Systemic sclerosis (SSc) vasculopathy: Improved clinical monitoring and treatment

Protocol Summary

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University of Utah IRB #:	IRB_00038705
Sponsor:	US DEPARTMENT OF VETERANS AFFAIRS
Principal Investigator:	Tracy Frech
Internal Staff and Sub-Investigators:	

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Background and Introduction

Systemic sclerosis (SSc) is a complex autoimmune disease characterized by multi-organ vascular alterations (vasculopathy) with subsequent varying degrees of fibrosis. It is a devastating autoimmune disease with limited therapeutics available. While both genetic and environmental factors are recognized as important in pathogenesis, much work needs to be done to characterize these effects in the setting of a heterogeneous clinical phenotype.

Purpose and Objectives

This study is being done to try to find out the causes of systemic sclerosis which is an autoimmune condition associated with changes to blood vessels (vasculopathy) and abnormal scarring (fibrosis) of skin, lungs, heart, gastrointestinal tract, and kidneys. We want to determine if there is a gene responsible for this disease, and we are interested in finding biomarkers (a biochemical characteristic that can be used to measure the progress of disease or the effects of treatment) that will help doctors predict who is at risk for developing lung, kidney, and gastrointestinal vasculopathy and fibrosis manifestations of this disease, and how best to treat them.

Study Population

Age of Participants: 14-17 yo and 18+

Sample Size:

At Utah:	850
All Centers:	850

Inclusion Criteria:

A diagnosis of systemic sclerosis.

We will include age cohort 14-17 to our already approved 18+ cohort

Family members of patients with a diagnosis of systemic sclerosis to be used as a control group.

Additionally, disgarded clinical forearm skin biospy specimens (de-identified) will used for comparison.

Number of participants:

University of Utah:

Affected: 500

Controls: 300

VA: 50 total

Exclusion Criteria:
None

Design

Prospective Biomedical Intervention or Experiment

Serum, biopsy tissue and DNA collection and storage.

Study Procedures

Recruitment/Participant Identification Process:
Dr. Frech will identify affected participants during the patients routine care visits from her scleroderma clinic, the general rheumatology clinics, or as an inpatient at the University of Utah and George E. Wahlen VA. Dr. Frech and sub-investigators will also identify healthy-control patients during routine care visits from the general rheumatology clinics at the University of Utah and George E. Wahlen VA. We plan to enroll healthy controls from families of consented and enrolled affected subjects. We will ask affected subjects if they want to approach friends or family members about participating as control subjects. If affected subjects decide they want to approach friends or family members, they will be instructed to give interested individuals an ICF and to have each interested person individually contact study staff to discuss the study and their participation. Those interested in participating will have their own separate study visit.

Dr. Gourh will use the analysis from the UPDB to help detect genetic relationships in SSc and then analyze DNA from certain pedigrees. Dr. Pravitt Gourh may be involved in evaluating and examining the SSc patients at the University of Utah Hospital and Clinics. He may interview the family members and, if needed, examine them at the University of Utah Hospitals and Clinics. Dr. Gourh will also be involved in reviewing identifiable data from patients and their family members that may have already been collected and stored in the study.

Dr. Gourh is an NIH fellow that is using his funding to better understand the genetic risk of SSc. With his help, this project will be funded.

Dr. Gourh will not conduct any research at the VA Medical Center and will not have access to any information obtained at the VA.

All study procedures and assessments will be performed at both the University of Utah and the George E Wahlen VA with the exception of the whole genome or exome sequencing. Dr. Pravitt Gourh from the NIH will not examine or see patients from the VA or collect any specimens from VA participants.

Informed Consent:

Description of location(s) where consent will be obtained:

University of Utah Medical Center Rheumatology Clinic 2 and at the George E. Wahlen VA Medical Center Internal Medicine Clinic

Description of the consent process(es), including the timing of consent:

No formal waiting period, unless requested by participant. Patients will be consented by Dr. Frech or her designated research staff. Consent form will be thoroughly reviewed with the patient and the patient will be given the opportunity to ask any questions. No study procedures will be performed prior to obtaining consent. The ICF will be signed by both parties and the patient will be given a copy for their records.

Requested Waivers/Alterations of Consent:

Waiver of Informed Consent	We request a waiver of consent for those participants who have already been consented to this study. Patients in this study have already consented to genetic research with the aim of improving the understanding the role of genetics in scleroderma. Linking patients to IRB# 31854 will allow additional scleroderma pedigrees to be created that assess potential links between scleroderma and other diseases. This will be a valuable tool and is consistant with the stated aims of the study. If/when participants are re-contacted for any further studies requiring face to face contact for this study, reconsent of participants will happen at that time.
Waiver of Informed Consent	We request a waiver of consent for patients who have already been consented to IRB#38705. Patients in this study have already consented to genetic research with the aim of improving understanding of the role of genetics in scleroderma. Linking patients to pedigrees created by IRB#31215 will be a powerful tool in achieving this aim and is consistent with the stated aims of the study. If/when participants are re-contacted for any further studies requiring face-to-face contact for IRB #38705 or #31215, re-consent of participants will happen at that time
Waiver of Informed Consent	The purpose of this waiver is to collect disregarded forearm specimens for comparison to forearm specimens of scleroderma patients.

Procedures:

SSc participants and the controls (family members) will be identified from clinic (Clinic 2, SSc clinic, VASLCHSC). If they are 18+, they will have serum drawn and biopsy performed in clinic. If they are part of the 14-17 yo cohort, they will only have a blood draw.

STUDY PROCEDURES

Baseline and Follow-Up Visits

No study-related procedures will be performed until patients have signed this consent form and agree to take part in this study.

Baseline Visit

This Baseline Visit will be scheduled to coincide with one of routine care visits. During this Baseline Visit the following procedures will be performed:

- Provide a complete medical history, family medical history and review past and current medications. This information will be obtained from medical records and questions answered by the patient. Examples of the types of records we may review include but are not limited to routine echocardiograms, pulmonary function tests, upper and lower endoscopy reports, pathology reports, questionnaires, blood work (such as chemistries), stool studies, radiographic images, diet or symptom diaries, and urine analyses. This information we obtain for this study will only be collected if it was performed as a procedure/assessment as part of a patient's standard of care visit;
- Have a physical exam with height, weight, and vital signs measured (such as blood pressure, heart rate, etc). These procedures are routine and normally performed during a routine care visit;
- Provide routine blood and urine samples that will be tested for clinical assessment and disease activity. These samples are normally collected for routine care;
- We may collect research-related blood samples including a DNA blood sample. The DNA sample will only be collected one time during the course of this study. If a DNA blood sample is not collected at the baseline visit, it may be obtained at the next available follow up visit. These samples may be collected for study-related purposes, and would not be collected for routine care. These samples are in addition to the samples collected for disease activity. No more than 5 tablespoons of blood (includes blood drawn for routine and study-related purposes) will be collected for this visit;
- We may ask for a skin biopsy. Biopsy specimens may provide key information about the causes of scleroderma. Family members and friends that agree to take part in this study, as part of the control group, may also be asked to provide a skin biopsy to use as a comparison to affected skin. Patients would not have this skin biopsy procedure as part of your routine care and this would be performed for study purposes only. Dr. Frech will collect two 3-4 millimeter biopsies using a punch biopsy instrument;
- Complete several questionnaires that will ask the patient to assess the impact of scleroderma on their quality of life and their physical and mental health. This will take about 20 minutes to complete. Participants will be asked to complete these questionnaires for the study and would not normally be asked to complete questionnaires during a routine care visit;
- Have other tests that may be ordered by your doctor for routine care.

Follow-Up Visits

Participants will be asked to return for first follow-up visit six months after the Baseline Visit, and then for a follow-up visit every six months thereafter for the duration of the study. Every effort will be made to have follow-up visits coincide with routine Rheumatology care visits. Visits are piggy-backed on standard of care,

participants will be seen when their visits correlate with their standard of care visits. If participant is not seen every six months we will capture study data when the participant returns to clinic.

During the Follow-Up Visit the following procedures will be performed:

- Review health and medication (s) for changes since the last visit. We would normally collect this information during a routine care visit.This information we obtain for this study will only be collected if it was performed as a procedure/assessment as part of a patient's standard of care visit;
- Have a physical exam with height, weight, and vital signs measured (such as blood pressure, heart rate, etc). These procedures are routine and normally performed during a routine care visit;
- Provide routine blood and urine samples that will be tested for clinical assessment and disease activity. These samples are normally collected for routine care;
- We may collect research-related blood samples. These samples will be collected for study-related purposes, and would not be collected for routine care. These samples are in addition to the samples collected for disease activity. No more than 2-4 tablespoons of blood (includes blood drawn for routine and study-related purposes) will be collected per visit;
- We may ask for a skin biopsy. Biopsy specimens may provide key information about the causes of scleroderma and may be collected up to three more times during your study participation. Patients would not have this skin biopsy procedure as part of their routine care and this would be performed for study purposes only. Dr. Frech will collect two 3-4 millimeter biopsies using a punch biopsy instrument.
- Complete several questionnaires that will ask the patient to assess the impact of scleroderma on their quality of life and their physical and mental health. This will take about 20 minutes to complete. Participants will be asked to complete these questionnaires for the study and would not normally be asked to complete questionnaires during a routine care visit;
- Have other tests that may be ordered by your doctor for routine care.

Questionnaires

Patients will be asked to complete questionnaires in-person at every study related visit as described above. If they would like to complete them electronically, they will have the option to provide the research staff with an email address. The electronic version of the questionnaires are identical to the paper version but will be made available through a link provided in an email and will allow patients access to a study portal called “REDCap” from their smart phone, mobile device or computer. Patients may switch between completing the questionnaires using the study portal or the paper version.

If you they the study portal to complete the questionnaires electronically, the email they receive will provide instructions on how to utilize the portal. The email address they provide to the study team will be used solely for the purpose of sending a link and instructions. It will

not be shared or disclosed in any other matter. Additionally, standard data rates that apply will be their responsibility.

Other examinations

Other examinations that may be performed at both baseline and follow-up visits include peripheral nerve testing and a nailfold capillary exam. The nailfold capillary exam is a simple and non-invasive test that uses a special microscope to look at the capillaries along the nailbed. This test can help determine any vascular changes or abnormalities associated with Raynaud's phenomenon and/or SSc. The peripheral nerve test is also a simple and non-invasive exam that assesses specific nerves and senses by placing the tip of a tuning fork on to certain extremities such as your toes and legs to see if patients can sense vibrations.

We may also measure blood flow in patients with SSc and their family members. Blood flow will be measured with an ultrasound machine. This is a non-invasive procedure. A blood pressure cuff will be wrapped around the forearm or around the lower leg. Gel will be applied on the area of the arm or leg that will be used for measuring blood flow. The blood pressure cuff will be inflated to 250 mmHg, the upper end of the normal inflation range, for five minutes to stop blood flow of the artery that will be examined for change in diameter upon cuff deflation using the ultrasound machine. This procedure is referred to as the measurement of flow-mediated vasodilation (FMD). Since obstructing the blood flow for five minutes may be painful for some individuals it should be noted that if patients wish to stop this test at any point during the measurement the research personnel will do so. This assessment may take about 30 minutes and will be performed at every study visit.

Another blood flow measurement may be collected by taking an image of the vessels under the tongue (sublingual) using a specific type of camera called a Laser Speckle Imaging (LSI) device. Patients will be asked to hold their mouth open wide and place the tip of their tongue on the roof of their mouth for a couple of minutes while the doctor captures images of the blood vessels under the tongue. This procedure is non-invasive and will take approximately 5 minutes.

Peripheral nerve testing, nailfold capillary exam, flow mediated dilation and sublingual imaging. These examinations will only be performed on the adult (18+) participants.

If patients undergo any assessments, procedures, or treatment as part of their routine care for digital ulcers and/or hand contractures, we ask that we be allowed to obtain records and information related to this care and use the data as part of this study to learn more about vasculopathy and fibrosis.

If an adverse event occurs (ie, bruising, bleeding) then it will be addressed in clinic.

After subjects at the University of Utah are identified through these sources, patient PHI (names, dates of birth, gender, and phenotypic information) will be passed to the Genetics and Molecular Characteristics of Interstitial Lung Disease study (IRB#31215) on which Dr. Frech is a co-investigator. Dr. Scholand is the primary investigator on IRB# 31215 and a co-investigator on this study. Subjects from the VA will be excluded in this portion of the study.

The information obtained from the control group (unaffected family members) in this study will be used in conjunction with IRB study #: 31854- An Improved Definition of Hereditability of Systemic Sclerosis (SSc), SSc Overlap Conditions, and Raynaud's Phenomenon Through Use of the Utah Population Data Base (UPDB). MRNs from the control subjects will be submitted to the UUHSC EDW through Dr. Frech's 31854 project in order to obtain UPDB numbers. This information (from controls only) will then be used to perform a kinship analysis under 31854 for SSc data identified from the University of Utah Health Sciences Center. Dr. Frech oversees both projects as the PI. Please refer to the study #: 31854 for further information.

The study will utilize the Master Subject Index that links the demographic records from the UUHSC EDW to the UPDB under IRB_00045234, Master Subject Index between the Utah Population Database and the University of Utah Health Sciences Center (Ken Smith, PI).

All data will remain behind the HSC computer firewall on password protected computers. Only associates affiliated with this research project and project #s 38705 & 31215 will have access to study information. Any information discussed or shared via email between the investigators will be encrypted.

The study staff for the Genetics and Molecular Characteristics of Interstitial Lung Disease study (IRB#31215) will submit the medical record numbers to the UUHSC EDW so that a UPDB number can be obtained from the Pedigree and Population Resource, the group that manages the UPDB.

The Pedigree and Population Resource will develop pedigrees as well as link participants to any existing pedigrees identified under IRB #31215. All UPDB pedigree data will be stored electronically by the Pedigree and Population Resource on their secure server, and may be shared with investigators for this trial as well as Dr. Pravitt Gourh, an external investigator for this study.

Pedigree information obtained in the IRB_31854 study will be coded by UPDB number, and phi will be removed. Pedigrees for analysis will retain the UPDB number, diagnoses, environmental exposures, other de-identified test data, age at diagnosis, demographic data essential for analysis (e.g., gender, race), and pedigree structure. This data, along with molecular data generated on pedigree members, will be shared by Drs. Scholand and Frech.

The GI biopsy specimens from healthy controls will be identified through Drs. Peterson and Gawron during routine endoscopy schedule. If they have extra tissue from a biopsy in a healthy control or irritable bowel specimen that is obtained for medically indicated reasons (not study purposes) they may bring the de-identified tissue to Tracy Frech for analysis. Thus, Dr. Peterson & Dr. Gawron will de-identify the patients and it will not be linked to PHI. The only information the investigators will have is that the patient does not have SSc and is healthy or has irritable bowel.

Study participant's family members may also be consented and included in the study as control subjects.

Whole Genome or Exome Sequencing: Research samples collected as part of this study may be analyzed for genetic purposes. In addition to standard genetic tests, we may want to perform whole genome or whole exome sequencing of the DNA from affected patients, and DNA from the controls if they are willing to provide DNA samples. A detailed description of genome and exome sequencing is provided in the ICF. The sequencing would be done by Dr. Pravitt Gourh at the NIH. These samples would be shipped to his lab at the NIH in Bethesda, Maryland where they would be stored for an undetermined amount of time. This is an optional sub-study offered to participants at the University of Utah only. VA participants are excluded from this optional sub-study.

Dr. Frech would like to share some de-identified, limited data sets with Dr. Baron and his group at Jewish General Hospital in Quebec, Canada. Dr. Baron's research in SSc mimics the data collected by Dr. Frech for the IRB 38705 project. Data would come from the assessments & related outcomes collected as part of the 38705 study. The UPDB data that is obtained as part of the linked project, IRB 31854, will not be used for this collaboration.

Procedures performed for research purposes only:

Research blood samples in the 14-17 year old cohort.

Research blood samples and skin biopsies in the 18+ cohort.

Nail fold capillary exam

Flow mediated dilation

Sublingual imaging

For participants at the VA, the above procedures/assessments will be performed for resear purposes only and at no cost to the veteran.

Statistical Methods, Data Analysis and Interpretation

Statistics will be run using SAS version 9.2. None of the variables will have an assumption of normality. SSc patient characteristics will be summarized using means and frequencies when appropriate. General linear models will be used to compare age-adjusted characteristics. T-test will be used to compare biopsy outcomes by the patients defined by bivariate clinical characteristics. Spearman correlation will be used to assess clinical and biopsy variables.