associated genetic variants are mainly localized in noncoding regions in the expression quantitative trait locus, influencing corresponding gene expression (9).

Specifically, Human leukocyte antigen class II genes are associated with SSc-related autoantibodies, rather than the disease itself (9).

A systematic approach with cross-linking of these data sources and generation of evidence synthesis for the obtained outputs may lead to: (a) identification of targets for drug development for whom no active compounds are currently available, (b) drug repurposing options (i.e. drugs that may be of benefit outside of their originally approved indication), some of which with available clinical trial data support and potentially ready for phase-4 randomized controlled trials, and (c) disease-causing drugs highlighting important disease-associated pathways.

23 Main outcome(s)

For Stage iii - Primary outcomes:

Population a) SSc

Population b) SSc progression

24 Additional outcome(s)

Population b) major internal complications (e.g., ILD, PAH, digital ulcers); all-cause mortality

25 Data extraction

We will use the approach developed by Kukendrarajah et al (10).

<https://www.thelancet.com/action/showPdf?pii=S2352-3964%2824%2900229-9>

Stage i: Information on genetic variants will be extracted.

We will use the OpenTargets variant to gene pipeline for annotation. This approach integrates information on QTL experiments, chromatin interaction experiments, in silico functional prediction and distance from transcriptional start site to provide an annotation score. For variants that were not present in the OpenTargets database we will use the original authors annotation. For each annotated gene/target we will obtain information on approved name, location, target class, and info on TWAS or eQTL.

Stage ii: For each annotated gene we will extract information on the available drugs: phase of development (I to IV), action type (agonist, antagonist, inhibitor, etc), drug target(s), disease/indication, status of drug development (N/A, completed, recruiting, withdrawn from market, discontinued) and presence of black box warnings.

Stage iii: We will extract information on the reported effect in SSc (existing treatment, beneficial, neutral or harmful), maximum level of available evidence/type of available evidence, and effect estimates, patient

populations, sample sizes and quality of evidence main study characteristics and findings.
We will use Microsoft Excel for data management.

26 Risk of bias (quality) assessment

Cochrane's Risk of Bias (RoB) V1 will be utilized for randomised controlled trials (RCTs) providing evidence for SSc outcomes on drugs linked to targets

<https://www.bmj.com/content/343/bmj.d5928>

27 Strategy for data synthesis

Data will be extracted and reported in tables using the approach developed by Kukendrarajah et al (10).

No formal data synthesis/meta-analyses will be conducted.

<https://www.thelancet.com/action/showPdf?pii=S2352-3964%2824%2900229-9>

28 Analysis of subgroups or subsets

Not applicable

29 Type and method of review

Evidence synthesis combining data from genetic variant repositories, drug target bioinformatics sources and clinical / clinical trial platforms.

30 Language

English

31 Country

United States of America, United Kingdom, and Belgium

32 Reference and/or URL for published protocol

Not applicable.

33 Dissemination plans

Yes, the review will be published in a peer-reviewed and MEDLINE-indexed journal.

34 Keywords

Systemic sclerosis (SSc); Scleroderma; drug development; genetics; variants ...

35 Details of any existing review of the same topic by the same authors

Not applicable.

36 Current review status

Searches to be run upon protocol publication

Protocol references

1. Katsumoto TR, Whitfield ML, Connolly MK. The pathogenesis of systemic sclerosis. *Annu Rev Pathol* [Internet]. 2011 [cited 2016 Jun 13];6:509–37. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21090968>
2. Denton CP, Khanna DK. Systemic sclerosis. *Lancet*. 2017;390(10103):1685–99.
3. Hughes M, Herrick AL. Systemic sclerosis. *Br J Hosp Med*. 2019;80(9):530–6.
4. Mayes MD, Trojanowska M. Genetic factors in systemic sclerosis. *Arthritis Res Ther* [Internet]. 2007;9 Suppl 2(Suppl 2):S5–S5. Available from: <https://pubmed.ncbi.nlm.nih.gov/17767743>
5. Altorok N, Almeshal N, Wang Y, Kahaleh B. Epigenetics, the holy grail in the pathogenesis of systemic sclerosis. *Rheumatology (Oxford)* [Internet]. 2015;54(10):1759–70. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24740406>
6. Tyndall AJ, Bannert B, Vonk M, Airò P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis*. 2010 Oct;69(10):1809–15.
7. Hughes M, Pauling JD, Armstrong-James L, Denton CP, Galdas P, Flurey C. Gender-related differences in systemic sclerosis. *Autoimmun Rev*. 2020;19(4):102494.
8. Flurey CA, Pauling JD, Saketkoo LA, Denton CP, Galdas P, Khanna D, et al. “I turned in my man card”: a qualitative study of the experiences, coping styles and support needs of men with systemic sclerosis. *Rheumatology (Oxford)*. 2023 Jun;62(6):2160–7.
9. Ota Y, Kuwana M. Updates on genetics in systemic sclerosis. *Inflamm Regen* [Internet]. 2021;41(1):17. Available from: <https://doi.org/10.1186/s41232-021-00167-6>
10. Kukendrarajah K, Farmaki A-E, Lambiase PD, Schilling R, Finan C, Floriaan Schmidt A, et al. Advancing drug development for atrial fibrillation by prioritising findings from human genetic association studies. *EBioMedicine*. 2024 Jul;105:105194.