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TITLE: Rare Variants in Systemic Sclerosis (SSc, Scleroderma)

PRINCIPAL INVESTIGATOR: Maureen D. Mayes, MD, MPH

CONTRACTING ORGANIZATION: University of Texas Health Science Center
Houston, Texas

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14. ABSTRACT

The subject/topic area of this research is Systemic Sclerosis (SSc, Scleroderma). The purpose of the research is to identify genetic variants that contribute to SSc disease susceptibility and influence outcome. The approach involves whole genome sequencing of 100 trios (300 individuals including affected case and both parents). Previous Genome-Wide-Association-Studies (GWAS) have identified gene regions that are associated with disease but the majority of these are in non-coding areas so the impact of these variants is unclear. This study will identify rare variants (both inherited and de novo mutations) and will analyze these mutations according to the role they likely plan in disease pathogenesis. The immediate outcome of this project will be identification of the causal variants in multiple pathways associated with SSc susceptibility with the long-range impact will be the identification of the role these variants plan in disease causation and severity/outcome.

15. SUBJECT TERMS
None listed.

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1. **INTRODUCTION:** The subject/topic area of this research is Systemic Sclerosis (SSc, Scleroderma). The purpose of the research is to identify rare genetic variants that contribute to SSc disease susceptibility and influence outcome. The approach involved whole genome sequencing of 100 trios (total of 300 individuals including affected case and both parents) completed in year 3. Previous Genome-Wide-Association-Studies (GWAS) have identified gene regions that are associated with disease but the majority of these are in non-coding areas so the impact of these variants is unclear. This study identified a rare variant and we are in the process of analyzing this mutation to identify the role it may play in disease pathogenesis. The immediate outcome of this project is the identification of a potential causal variant associated with SSc susceptibility with the long-range impact being the identification of the role these variants plan in disease causation and severity/outcome.
2. **KEYWORDS:** Systemic Sclerosis, Scleroderma, Whole Genome Sequencing (WGS), genetic variants, rare variants.
3. **OVERALL PROJECT SUMMARY:** This past year has seen the analysis of the largest whole genome sequencing (WGS) project to date in scleroderma. The samples were successfully sequenced and quality control procedures applied in year 2. (see separate Progress Report by Co-PI Dr. Brendan Lee) for mapping, alignment, sorting, duplicate marking and variant calling. The analysis continues in process for data interpretation, variant calling and identification of rare variants and de novo variants in individual cases and those in common among scleroderma cases. A rare variant has been identified in one of the trios and pathway analysis is underway.

   This represents the largest, most complete and detailed whole genome sequencing (WGS) project done to date in scleroderma. We continue the process of interpretation and discussion among the investigators and preparation of the “main” manuscript as well as other related manuscripts (analysis approaches, etc.) is underway. These data are expected to result in multiple publications as well as additional avenues of investigation and, finally, insight regarding susceptibility and pathogenesis.

4. **ACCOMPLISHMENTS:**
   - **What were the major goals of the project?**
     - Task 1 **COMPLETED and reported previously.**
     - Task 2 **COMPLETED and reported previously.**
     - Task 3 **COMPLETED and reported previously.**:
     - Task 4 **COMPLETED and reported previously.** :
     - Task 5 **mostly COMPLETED in year 3 with validation in a separate cohort with targeted genotyping of additional samples in ~ 3,000 cases and 1,000 controls.** Data analysis however is ongoing with expected completion in the next 6 months (anticipated by July/August 2022
     - Task 6 **IN PROCESS**: Association analysis underway of the most likely identified variants with clinical disease features. **This is ongoing and close to completion as we prepare the manuscripts. – expected in the next few months; additionally, targeted genotyping of additional samples in > 3,000 cases and 1,000 controls is underway.**
     - Task 7 **IN PROCESS**: Preparation of manuscripts for publication. **The manuscript describing the main finding to date – the rare variant**

identification has been completed and further analysis is planned as we prepare the manuscripts with consideration of potential pathogenetic implications. Task 8 **ONGOING:** Quarterly meetings between the UT-H and BCM teams to coordinate all aspects of the project and review and interpret data and manuscripts. . Timeline months August 2021- Aug 2022). **Ongoing.**

- We continue to **meet monthly** in virtual capacity (via Zoom) due to the pandemic. Monthly meetings are considered necessary at this stage due to the volume of data and complexity of the analysis. We are up-to-date on these and plan to continue with monthly meetings in this exciting and final phase of the project.

- **What was accomplished under these goals?**
  - Tasks 1 through 5 have been completed; Tasks 6-8 are still underway with most data collection completed, but requiring analyses and interpretation. These should be completed in the no-cost-extension period of the project.
- **What opportunities for training and professional development has the project provided?**
  - Nothing yet to report**.**
- **How were the results disseminated to communities of interest?**
  - Nothing yet to report.
- **What do you plan to do during the next reporting period (no-cost extension)to accomplish the goals?**
  - Now that the sequencing data have been generated, uploaded to the DRAGEN platform for variant calling, and analysis is underway, the manuscript preparation including genotype-phenotype correlations and validation in our larger cohort is underway and expected to be completed in the no-cost extension year.

5. **IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*
   - **What was the impact on the development of the principal discipline(s) of the project?**
     - Nothing to yet report – the publication of the manuscript is expected to be in a high-impact journal which should generate considerable interest and lead to a better understanding of pathogenetic pathways in systemic sclerosis/scleroderma.
     - Nothing yet to Report at this time.
   - **What was the impact on other disciplines?**
     - Nothing yet to report – the publication of a statistical method approach to the analysis of this richly detailed genetic date is expected to have an impact on genetic sequencing approaches to multiple diseases.
   - **What was the impact on technology transfer?**
     - Nothing yet to Report.

- **What was the impact on society beyond science and technology?**
  - Nothing yet to Report.

6. **CHANGES/PROBLEMS:** *The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*
   - **Changes in approach and reasons for change**
     - There have been no changes in approach.
   - **Actual or anticipated problems or delays and actions or plans to resolve them**
     - There was a delay in HRPO approval due to a miscommunication, but this was resolved and the project was able to move forward in a timely fashion.
   - **Changes that had a significant impact on expenditures**
     - There were no changes that had a significant impact on expenditures.
   - **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
     - None
   - **Significant changes in use or care of human subjects - None**
   - **Significant changes in use or care of vertebrate animals. None**
   - **Significant changes in use of biohazards and/or select agents None**
7. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*
   - **Publications, conference papers, and presentations**
     - **Journal publications.** None to date.
     - **Books or other non-periodical, one-time publications.** None to date.
     - **Other publications, conference papers, and presentations.** None to date.
   - **Website(s) or other Internet site(s)**
     None to date.
   - **Technologies or techniques**
     None to date.
   - **Inventions, patent applications, and/or licenses**
     None to date.
   - **Other Products**
     None to date.
8. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**
   - **What individuals have worked on the project?**

- *Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."*

Name:	Maureen D. Mayes, MD, MPH (No change from submission)
Project Role:	Principal Investigator; Initiating PI
Researcher Identifier (e.g. ORCID ID):	ORCID ID = 0000-0001-5070-2535
Nearest person month worked:	3.0 calendar months
Contribution to Project:	Dr. Mayes is responsible for the overall conduct of the study and for the timely completion of all aspects (Tasks 1 through 8); she supervises UT project personnel and organizes the weekly UT meetings and the now monthly UT-BCM team meetings to review progress, potential problems, data collection and results.
Funding Support:	**New** sources of funding support since last annual progress report (9/14/2020): **Horizon Therapeutics**: Randomized, double-blind, placebo-controlled, repeat-dose, multicenter study to evaluate the safety, tolerability, pharmacokinetics, and explore efficacy of TEPEZZA in patients with diffuse cutaneous systemic sclerosis**; Period of Award 3/18/2021 – 3/17/2022;** per patient reimbursement; Mayes, PI at UTH site **Mitsubishi Tanabe Pharma Development America**: MT7117 in subjects with diffuse cutaneous systemic sclerosis; **Period of Award 2/22/2021 to 2/21/2026;** per patient reimbursement; Mayes, PI at UTH site. Other projects, listed previously, are ongoing.

Name:	Dianna Milewicz, MD
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	

Nearest person month worked:	0.6 calendar months
Contribution to Project:	Dr. Milewicz has a strong background in the genetic basis of vascular diseases. Her role has been to provide guidance on study design and provide advice on the analysis and interpretation of the genetic data. She has served as an advisor on Dr. Mayes' previous scleroderma genetic studies and has worked with the Baylor College of Medicine Genetics group on multiple projects. Her role in this project has ended and she will **not be needed** to participate in the no-cost extension period.
Funding Support:	No new funding to report since 8/2020

Name:	Claudia Pedroza, PhD (no change from submission)
Project Role:	Co-Investigator, statistician
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.6 calendar months
Contribution to Project:	Dr. Pedroza has been involved in the planning and implementation of the project to date to ensure that data will be interpreted in light of available clinical outcomes.
Funding Support:	New since last report: NIH/NIAMS: Combined Optical Coherence Elastography and Tomography for Assessing Skin Involvement in Systemic Sclerosis

Name:	Patricia Gonzales, LVN (no change from submission)
Project Role:	Project Coordinator

Researcher Identifier (e.g. ORCID ID):	Not Applicable
Nearest person month worked:	3.6 calendar months
Contribution to Project:	Ms Gonzales is responsible for the day-to-day operations of the study, overseeing database queries and reporting to the investigators regarding progress, time lines and review of expenditures.
Funding Support:	Not applicable

Name:	Julio Charles (no change from submission)
Project Role:	Laboratory Manager
Researcher Identifier (e.g. ORCID ID):	Not applicable
Nearest person month worked:	3.0 calendar months
Contribution to Project:	Mr Charles is responsible for overseeing the selection, aliquoting and distribution of samples for genotyping and sequencing studies. He coordinates delivery to the Baylor research lab; he attends the weekly lab meetings as well as the project-specific quarterly meetings between the UT and Baylor research groups.
Funding Support:	Not applicable

Name:	Hau Pham (no change from submission)
Project Role:	Research Assistant
Researcher Identifier (e.g. ORCID ID):	Not applicable
Nearest person month worked:	3.0 calendar months
Contribution to Project:	Ms. Pham is responsible for the day-to-day work in the Rheumatology Research Lab, to implement sample selection, DNA quantification, DNA measurement and record keeping of samples distributed to Baylor as well as DNA extraction on new samples as needed, and autoantibody determination on these new samples.
Funding Support:	Not applicable

Name:	Marka Lyons
Project Role:	Data Manager, Clinical Research
Researcher Identifier (e.g. ORCID ID):	Not applicable
Nearest person month worked:	1.8 calendar months
Contribution to Project:	Ms. Lyons is responsible for coordinating the genetic data and ensuring that clinical phenotype and pedigrees are complete and accurate. She will also coordinate with the database managers.
Funding Support:	Not applicable

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
  - Yes for the PI only – see above. This does not influence the conduct of the study and it does not change the proportion of time and effort that the PI (Dr. Mayes) devotes to this project.
- **What other organizations were involved as partners?**
  - Note: Dr. Brendan Lee at Baylor College of Medicine was included in the original application as Collaborating/Partnering PI. and no changes have been made to this relationship; he continues as Collaborating/Partnering PI. As collaborating PI he will submit his own annual report.

9. **SPECIAL REPORTING REQUIREMENTS**
   - **COLLABORATIVE AWARDS:** The Collaborating PI (Dr. Brendan Lee, Baylor College of Medicine) will submit a separate report as required.
   - **QUAD CHARTS:** The Quad chart will be attached and uploaded on the website.
10. **APPENDICES:** Not applicable.