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TITLE: Multispecies, Integrative GWAS for Focal Segmental Glomerulosclerosis

PRINCIPAL INVESTIGATOR: Simone Sanna-Cherchi

RECIPIENT: TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NY
NEW YORK, NY 10032

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The overall goals of this project are to identify novel susceptibility variants to human nephrotic syndrome caused by focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD). Using a variety of statistical and genetic approaches, including genome wide association analysis and rare copy number variations (CNVs) mapping. Data are then integrated with genetic analyses from mouse models from the partnering project. The identification of novel variants will provide insight into some of the genetic mechanisms that underlie FSGS.

15. SUBJECT TERMS

FSGS, MCD, GWAS, CNV

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

The overall goals of this project are to identify novel susceptibility variants to human nephrotic syndrome caused by focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD). Using a variety of statistical and genetic approaches, including genome wide association analysis and rare copy number variations (CNVs) mapping. Data are then integrated with genetic analyses from mouse models from the partnering project. The identification of novel variants will provide insight into some of the genetic mechanisms that underlie FSGS.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

FSGS, MCD, GWAS, CNV

3. **ACCOMPLISHMENTS:** The 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.

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Specific aim 1: A Genome-wide association study for common single nucleotide polymorphisms and rare copy number variations in 7,559 FSGS and over 50,000 controls.

1a. Genotyping of 7,559 FSGS patients with the Illumina Global MEGA Power Chip.

Sample Collection, preparation and genotyping is ongoing and anticipated to be completed by June 2020.

Currently genotyping increased from ~3,000 cases in Year 2 to >4,500 cases in Year 3.

1b. CNV burden analysis and annotation of deleterious structural variants

In progress (see interim analyses): will be completed after Year 3 completion of genotyping

1c. Joint-cohorts genome-wide association study

Preliminary analysis completed by July 2019. Interim analysis on ~2,600 cases and ~16,000 matched controls completed (see below). Analysis on >4,000 and 16,000 matched controls in progress.

Specific aim 2: A GWAS for FSGS in mouse.

See progress report from Dr Gharavi

Specific aim 3. Cross annotation between human and mouse GWAS and identification of downstream dysregulated pathways and networks.

In progress, expected to be completed by June 2020.

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Specific aim 1: A Genome-wide association study for common single nucleotide polymorphisms and rare copy number variations in 7,559 FSGS and over 50,000 controls.

1. We are genotyping clinically ascertained nephrotic syndrome (FSGS and MCD) samples to increase the overall GWAS and CNV analysis cohort size according to the project milestones and goals.

2. During Year 3 we conducted an interim analysis expanding our GWAS from ~1,100 cases from years 1 and 2 to 2,639 cases and 16,765 ethnically-matched (76% EUR, 14% AFR, 8% AMR, and 2% ASN). This cohort was composed of 11 subpopulations of cases and controls strictly genetically-matched. The primary association analyses was first performed within each ethnic group using an additive model as implemented in PLINK. After imputation, meta-analysis was then performed using an inverse variance-weighted method (METAL software), and heterogeneity across cohorts by performing Cochrane's Q test and deriving heterogeneity index (I^2). **In the combined meta-analysis** (2,639 cases), we discovered significant associations for *APOL1* (OR=2.87, P= 7.68x10^{-31}), which were driven solely by African individuals (OR=2.82, P=1.45x10^{-37}), the *HLA-DQA1* locus (OR=1.43, P= 3.2x10^{-22}), and **two novel loci** on chr.1q42.2 (OR=1.34, P=3.29x10^{-08}) and chr.16q21 (OR=2.72, P=2.07x10^{-8}). **After conditional analysis** on the top two SNPs at *APOL1* and *HLA* loci, a second independent *HLA* genome-wide significant signal was discovered (OR=1.36, P=2.18x10^{-10}). **Among adult-onset patients** (n=1,391), the strongest signals were at the *APOL1* locus (OR=3.14, P=1.82x10^{-21}) and a **novel locus** on chr.14q21.3 (OR=1.54, P=1.62x10^{-8}). The *HLA-DQA1* locus was the highest among **pediatric cases** (OR=2.01, P=4.06x10^{-32}). The *HLA* signal in Caucasians was genome-wide significant also in adults (OR=1.33; P=1.20x10^{-8}). Additional significant and suggestive signals were found in adult and pediatric cohorts stratified by race and response to therapy. **In conclusion,** our results demonstrate multiple novel FSGS loci, pleiotropic risk alleles that predispose to NS across different subphenotypes, and signals specific to race, age of onset and response to therapy. Specifically, we can now implicate variation in the *HLA* locus as a major contributor to the risk of FSGS in adults. Fine-mapping the HLA and non-HLA risk loci and integrating these GWAS alleles with other FSGS-associated genetic factors (Mendelian alleles, CNVs) holds promise in further elucidating the genetic architecture of FSGS.

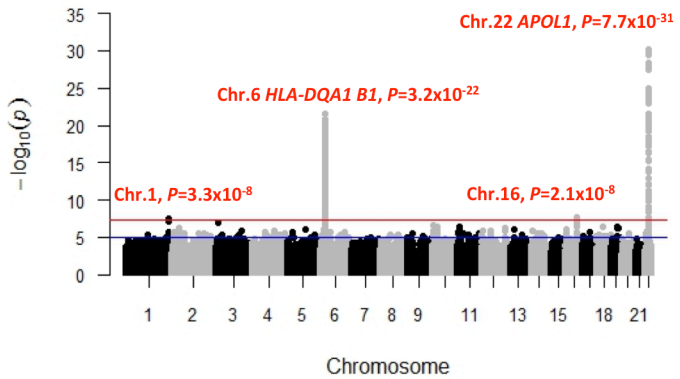

Figure 1. Manhattan plot of GWAS in the entire cohort of 2,639 FSGS cases and 16,765 controls showing highly significant association at the HLA and APOL1 loci.

3. Analysis of rare CNVs identifies known and novel disease causing structural variants. We conducted CNV analysis using the same DNA microarray data used for GWAS as previously described. Additional QCs for CNVs resulted in a final cohort of 2,230 FSGS cases that we compared to 24,765 controls. We identified syndromes that might cause secondary / maladaptive forms of FSGS that result in phenocopy of disease, including a patient with the 17q12 RCAD microdeletion; 5 patients with CNVs at the 1q21 locus; one patient with a duplication at the CMT1A locus. Annotation of large, rare CNVs that affect coding regions (**Table 2**) identified potential pathologic lesions in 18% (12.5% >500kb; 5.5% >250kb) of the cohort, suggesting a significant role for rare large CNVs in FSGS. Further prioritization via stringent criteria identified potentially diagnostic CNVs that affected known kidney genes in 3.6% of the cases. These included homozygous/heterozygous deletions affecting *NPHS1*, *WDR73*, as well as duplications affecting *INF2*. 12 cases harbored homozygous deletions that were absent in 24,765 controls, suggesting novel candidate genes for FSGS. Since rare variants with large effect size can confound genetic association tests for variants with small to moderate effect size like in the GWAS approaches, individuals carrying such variants (as well as high-risk *APOL1* genotypes and Mendelian mutations) should be removed to maximize GWAS power.

CNVs	CNVs	Pos_Case (N=2,230)	% of Pos_Case (N=2,230)
Size >= 500kb, Freq_Ctrl < 0.02%, ISCA_BEN = 0 , Exonic			
All	145	278	**12.50%**
Overlap ISCA Pathogenic CNV	13	19	0.90%
Overlap Kidney genes	20	53	2.40%
Size between 250Kb and 500Kb, Freq_Ctrl = 0 , ISCA_BEN = 0 , Exonic			
All	102	122	**5.50%**
Overlap ISCA Pathogenic CNV	2	3	0.10%
Overlap Kidney genes	8	13	0.60%
Autosomal Dominant Kidney Genes, Pos_Ctrl < 2, ISCA_BEN = 0 , Exonic			
All	15	17	**0.80%**
FSGS	10	12	0.50%
Recessive Kidney Genes, Pos_Ctrl < 1%, ISCA_BEN = 0 , Exonic			
All	30	63	**2.80%**
FSGS	12	13	0.60%
Homozygous Deletion, CN=0, ISCA_BEN = 0 , Exonic			
All	12	12	0.50%
FSGS	1	1	0.00%
Heterozygous Deletion, CN=1, ISCA_BEN = 0 , Exonic, Dominant Kidney Gene			
All	3	3	0.10%
FSGS	2	2	0.10%
Heterozygous Deletion, CN=1, ISCA_BEN = 0 , Exonic, Recessive Kidney Gene			
All	6	6	0.30%
FSGS	3	3	0.10%

Table 2. Likely pathogenic CNVs of potential causal relation with FSGS etiology.

4. During year 2-2 we also gained access to a fully imputed dataset (6,039,567 imputed SNPs) of 775 FSGS and 954 controls of East Asian Ancestry (from Co-I Dr Kiryluk) that will be used for replication and joint analyses with our existing dataset. This will boost power for detecting novel significant signals and will expand our search for genetic susceptibility variants for FSGS to individuals of Asian ancestry.

5. WES was performed in 2,527 patients from the FSGS Columbia Cohort (1,785 of these cases included in the GWAS analysis above). Analysis by querying for causal variants in a curated list of 127 genes known to cause FSGS or kidney diseases that can phenocopy FSGS using the ACMG criteria for clinical variant annotation, identified 18.2% of patients with pathogenic or likely pathogenic variant in a MEndelisan gene of a high-risk genotype for APOL1. WES/WGS is also available for the remaining ~900 cases (which include Dr. Hildebrandt and Dr. Sampson's cohorts) with similar "solving rate". Since genotypes with large effect size can confound and reduce power in the identification of common risk alleles with small-to-moderate effect size, removal of cases that carry such variants will increase our power to detect true associations and help refine the new loci. We are currently conducted GWAS analyses after removal of all these cases.

6. With the partnering PI project (see Dr. Gharavi's report), we generated transgenic F1 hybrids between the TgFVB mice and 20 inbred strains of mice, characterizing the phenotypes based on the proteinuria, urine NGAL and the histopathology

Currently we have completed the pathology in 17 strains of mice, and in 20 strains for urine analysis (NGAL, proteinuria, and hematuria) and serum analysis (BUN, IgA and IgG). Our data has demonstrated, that not all the Tg-F1 hybrids develop proteinuria. The Tg-F1 hybrids derived from the A/J, C3H/HeJ, C57BL/6J, CBA/J, DBA/1J and NZO/HILtJ mice had significantly more propensity to FSGS compared to the Tg-F1 hybrids generated from the other strains of mice. To map genes for glomerulosclerosis we performed a GWAS using 450,000 SNPs, searching for haplotype distribution patterns that matched the high/low strain susceptibility pattern. This search identified 20 discrete segments, totaling 30.7 Mb of mouse genome that have a haplotype distribution that exactly matches the strain susceptibility pattern. These include two intervals that coincide with QTL loci we had previously mapped using segregating crosses. Notably, the Chr 6 interval contains the *Ptpro* gene, encoding a podocyte protein implicated in Mendelian FSGS. Cross-annotation of these loci with the results from the human GWAS will increase our power to detect true associations and novel genes.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

This award currently provides full support for a postdoctoral scientist in my lab with the opportunity to identify and promote her skill set as part of her training experience. As part of her training she has one-on-one meetings with me on a weekly base for both scientific and career development; she has partnership and additional mentorship with bioinformaticians and statistical geneticists (Dr Ionita-Laza) to foster her training in programming and statistics; she is engaged in presenting her results to national and international meeting as well as manuscript preparation. She is now also interacting with adult (Dr Bomback) and pediatric (Dr Lin) nephrologists at CUMC, as well as with Dr Vivette D'Agati (Director of the Renal Pathology lab at CUMC) to train her also in the clinical and pathological aspects of FSGS. Dr. Ahram is also participating to annual meetings in nephrology and human genetics to foster her career advancement.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Presentations/Abstracts

1. Ahram D, Gilles C, Mitrotti A, …. Gharavi A, Hildebrandt F, Sampson MG, Sanna-Cherchi S. HLA Alleles Confer Risk to Primary Idiopathic Nephrotic Syndrome in Individuals of Caucasian Ancestry. ASN SA-PO593. American Society of Nephrology Kidney Week, 2017

2. Ahram D, Gilles C, Mitrotti A, …. Gharavi A, Hildebrandt F, Sampson MG, Sanna-Cherchi S. HLA Alleles Confer Risk to Primary Idiopathic Nephrotic Syndrome in Individuals of Caucasian Ancestry. Human Genetics in New York (Sept 12 2017)

3. Ahram D, Gilles C, Mitrotti A, …. Gharavi A, Hildebrandt F, Sampson MG, Sanna-Cherchi S. Multiethnic GWAS for Idiopathic Nephrotic Syndrome in Adults and Children. ASN PO1002-3. American Society of Nephrology Kidney Week, 2019

4. NJ. Steers NJ, Na YJ, DeMaria ND, Lam WY, D'Agati VD, Gharavi AG. Interstrain variation in severity of nephropathy and immunoglobulin levels in HIV-1 transgenic mice. ASN FR-PO1019. American Society of Nephrology Kidney Week, 2018

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Nothing to Report
This is the 3rd year report, we are currently in a no-cost extension to complete final analyses and prepare manuscripts.

4. **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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge,

theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

In the first 3 years of funding we identified several new loci and genes associated to nephrotic syndrome in human and mouse, and we are currently finalizing analyses and preparing manuscripts describing our findings. The study makes use of novel methods to find new genes involved in kidney diseases and the pathogenesis of FSGS in mammals that might have repercussions in diagnosis, clinical management, and treatment.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report

5. **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
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Nothing to Report

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to Report

Significant changes in use or care of vertebrate animals.

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to Report

6. **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**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report

Other publications, conference papers, and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

1. Ahram D, Gilles C, Mitrotti A, …. Gharavi A, Hildebrandt F, Sampson MG, Sanna-Cherchi S. HLA Alleles Confer Risk to Primary Idiopathic Nephrotic Syndrome in Individuals of Caucasian Ancestry. ASN SA-PO593. American Society of Nephrology Kidney Week, 2017

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- **Website(s) or other Internet site(s)**
List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to Report

- **Technologies or techniques**
Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

Nothing to Report

- **Inventions, patent applications, and/or licenses**

  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report

- **Other Products**

  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

  - *data or databases;*
  - *biospecimen collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

Nothing to Report

7. 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."

Example:

Name: *Mary Smith*
Project Role: *Graduate Student*
Researcher Identifier (e.g. ORCID ID): *1234567*
Nearest person month worked: *5*

Contribution to Project: *Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support: *The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name: *Simone Sanna-Cherchi*
Project Role: *Principal Investigator*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *2.4*

Contribution to Project: *Study design and conceptualization, mentoring of postdoc and technician, data dissemination.*
Funding Support: Dr. Sanna-Cherchi' s funding portfolio currently includes NIH 1R01DK103184 and 1R01DK115574

Name: *Dina Ahram*
Project Role: *Post Doc*
Researcher Identifier (e.g. ORCID ID): *N/A*
Nearest person month worked: *12.0*

Contribution to Project: *Study design and data analysis, supervision of wetlab experiments, statistical analyses, preparation of results for presentations*
Funding Support: *N/A*

Name: *Qingxue Liu*
Project Role: *Technician*
Researcher Identifier (e.g. ORCID ID): *N/A*
Nearest person month worked: *4.8*

Contribution to Project: *Wet lab experiments, DNA preparation and plating*
Funding Support: *NA*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to Report

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

- *Nothing to report*

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

Dr. Gharavi and Dr. Sanna-Cherchi will submit cognate reports.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.
N/A

9. **APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.