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TITLE: Genetic Mechanisms of Neurofibromatosis-Related Arteriopathy and Renovascular Hypertension

PRINCIPAL INVESTIGATOR: Dr. Santhi Ganesh

CONTRACTING ORGANIZATION: University of Michigan, Ann Arbor, MI

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8. PERFORMING ORGANIZATION REPORT NUMBER

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U.S. Army Medical Research and Development Command
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

: Renovascular hypertension (HTN) secondary to renal artery and abdominal aortic stenosis (arterial dysplasia, AD) is an important cause of pediatric HTN, the natural history of which, left untreated, risks heart failure, hypertensive encephalopathy, stroke and early mortality. Neurofibromatosis type 1 (NF-1) is a common cause of pediatric renovascular HTN. A third of pediatric AD patients in the University of Michigan experience carry a diagnosis of NF-1 and vasculopathy has been identified in up to 18% of individuals with NF-1 in other series. Histopathology of operative renal artery samples from these patients, including cases of NF-1, shows significant intimal hyperplasia, medial thinning and disruption of the elastic lamina. Interestingly, the histopathology and angiographic appearance of aortorenal lesions appears similar in children with developmental AD with and without a clinical NF-1 diagnosis. The specific inheritance mode and genetic basis of vascular involvement in NF-1 remains undefined. Somatic mutation as a mechanisms of arterial disease has not been previously investigated.

15. SUBJECT TERMS
Genetics, neurofibromatosis, hypertension, vascular disease, aortic coarctation

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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Unclassified	Unclassified	Unclassified	Unclassified	18	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION:

Renovascular hypertension (HTN) resulting from renal artery and abdominal aortic narrowing is due to a process known as arterial dysplasia (AD) and is an important cause of high blood pressure in children that may lead to heart failure, stroke and early death. Neurofibromatosis type 1 (NF-1) is a common cause of pediatric renovascular HTN. A third of pediatric AD patients in the University of Michigan experience carry a diagnosis of NF-1 and others have described vascular involvement in nearly 20% of individuals with NF-1. It remains unclear why some children with NF-1 develop AD. The relationship of specific gene mutation in the NF1 gene to the severity of disease has not been previously reported. The possibility of mutations in tissues that were not present in the original fertilized egg ("somatic mutations") has not been previously explored as a cause or pediatric AD. NF-1 is characterized by variable symptoms and disease presentation. The protein product of the neurofibromin gene (NF1), is involved in regulating the growth of several cell types including those that make up the arterial wall, in particular, vascular smooth muscle cells (VSMCs). Neurofibromin regulates a cell-signaling pathway (Ras-Erk) and it is speculated that vascular cells that have lost neurofibomin will develop excessive tissue on the inside of the artery resulting in narrowing. If these same vascular cells are removed from mouse models of NF-1, the cells grow more rapidly in culture than expected. Research Questions and/or Concepts: The overall goal of our proposed study is to identify the underlying causes of arterial disease in NF-1. We are conducting unbiased genetic analyses of pediatric patients with AD by examining the subset of DNA (genetic 'code') that encodes proteins (exons) across the entire human genome. Thus far, our preliminary data has confirmed damaging NF1 mutations in approximately 25% of pediatric renovascular hypertension cases. Our overall goal is to identify why only a subset of patients with NF-1 develop AD. We hypothesize that specific mutations in the fertilized egg ("germline mutations", such as those that can be inherited) and/or mutations in tissues after the egg is fertilized ("somatic mutations") may underlie developmental AD. The information we gain in the proposed studies will improve our understanding of how genetic changes influence vascular disease in NF-1 patients and may identify novel targets for treatment of AD.

2. KEYWORDS:

Genetics, neurofibromatosis, hypertension, vascular disease, aortic coarctation

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim 1: Characterize spectrum of mutations in the NF1 gene and other genes that may contribute to arterial disease in NF-1 using a whole exome sequencing approach integrated with RNASeq to identify mutations that alter proper RNA expression.

Specific Aim 2: Sequence DNA from arterial tissue, to determine whether mutations have occurred in the tissue itself, which could contribute to abnormal growth of the artery or AD. We will look in patients with known NF-1 to see if there is additional loss of genes in the arterial tissue and cells, and we will look in patients without a diagnosis of NF-1 but who may have a loss of NF-1 expression or function due to somatic mutation arising in the arterial tissue itself.

What was accomplished under these goals?

1. We have published an analysis of 13 individuals with NF-1 and PRVH (Coleman D, Wang Y et al. Human Molecular Genetics, 2021, PMID: 34476477). We validated through RNASeq analysis over-activation of the MAPK/Erk pathway that has been shown to have increased activity in a mouse model of NF-1, and protein level analysis of phosphorylate Erk in human tissues confirmed activation of this signaling pathway.
2. As part of the study of the 13 children with NF-1 and PRVH, we analyzed a genotype-phenotype correlation of DNA sequence variants in the NF1 gene. We identified a preliminary signal for enrichment of variants in a particular domain of the NF1 gene, the SEC domain, and truncating variants were associated with a more severe phenotype. As this finding has potential clinical implications, we are working towards additional replication analyses to see if the preliminary association is robust before publishing this finding.
3. We have conducted integrative analysis of RNASeq data and exome sequencing data of genomic (germline) DNA from patients with PRVH, to enhance the yield of DNA variants affecting RNA splicing. Thus far, splice variants in the NF1 gene have not been identified suggesting this is not a genetic mechanism for NF-1 associated PRVH, at least not in the samples we have studied thus far. We have identified a splice variant in the ELN (elastin) gene.
4. We have designed and tested the MIPS sequencing panel that will be used for detection of somatic DNA variants.
5. We have derived primary vascular cells from patient tissue samples for the somatic MIPS sequencing analysis and continue to accrue this sample resource from patients undergoing surgery at the University of Michigan.

Abbreviations: NF-1, Neurofibromatosis type 1; NF1, Neurofibromin gene; PRVH, pediatric renovascular hypertension; MIPS, molecular inversion probe sequencing.

Additional requested progress details:

Our team has been successful at completing the analyess of WES and RNASeq data. The major findings of these analyses are as follows:

1. Whole exome sequencing of 141 children with renovascular hypertension (RVH), including additional samples provided through external collaborations, identified through annotation of syndromic genes that are known to be associated with PRVH, 84 variants that were predicted to be deleterious by in silico analysis. Pathogenicity estimation according to clinical guidelines for variant interpretation was that 26 variants in 26 individuals were annotated as pathogenic or likely pathogenic. Truncating variants in NF1 were associated with abdominal aortic coarctation in individuals with PRVH. The variant distribution in syndrome genes is summarized in the figure below (Fig. 1), with detailed evaluation of the NF1 gene (Fig. 2)

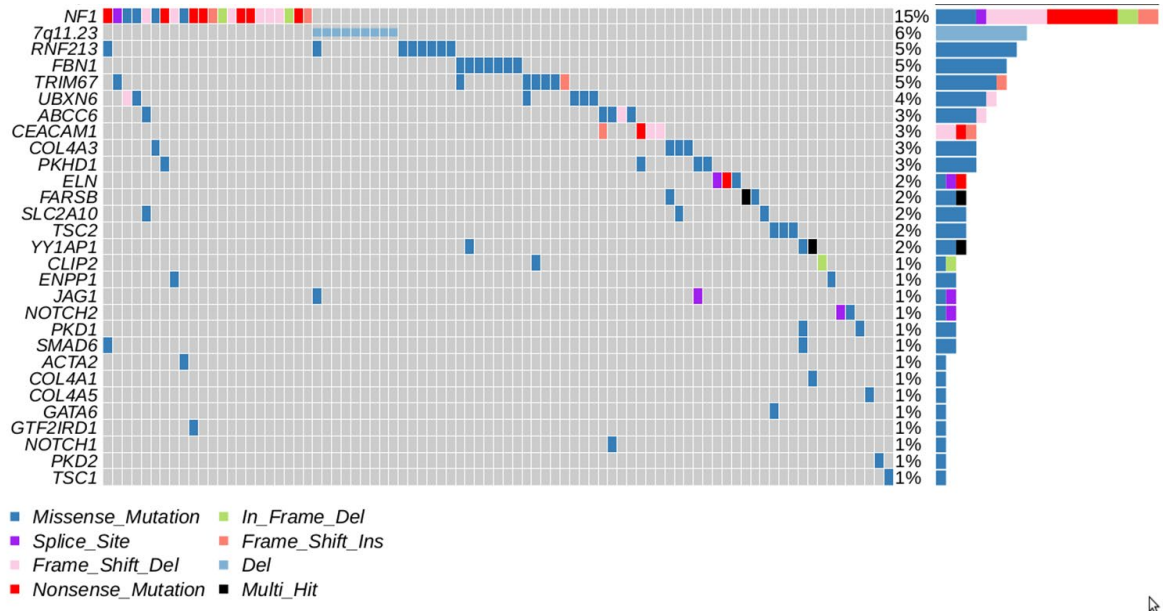

Figure 1. WES discovery of genetic variants in PRVH.

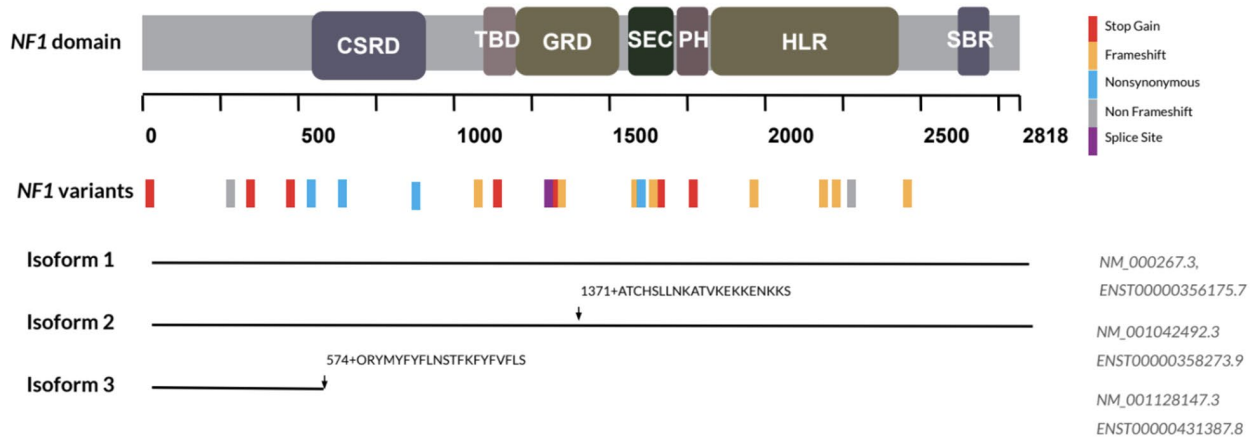

Figure 2 WES-defined variants in the *NF1* gene in PRVH.

2. Analyses of parent-child trios of 34 children with RVH identified 12 de novo variants in 10 individuals.

3. Copy number analysis exomeusing the Illumina BeadChip GWAS platform identified tTwo recurrent deletions at chromosome (7q11.23 and chromosome 11q14.1,) were identified in 9 and 2 samples, respectively. Accounting for deletion of the ELN gene within the 7q11.23 microdeletion along with single nucleot cide variations that were predicted to be deleterious in the ELN gene in the larger cohort, identified a statistically significant association of the ELN gene with RVH

4. Arterial transcriptome analyses identified MAPK signaling pathway activation in individuals harboring variants in NF1, but not in individuals with ELN gene variants or deletion. The pattern of downstream MAPK signaling pathway activation involving the Ras/Erk1 and PI3K/mTOR cellular signaling pathways varied according to genotype, which may have translational implications as these cellular signaling events are targetable by existing therapeutics. Gene ontologies of the top RNASeq findings are summarized in Fig. 3. By integrating WES and RNASeq data, we identitifed in one child a novel splice variant in the ELN (elastin) gene, that had not been identified through standard variant annotation of the WES results, adding to the discovered findings (Fig. 4).

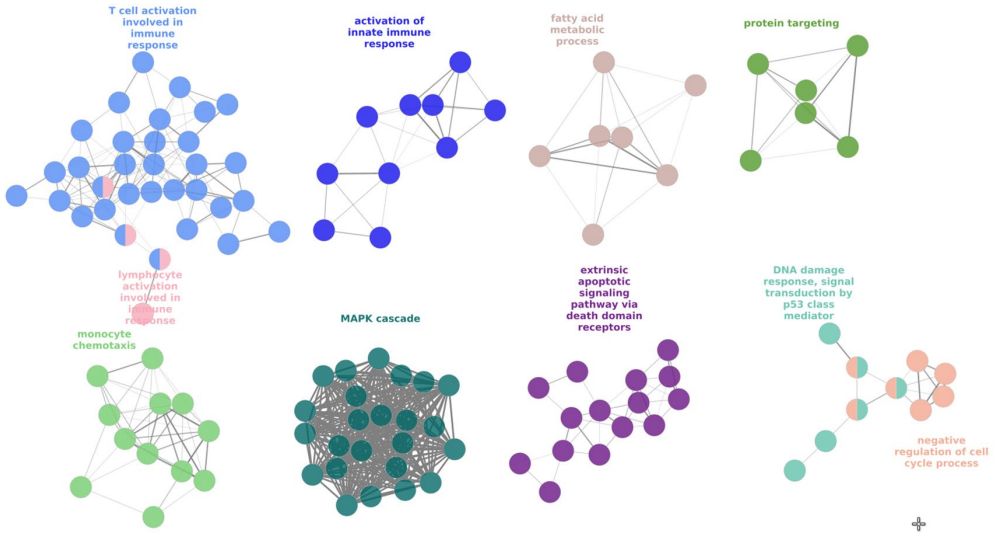

Figure 3. Clustering of gene ontologies of PRVH arterial lesion RNASeq analysis.

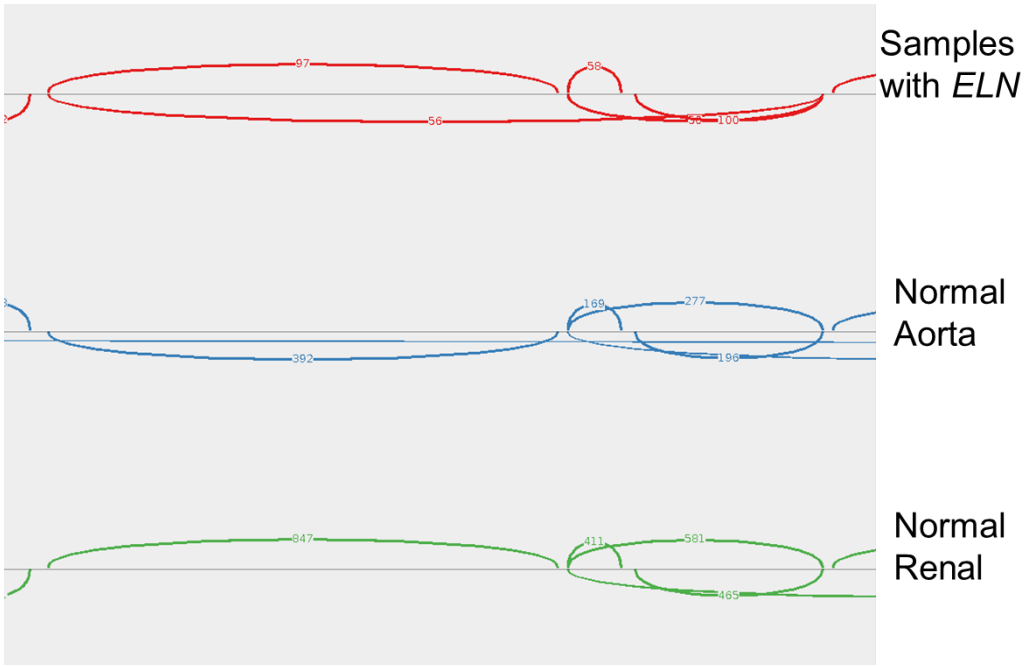

Figure 4. *ELN* gene splice variant in a child with PRVH, detected through integration of WES and RNASeq data.

What opportunities for training and professional development has the project provided?

Postdoctoral research fellow Yu Wang, PhD has conducted analyses of the sequencing data for this project, and worked with our team to design the MIPS panel that we are now validating. This has provided training relevant to somatic genetic variant detection He is learning how to handle RNASeq data and applying this new skill to study the relevant signaling pathways. He was a co-first author on the manuscript published last year (Coleman, Wang et al. Human Molecular Genetics 2021, PMID: 34476477). Yu Wang was promoted to Research Investigator status, which is a pre-tenure position, at the University of Michigan and then moved to an Industry senior staff scientist role where he continues to work on optimal sequencing methods to detect low frequency DNA events.

A graduate student, Shirley Liu, conducted the analyses to detect splice variants, and gained bioinformatics and genetics training. She completed her master's degree under the mentorship of Dr. Ganesh and started medical school at the University of Pittsburgh in 2022.

How were the results disseminated to communities of interest?

We have published a manuscript as referenced above and presented the data at national scientific conferences and institutional meetings.

What do you plan to do during the next reporting period to accomplish the goals?

With the newly designed MIPS panel that we validated, we have completed the vascular cell sequencing and currently have confirmed germline variants expected to be present in NF1 gene exons. We are now training an undergraduate student to create visual plots of putative somatic variants, which we are actively reviewing manually one-by-one. Any detected somatic variants will be validated using Sanger sequencing as an orthogonal method.

4. **IMPACT:**

What was the impact on the development of the principal discipline(s) of the project?

The published manuscript characterizes the clinical and histologic features alongside sequence variation in the NF1 gene. RNASeq analysis demonstrated not only activation of the MAPK/Erk pathway, but specific targets within this pathway that are aberrantely expressed, providing novel therapeutic targets. Importantly, there are existing drugs to target identified targets; thus these data support a rationale for future clinical trials of drug therapy targeting the abnormal, adverse vascular remodeling we observe in afflicted patients. Additionally, we have identified new candidate genes for PRVH in the whole exome sequencing data that we are evaluating, and a manuscript to report the findings is in preparation. This work has been integrated into the teams' larger framework of clinical, genetic and molecular efforts to understand PRVH. Dr. Coleman has received funding from PCORI to galvanize a clinical consortium for PRVH, and Dr. Ganesh is a co-lead of this effort. The Ganesh laboratory will be the "molecular and genetics core" for future efforts with this team, and once new discovered genes are statistically validated, we will pursue further functional experiments to define the mechanisms of vascular disease and potential interaction with NF1 to regulate cellular signaling. The identification of an early genotype-phenotype correlation of specific regions of the NF1 gene and pediatric renovascular hypertension provides an important clue for clinicians caring for NF1 patients to consider; this may assist with early detection of hypertension and prevention of some of the more severe cardiovascular complications that can occur as a result of untreated vascular disease and hypertension. These steps are being considered for the future plans of our new consortium.

What was the impact on other disciplines?

An important distinction between adult and pediatric forms of arterial dysplasia leading to renovascular hypertension is emerging from our work. Whereas the disease in adults is increasingly understood to have a complex genetic architecture in most individuals, pediatric disease is more often monogenic. We have examined the genetic influences on pediatric disease in adult fibromuscular dysplasia, and find that there is no overlap of germline variation , supporting distinct consideration of adult and pediatric forms of disease. Our findings regarding an early genotype-phenotype correlation will be potentially useful to individuals caring for patients with NF-1, once validated, especially medical genetics specialists. In a very recent update, we have identified one adult with renovascular hypertension due to fibromuscular dysplasia, with a somatic *NF1* gene variant detected in blood, consistent with mosaicism. Based upon this finding, we plan to see out additional funding through new grants to further test the hypothesis that *NF1* mosaicism may exist in a subset of adult individuals with fibromuscular dysplasia and renovascular hypertension. This new finding has the potential to be very impactful to understand renovascular hypertension across the lifespan.

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

As part of our collective work on pediatric renovascular hypertension at the University of Michigan, Dr. Dawn Coleman (Co-I for this project) has received PCORI funding to conduct patient-centered outcomes research. We now have a Virtual Research Network associated with the program, inclusive of patients, their family members, clinicians, and research investigators (PRVH PCOR Collaborative). The patients and families involved in this initiative have expressed gratitude, as well as a sense of reassurance and hope that our team is pushing forward the genetics research as supported by this award.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

The development and testing of the MIPS panel was expected to move forward more quickly than it had over the last 2-3 years, which coincided with the workspace restrictions and high employee absenteeism related to the COVID-19 pandemic. We are now on track with the MIPS experiments and have completed WES studies as proposed. We have generated RNASeq data and are currently analyzing this as well with a new analyst, Dr. Ozel, hired after postdoctoral fellow Dr. Yu Wang departed from our group.

Actual or anticipated problems or delays and actions or plans to resolve them

All work in the laboratory was on hold during the COVID-19 pandemic in and related stay-home orders at our location in 2020. In 2021, we were up to 75% occupancy of the laboratory, and began resuming work as capacity allowed. We are now at full capacity and physical presence in the laboratories, according to the guidance of state, local, and institutional authorities, and the work is proceeding as planned.

Changes that had a significant impact on expenditures

Nothing to Report

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

Nothing to report

Significant changes in use or care of human subject

Nothing to report

Significant changes in use or care of vertebrate animals

N/A

Significant changes in use of biohazards and/or select agents

N/A

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications

Coleman DM, Wang Y, Yang ML, Hunker KL, Birt I, Bergin IL, Li JZ, Stanley JC, Ganesh SK. Molecular genetic evaluation of pediatric renovascular hypertension due to renal artery stenosis and abdominal aortic coarctation in neurofibromatosis type 1. Hum Mol Genet. 2022 Feb 3;31(3):334-346. PMID: 34476477

Books or other non-periodical, one-time publications.

Nothing to report

Other publications, conference papers and presentations.

Invited presentations:

6/2022 Johns Hopkins Institute of Cardioscience Basic Seminar Series, "Genetic considerations in fibromuscular dysplasia and spontaneous coronary artery dissection," Virtual/Baltimore, Maryland, USA

5/2023 Annual Fibromuscular Dysplasia Society of America (FMDSA) Conference, 2023. Invited speaker: "Discovering genes for FMD: What we currently know, what we do not know, and how do we use genetic information in the clinic." Cleveland, Ohio, USA

9/2/2023 American Heart Association, Hypertension Scientific Sessions 2023, Renovascular Hypertension session, "Fibromuscular dysplasia"

Scientific conference abstracts:

Coleman DM, Wang Y, Hill H, Yang M, Blackburn S, Hunker K, Stanley JC, Ganesh SK: Genomic Analysis of Neurofibromatosis-Related Arteriopathies Associated with Pediatric Renovascular Hypertension, Vascular Discovery: From Genes to Medicine 2019 Scientific Sessions, Boston, MA, 2019.

Wang Y, Coleman DM, Yang ML, Blackburn S, Hunker K, Gornik H, Stanley JC, Ganesh SK: Adult and Pediatric Fibromuscular Dysplasia are Genetically Distinct Dysplasia-associated Arterial Disease, AHA Vascular Discovery meeting, Meeting held virtually due to COVID-19, 2020.

Coleman DM, Birt I, Want Y, Blackburn S, Hunker K, Stanley JC, Ganesh SK: NF1 genetic variation in pediatric artery dysplasia is associated with vascular smooth muscle cell MAPK signaling pathway activation, ATVB Vascular Discovery: From Genes to Medicine, Meeting held virtually due to COVID-19, 2020.

Liu S, Wang Y, Hunker K, Coleman DM, Ganesh SK: Identifying Splicing Genetic Variants from RNA-seq Data: A Comparative Analysis, University of Michigan - Internal Medicine Research Symposium, Meeting held virtually due to COVID-19, 2021.

- **Website(s) or other Internet site(s)**

Ganeshlab.org
Our lab website maintains a list of publications and periodically provides updates on the lab's research progress and findings.

The Ganesh lab website is linked to the above mentioned PRVH PCOR Collaborative website: https://www.prvh-pcor.org

- **Technologies or techniques**

Nothing to report

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

Nothing to report

- **Other Products**

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Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name	Project Role	Nearest Person Month Worked	Contribution to Project	Funding Support
Santhi Ganesh, MD	PI	1.2 CM	Dr. Ganesh directs all of the proposed analyses and experiments	DOD
Kristina Hunker	Lab Specialist	1.2 CM	Responsible for the cell culture experiments, sample management and confirmation qPCR and Sanger sequencing	DOD
Min-Lee Yang	GSRA	1.5 CM	Statistical analyses, bioinformatics analysis and annotation, and summarization of the statistical findings	DOD
Yu Wang	Research Fellow	3.0 CM	Rresponsible for variant calling and executing data analyses in the proposed Aims 1 and 2, with the guidance of PI Dr. Ganesh for the analyses to detect germline and somatic mutations	NIH T32 Training Grant
Jacob Kitzman, MD	Co-I	0.3 CM	Coordinates sequencing and analyze these data with PI Dr. Ganesh	DOD
Dawn Coleman, MD	Co-I	0.5 CM	Works closely with Dr. Ganesh and her laboratory group to identify and enroll subjects, phenotype cases angiographically and histologically and interpretation of the genetic analyses	DOD

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Please see attachments

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS

QUAD CHARTS

9. APPENDICES

PHS OTHER SUPPORT
For All Application Types – DO NOT SUBMIT UNLESS REQUESTED

Name of Individual: Ganesh, Santhi
Commons ID: SANTHIGANESH

Other Support – Project/Proposal

ACTIVE

Title: *Michigan Medicine Dysplasia-Associated Arterial Disease Precision Medicine Network*

Major Goals: To establish a patient resource to facilitate research and clinical care of patients afflicted with non-atherosclerotic vascular diseases, defined as arterial dysplasia.

Status of Support: Active

Project Number: N/A

Name of PD/PI: Santhi Ganesh/Dawn Coleman (MPI)

Source of Support: University of Michigan Taubman Institute

Primary Place of Performance: University of Michigan, Ann Arbor, MI

Project/Proposal Start and End Date: 03/2019-02/2024

Total Award Amount (including Indirect Costs): $2,487,230

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
5. 2024	1.20

Title: *Genetic Mechanisms of Neurofibromatosis-related Arteriopathy and Renovascular Hypertension*

Major Goals: To identify why only a subset of patients with Neurofibromatosis Type 1 develop arterial dysplasia.

Status of Support: Active

Project Number: W81XWH2010213

Name of PD/PI: Santhi Ganesh

Source of Support: DOD

Primary Place of Performance: University of Michigan, Ann Arbor, MI

Project/Proposal Start and End Date: 04/2020-03/2024 (NCTX)

Total Award Amount (including Indirect Costs): $702,000

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
4. 2023	1.20

Title: *Genomic and Functional Studies of Dysplasia-Associated Arterial Diseases*

Major Goals: To conduct human genetic and functional analyses of fibromuscular dysplasia and related arterial manifestations.

Status of Support: Active

Project Number: R35-HL161016

Name of PD/PI: Santhi Ganesh

Source of Support: NIH/NHLBI

Name of Individual: Ganesh, Santhi
Commons ID: SANTHIGANESH

Primary Place of Performance: University of Michigan, Ann Arbor, MI

Project/Proposal Start and End Date: 02/2022-01/2029

Total Award Amount (including Indirect Costs): $6,444,947

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
2. 2024	6.0
3. 2025	6.0
4. 2026	6.0
5. 2027	6.0
6. 2028	6.0
7. 2029	6.0

Title: *Canadian Spontaneous Coronary Artery Dissection (SCAD) Study*

Major Goals: The Canadian SCAD Study goal is to ascertain the natural history of predisposing arteriopathies and treatment strategy on short and long-term CV outcomes to design future randomized controlled trials.

Status of Support: Active

Project Number: F22-01172

Name of PD/PI: Jacqueline Saw

Source of Support: University of British Columbia/Heart and Stroke Foundation of Canada

Primary Place of Performance: University of Michigan, Ann Arbor, MI

Project/Proposal Start and End Date: 04/2022-12/2033

Total Award Amount (including Indirect Costs): $4,345 (U-M)

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
2. 2024	0.01
3. 2025	0.01
4. 2026	0.01
5. 2027	0.01
6. 2028	0.01
7. 2029	0.01
8. 2030	0.01
9. 2031	0.01
10. 2032	0.01
11. 2033	0.01

Title: *Pediatric Renovascular Hypertension: A pRVH PCOR Collaborative*

Major Goals: To expand existing PCOR Collaborative; to prioritize PCOR around critical early diagnostic and referral decisions; To conduct a pRVH conference in 2024 that will expand on the Collaborative's interim work.

Status of Support: Active

Project Number: N/A

Name of PD/PI: Coleman / Eliason

Source of Support: PCORI / Duke University

Primary Place of Performance: University of Michigan, Ann Arbor, MI

Name of Individual: Ganesh, Santhi
Commons ID: SANTHIGANESH

Project/Proposal Start and End Date: 01/2023-12/2024

Total Award Amount (including Indirect Costs): $36,960 (U-M)

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	0.12
2. 2024	0.12

Title: *From GWAS loci to blood pressure genes, variants & mechanisms*

Major Goals: To define genetic influences on blood pressure and conduct follow up studies to understand which organs and tissues in the human body are driving genetic effects. We will combine computational analyses, genetics, epigenomics, and functional assays in vitro to study blood pressure genetics.

Status of Support: Active

Project Number: R01

Name of PD/PI: Aravinda Chakravarti

Source of Support: NIH/New York University

Primary Place of Performance: University of Michigan, Ann Arbor, MI

Project/Proposal Start and End Date: 04/2023-03/2027

Total Award Amount (including Indirect Costs): $849,197 (U-M)

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	0.60
2. 2024	0.60
3. 2025	0.60
4. 2026	0.60
5. 2027	0.60

Title: *New Computational Tools for Advanced Analytics in Genome-wide Association Studies*

Major Goals: To develop new computational methods to advance GWAS analytics beyond simple variant association analysis and move towards the understanding of the biology of disease and enable potential clinical translations.

Status of Support: Active

Project Number: R01-HG009124

Name of PD/PI: Xiang Zhou

Source of Support: NIH

Primary Place of Performance: University of Michigan, Ann Arbor, MI

Project/Proposal Start and End Date: 01/2023-12/2027

Total Award Amount (including Indirect Costs): $1,276,804

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	1.20
2. 2024	1.20

Name of Individual: Ganesh, Santhi
Commons ID: SANTHIGANESH

Year (YYYY)	Person Months (##.##)
3. 2025	1.20
4. 2026	1.20
5. 2027	1.20

PENDING

Title: *Targeting Arterial Matricellular Defects in Fibromuscular Dysplasia*

Major Goals: To define the cellular events that may contribute to FMD and potential interventions

Status of Support: Pending

Project Number: N/A (U-M 24-PAF00315)

Name of PD/PI: Santhi Ganesh

Source of Support: Harrington Discovery Institute

Primary Place of Performance: University of Michigan, Ann Arbor, MI

Project/Proposal Start and End Date: 07/2024 – 06/2026

Total Award Amount (including Indirect Costs): $100,000

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2025	0.18
2. 2026	0.18

Title: *Defining Genetic Risk for Cardiovascular Complications of Fibromuscular Dysplasia*

Major Goals: To sequence and analyze human subjects samples and model polygenic risk using simulated and real data.

Status of Support: Pending

Project Number: N/A (U-M 23-PAF07119)

Name of PD/PI: Santhi Ganesh

Source of Support: DOD

Primary Place of Performance: University of Michigan, Ann Arbor, MI

Project/Proposal Start and End Date: 09/2024 – 09/2028

Total Award Amount (including Indirect Costs): $1,762,300

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2025	0.90
2. 2026	0.90
3. 2027	0.90
4. 2028	0.90

IN-KIND
Summary of In-Kind Contribution: None

Overlap (summarized for each individual):

Name of Individual: Ganesh, Santhi
Commons ID: SANTHIGANESH

There is no other effort, budgetary or scientific overlap at any level with any of the other projects in which I participate either as key personnel, Co-Investigator or PI, whether funded by NIH or other agencies or with institutional funds.

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

Signature: 
SignNow e-signature ID: e4db8c7e8d...
08/10/2023 17:01:32 UTC

Date: 08/10/2023