PI: **Aslibekyan, Stella**	Title: Integrative -omics study of postprandial lipoprotein phenotypes	
Received: 06/09/2016	FOA: PA16-190	Council: 01/2017
Competition ID: FORMS-D	FOA Title: MENTORED RESEARCH SCIENTIST DEVELOPMENT AWARD (PARENT K01)	
1 K01 HL136700-01	Dual:	Accession Number: 3944143
IPF: 1288803	Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM	
Former Number:	Department: Epidemiology	
IRG/SRG: MCBS (JA)	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 127,943 Year 2: 127,943 Year 3: 127,943 Year 4: 127,943	Animals: N Humans: Y Clinical Trial: N Current HS Code: E4 HESC: N	New Investigator: N Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*
Stella Aslibekyan Ph.D	University of Alabama at Birmingham	PD/PI
Hemant Tiwari Ph.D	University of Alabama at Birmingham	Other (Specify)-Primary Mentor
Donna Arnett Ph.D	University of Kentucky	Other (Specify)-Co-Mentor
W Garvey M.D.	University of Alabama at Birmingham	Other (Specify)-Co-Mentor
Goncalo Abecasis DPhil	University of Michigan	Other (Specify)-Other Significant Contributor
Braxton Mitchell Ph.D	University of Maryland School of Medicine	Other (Specify)-Other Significant Contributor
Devin Absher Ph.D	HudsonAlpha Institute for Biotechnology	Other (Specify)-Other Significant Contributor

Reference Letters

Bert Boyer	University of Alaska Fairbanks	06/09/2016
Ana Baylin	University of Michigan	06/09/2016
Jose Ordovas	Tufts University	06/09/2016

OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	**State Application Identifier**

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier

b. Agency Routing Number

c. Previous Grants.gov Tracking Number

2. DATE SUBMITTED | **Application Identifier**

5. APPLICANT INFORMATION **Organizational DUNS*:** 063690705

Legal Name*: University of Alabama at Birmingham
Department: Office of Sponsored Programs
Division:
Street1*: AB 1170
Street2: 1720 2nd Avenue South
City*: Birmngham
County: Jefferson
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 352940111

Person to be contacted on matters involving this application
Prefix: First Name*: Celesta Middle Name: Last Name*: Smith Suffix: BSHRM, MSM
Position/Title: Grants and Contracts Officer
Street1*: AB 1170
Street2: 1720 2nd Avenue South
City*: Birmingham
County: Jefferson
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 352940111
Phone Number*: 205-934-5266 Fax Number: 205-975-5977 Email: celesta@uab.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 1636005396A6

7. TYPE OF APPLICANT* H: Public/State Controlled Institution of Higher Education

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

● New ❍ Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).

❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Integrative -omics study of postprandial lipoprotein phenotypes

12. PROPOSED PROJECT
Start Date* Ending Date*
04/01/2017 03/31/2021

13. CONGRESSIONAL DISTRICTS OF APPLICANT
AL-007

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Stella Middle Name: Last Name*: Aslibekyan Suffix: Ph.D
Position/Title: Assistant Professor
Organization Name*: University of Alabama at Birmingham
Department: Epidemiology
Division: School of Public Health
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County: Jefferson
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 352940111
Phone Number*: 205-975-7675 Fax Number: 205-934-8665 Email*: saslibek@uab.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*
b. Total Non-Federal Funds* $0.00
c. Total Federal & Non-Federal Funds*
d. Estimated Program Income* $0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ❍ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:
b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR
❍ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Richard Middle Name: B Last Name*: Marchase Suffix: PhD
Position/Title*: Vice President, Research & Economic Dev
Organization Name*: University of Alabama at Birmingham
Department: Office of Sponsored Programs
Division:
Street1*: AB 1170
Street2: 1720 2nd Avenue South
City*: Birmingham
County: Jefferson
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 352940111
Phone Number*: 205-934-5266 Fax Number: 205-975-5977 Email*: osp@uab.edu

Signature of Authorized Representative*
Celesta Smith

Date Signed*
06/09/2016

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:1235-Cover Letter.pdf

424 R&R and PHS-398 Specific Table Of Contents

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	University of Alabama at Birmingham
Duns Number:	0636907050000
Street1*:	1665 University Blvd
Street2:	RPHB 230J
City*:	Birmingham
County:	Jefferson
State*:	AL: Alabama
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	352940022
Project/Performance Site Congressional District*:	AL-007

File Name

Additional Location(s)

Funding Opportunity Number: PA-16-190. Received Date: 2016-06-09T16:27:00.000-04:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ● **Yes** ❍ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ● Yes ❍ No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 ✔ 4 _ 5 _ 6

If NO, is the IRB review Pending? ❍ **Yes** ❍ **No**

IRB Approval Date:

Human Subject Assurance Number 00005960

2. Are Vertebrate Animals Used?* ❍ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ❍ Yes ❍ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ❍ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ❍ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ❍ Yes ❍ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ❍ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ❍ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	1236-Project Summary.pdf
8. Project Narrative*	1237-Project Narrative NEW.pdf
9. Bibliography & References Cited	1238-References.pdf
10.Facilities & Other Resources	1239-Facilities and Resources_Updated.pdf
11.Equipment	
12. Other Attachments	1240-List of Referees.pdf

Funding Opportunity Number: PA-16-190. Received Date: 2016-06-09T16:27:00.000-04:00

Project Summary
Disordered lipid metabolism (dyslipidemia) is a critical risk factor for cardiovascular disease. Although dyslipidemia can be reduced by dietary interventions, the changes in lipid profile that occur in response to diet are highly variable. Prior studies have identified genetic factors that contribute to interindividual variation, but due to insufficient genomic coverage, lack of integration with epigenetic data, and reliance on traditional lipid measures, they were unable to capture the full range of heritable influences or to distinguish between lipoproteins with differential impact on disease risk. This project will capitalize on the whole-genome sequencing data generated by the NHLBI TOPMed program to identify and characterize novel genetic predictors of lipoprotein response to a high-fat meal. Using nuclear magnetic resonance (NMR)-based measurements of lipoprotein subfractions taken at baseline and after a high-fat meal, this project aims to: 1) identify and validate novel predictors of postprandial lipoprotein response via whole-genome sequencing analysis of ~1800 participants of the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) and the Heredity and Phenotype (HAPI) Heart cohorts; 2) test for associations between postprandial changes in lipoprotein subfractions and those in small molecule lipids, as well as identify shared genetic determinants of these phenotypes; and 3) conduct follow-up analysis of top genetic regions implicated in lipoprotein subfraction response by bisulfite sequencing and tests for association between DNA sequence variation, DNA methylation, and gene expression. The proposed project leverages the rich multilayered –omics data available in GOLDN and HAPI Heart and emerging methods of integrated analysis, providing Dr. Aslibekyan's with crucial tools and experience to become an independent 'big data' cardiovascular scientist and a successful TOPMed investigator.

Project Narrative

Disordered metabolism of dietary fats is a well-known risk factor for cardiovascular disease. This project uses cutting-edge genomic and lipids data to identify novel genes that may be important to dietary fat metabolism, and to investigate whether biochemical modification of these genes (methylation) is correlated with changes in lipid profile following a high-fat meal. My findings could lead to a deeper understanding of how genes impact fat metabolism and may suggest new, personalized ways of preventing cardiovascular disease.

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FACILITIES AND RESOURCES

University of Alabama at Birmingham

Scientific Environment: The scientific environment at UAB has been cultivated and refined to insure the success of this and all other research projects. UAB has a proven track record in providing an efficient and effective environment to its investigators that serves to increase the probability of conducting successful research. UAB provides outstanding and excellent institutional support in the form of state-of-the-art facilities, highly qualified and trained staff, a supportive administrative infrastructure that functions to assist investigators and minimize their administrative burden. UAB's collaborative spirit provides a unique scientific environment designed to benefit the investigators as well as the science. The physical resources provided by each department are delineated below. As this is an inter-departmental study and also employs collaborative arrangements with other institutions, the intellectual rapport between the investigators in each of these units will serve to increase the likelihood of success of the study. The currently proposed study will not only benefit from the unique features of the scientific environment provided at UAB and the collaborating institutions, but also from the unique features of the REGARDS subject population and the support of the expert consultants. These combined elements provide a strong scientific environment that will contribute to the success of this research.

Early Stage Investigator: UAB has a history of providing resources to early stage investigators (ESIs) to foster their success. UAB provides internal classes and/or training as well as funds for outside training to help early stage investigator to continue their education and refine their special areas of expertise. UAB also provides funds for early stage investigators to travel to scientific meetings to present preliminary findings or to interact with other investigators to develop a support network and intellectual rapport. Collegial support from UAB is provided in the form of career enrichment programs, mentorship of ESIs by senior faculty, and availability of organized peer groups. Logistical support is provided through administrative management and oversight and best practices training. ESIs have been given financial support from UAB by providing them with protected time for research through salary support and greater administrative support during the first years of their careers.

UAB School of Public Health: Max Michael M.D. - Dean. The UAB School of Public Health is accredited by the Council on Education for Public Health (CEPH) which is an independent agency recognized by the US Department of Education to accredit schools of public health. UAB School of Public Health is comprised of about 60 faculty members complemented by over 100 part-time and volunteer faculty in Departments of Biostatistics, Environmental Health Sciences, Epidemiology, Health Behavior, and Health Care Organization and Policy. The school is second only to the School of Medicine at UAB for extramural research funding among all 12 schools at UAB. UAB has been identified by the Carnegie Foundation as one of the top twenty research institutions in the country. UAB School of Public Health has an increasingly broad and skilled faculty that provides leadership and support for several key national and international health initiatives while undertaking an array of important research projects. These projects focus on cancer and environmental epidemiology, industrial hygiene, health care organization, health services research, health behavior, biostatistical and epidemiology methods for chronic and infectious diseases, cardiovascular diseases, HIV infection, vitamin depletion, toxicology, and a variety of international health issues in numerous countries. The School supports six centers that play key roles in its mission to prevent and control disease: the Center for Community Health Resource Development, the Deep South Center for Occupational Health and Safety, and John J. Sparkman Center for International Public Health Education, the Center for Health Promotion, the Center for Health Risk Assessment and Disease Prevention, and the Lister Hill Center for Health Policy. Faculty in the Department of Health Behavior, Epidemiology and Biostatistics all actively participate in HIV research. The School of Public Health offers a Master of Public Health (M.P.H.), Master of Science (M.S.), Coordinated MD/MPH, Doctor of Public Health (Dr.P.H.), as well as Doctor of Philosophy (Ph.D.).

Department of Epidemiology: Gerald McGwin, PhD – Interim Chair. The Department of Epidemiology has a two-fold mission: First, it provides a scientific basis for disease control and health promotion through its epidemiology teaching, research, and service programs. Second, it applies public health knowledge and technology to less developed areas of the world through academic and research programs carried out both in the United States and in international settings. The Department has 24 faculty members, approximately 100 masters students, and 30 doctoral students. As degrees it offers the Master of Public Health (MPH), Master of Science in Public Health (MSPH), Master of Science in Clinical Research, Doctor of Public Health (DrPH) and the Doctor of Philosophy (PhD) degrees. The Department encompasses research and educational foci in epidemiology, the distribution and determinants of disease in humans, with particular emphasis on cancer, occupational and environmental epidemiology, cardiovascular diseases, infectious diseases, population genetics, reproductive health and chronic diseases; and in international health, a multidisciplinary approach to tropical diseases, public health nutrition, environmental hygiene, reproductive health and program management in developing countries and under-resourced areas of the United States.

Computer support: The UAB School Of Public Health (SOPH) Multimedia and Information Technology Services, MITS, is comprised of three groups, Instructional Media, Data Management, and IT support. MITS is available to all departments within the School of Public Health as a resource for teaching and support of grant based activities. Basic desktop support, classroom support, email service are funded from school sources. Software development and multimedia production are funded by the requestor, typically as part of a grant.

Research Computing:

Hardware: Departmental hardware and networks: As mentioned above, all investigators and staff at UAB's Section on Statistical Genetics (SSG) have access to desktop PCs for word processing and analysis of small to medium sized data sets. For more computationally intensive tasks, there are numerous options.

Distributed Computing Solutions:

For distributed computing and parallel programming there are a number of Beowulf-style clusters, including compute nodes/cores from four different generation totaling close to 900 compute cores, 3.9TB of RAM, and over 200TB of storage.

Generation 1 (Gen #1) : 50 nodes with a total of 100 cores based on AMD Opteron 242 processors with access to 2 GB of memory per node. Generation 1 hardware was deployed in 2005 and the nodes are connected using a Gigabit interconnect backbone.

Generation 2 (Gen #2): 24 nodes with a total of 192 cores based on Intel quad-core E5450 processors with access to 16 GB of memory per node. Generation 2 hardware was added to the existing Gen #1 in 2008 using a dual data rate Infiniband interconnect and an initial high-performance storage implementation using 60TB DDN.

Generation 3 (Gen #3): 48 nodes with a total of 576 cores based on Intel Xeno X5650 processors with access to 48 GB of memory per node. Generation 3 hardware purchased in 2010 with the NIH Shared Instrumentation Grant (SIG) funds quad data rate Infiniband, ScaleMP, and the high-perf storage build-out for capacity and redundancy with 120TB DDN.

Generation 4 (Gen #4): 3 nodes with a total of 48 cores based on Intel Xeon E5-2680 @ 2.70GHz with access to 384GB of memory per node. These so-called "fat" nodes give the Cheaha cluster the oft-requested flexibility of supporting highly memory-intensive compute jobs (in addition to the computationally-intensive jobs already well-supported by the existing hardware). Prior to this upgrade, users were limited to writing programs with memory requirements of less than 48 GB of RAM per job on the Cheaha cluster. Now, with this timely investment, users can submit jobs up to 384 GB in size and do so simultaneously with three other users.

Generation 5 (Gen #5): 12 nodes with a total of 192 cores based on Intel Xeon E2650 @ 2.00GHz.

Generation 6 (Gen #6 Latest): 40 nodes with a total of 960 cores based on Intel Xeon E2680 V3 @ 2.50GHz.

Furthermore, this UAB HPC upgrade has benefits beyond the obvious order-of-magnitude increase in big-memory capability. In particular, because these new nodes are installed as part of the Cheaha cluster and not a completely separate computer, researchers can leverage the existing investments in workflow (no change in how jobs are submitted), storage (no need to painstakingly move data back and forth between different computers), and software (no need to test new installations, researchers can continue to rely on the same well-tested, stable version of data analysis programs that they had been using on Cheaha).

These resources allow us to orchestrate the computational workflows of our research through a distributed computing approach, thereby dramatically reducing the runtime and improving the performance of the involved statistical genetics, genomics, bio-computing and bioinformatics processes.

High-end Servers:

(a) For prototyping solutions to problems requiring large amounts of memory, there is a 64-bit Dell PowerEdge R710 server running Linux and configured with two quad-core Intel Xeon E5530 processors, 144 GB of memory, and 6 TB of disk storage. This server has appreciably more memory than the average desktop computer and allows the user to assess their RAM requirements in a Linux environment. For other bigger large-memory problems that this server cannot handle, we have full access to the SGI Altix supercomputer hosted by the Alabama Supercomputer Authority (http://www.asc.edu) with 162 CPU cores, 1,340 GB of shared memory, and 15 TB in the Panasas filesystem.

(b) For our data warehousing needs, we have recently purchased and upgraded to a Dell R510 with 12 cores, 128 GB of RAM, and 24 TB of disk storage. This server will be our unified storage engine that would facilitate data integration and process orchestration tasks in our information workflow systems. The Unified Storage Engine will allow us to stage different data store standards like XML, SQL, RDF, and Free Text. This server will allow us to locally mirror important genomics data and biorepositories (like UCSC, 1000 Genomes Project, HapMap, etc.) that are non-optimal to access over the Internet. With this server, we will have the flexibility to install frameworks, facilitate data integration, deploy database engines, and rapidly prototype massively scalable web-based applications that are driven by the underlying data warehouse. As data providers, this server will act as a knowledge hotspot by offering community members access to our data center through appropriate service-oriented architectures, SPARQL Endpoints, FTP mediums and common message passing standards like SQL, XML, RDF and JSON.

All servers are physically secured, follow appropriate multilevel access control protocols, and maintain long term data security via daily and monthly archival procedures. All investigators at UAB are connected to a TCP/IP local area network within the School of Public Health Building. Desktop resources, network storage, and email systems are protected from virus attacks via antivirus software that is automatically updated on a

weekly basis or manually within minutes notice during emergencies. Desktop PCs and campus networks are behind appropriate firewalls. Desktops and their corresponding network resources follow appropriate multilevel access protocols; network data storage availability is assured via nightly and monthly archival procedures.

Software:

Investigators have access to a wide range of statistical software including Microsoft products as well as SAS, S-plus, SPSS, and R. We also maintain many more specialized software programs including some specifically for statistical genetics. For software development purposes, our group has access to compilers for Fortran, C/C++, Perl, and Java as well as Fortran and Java IMSL libraries. In addition, in 2011, UAB negotiated a campus-wide Matlab license with investigator access to over two dozen toolboxes, including the Statistics, Bioinformatics, Optimization, Symbolic Math, and Parallel Computing toolboxes. To facilitate collaborative software development, tools like Subversion (Source Code Management System), Confluence Wiki (Content Management System), and JIRA (Project Management Tool) will be employed from our intranet resource pool.

Omic Technology - Riding the NGS Wave:

Biomedical researchers have unprecedented access to public biorepositories, interoperable computing tools, and multiple technology architectures, and to use these together efficiently requires the power of the web. Orchestration of data-centric workflow computing tools (Cressexpress, Genepattern, Galaxy, Taverna) for omic technologies (Microarrays, GWAS, CNV and NGS) has revealed coordinated genetic responses at major genome landmarks like snps, cnvs, genes, and pathways. With the arrival of the life science data tsumani, there has been a shift in focus from data interpretation to data integration.

Table 1			
Property	**Exome Power**	**Cress Express**	**Power Atlas**
Web link	www.exomepower.org	www.cressexpress.org	www.poweratlas.org
Omic Technology	Next-Generation Sequencing (NGS)	Microarray	Microarray
Release Date	June 2012	May 2008	Sept 2004
Web Computing Models	Web-Applications & Web-Services	Web-Applications & Web-Services	Classic Three-Tier Web Application
Technologies Used	J2EE Framework and R (Core Engine)	J2EE Framework , JAVA, Python & R (Data Pre-processing), MySQL	J2EE, MySQL
Number of Citations	**18 Citations:** Statistical guidance for experimental design and data analysis of mutation detection in rare monogenic mendelian diseases by exome sequencing . D Zhi, R Chen - PloS one, 2012	**102 Citations** - CressExpress: A Tool For Large-Scale Mining of Expression Data from Arabidopsis. Plant Physiology July 2008 vol. 147 no. 3 1004-1016 . doi: 10.1104/pp.107.115535	**72 Citations** - Gadbury et al, Power and sample size estimation in high dimensional biology, Stat Methods Med Res August 2004 vol. 13 no. 4 325-338, doi: 10.1191/0962280204sm369ra. **68 Citations** - Page et al, The PowerAtlas: a power and sample size atlas for microarray experimental design and research, BMC Bioinformatics 2006, 7:84 doi:10.1186/1471-2105-7-84.

The Section on Statistical Genetics (SSG) has implemented and deployed computing solutions representing a broad zone of omic technologies ranging from Microarrays to GWAS to Genotyping to the latest Next-generation sequencing. **Table #1** showcases a short list of deployed web-applications authored by the computing team of SSG. A complete list of softwares, libraries and applications authored by affiliated of SSG can be accessed at http://www.soph.uab.edu/ssg/software. Much of our latest focus and energies have been expended in implementing computing pipelines, deploying frameworks and integrating systems that would make our Next Generation Sequencing initiatives operate more seamless through well established information supply chain from sequencing core labs to data analysis sandboxes and back in the hands of researchers.

Our Cheaha cluster environment provides a well-knit ecosystem for NGS activities. The 200+ TB data storage on cheaha gives the sequencing labs unprecedented access and opportunity to deposit the rawest forms of NGS data (FASTQ) without compromising on the data quality. After data deposition is complete, our team of researchers, bioinformaticians and statisticians get associated with a shared, secure data staging area on Cheaha where they can orchestrate their NGS data analysis pipelines. A broad range and multiple versions of tools, libraries and softwares are available on cheaha to conduct RNASeq, Exome Sequencing and ChipSeq data analysis efforts. In 2011, to add an layer of user-friendliness and promote research reproducibility on NGS data analysis initiatives, we deployed Galaxy, a customizable workflow management framework, on cheaha which will allow researchers to analysis their NGS data using a variety of tools right from their web-browsers and at a fewer keystrokes. With the addition of Galaxy on cheaha, SSG community has a one-stop place to connect, conduct, combine and collaborate their NGS efforts and also add a research reproducible guarantee stamp on the analyzed results. A team of dedicated computing members and omic domain experts administer the Galaxy framework and make sure the latest versions of the genomes, tools and softwares are available on Cheaha to ensure better utilization of the well tested, recommended latest releases of bioinfomatics tools and services are available to the SSG community. Galaxy deployed at UAB can be accessed at https://docs.uabgrid.uab.edu/wiki/Galaxy.

Peopleware:

Our computing team has mastered the lifecycle of software development for a broad range of computing models like scientific computing, application computing, distributed computing and systems computing. Through two major intramural grants from UAB and one grant from the National Science Foundation we have developed two of our own software packages (HDBStat! and Power Atlas) as well as compiled an extensive library of software for linkage and linkage disequilibrium based analyses. HDBStat! is a desktop application for microarray data analysis that includes methods developed by members of the SSG like the mix-o-matic and chebby checker (http://www.ssg.uab.edu/hdbstat/). The Power Atlas is a web application that provides power and sample size estimates on both existing microarray datasets and user-supplied pilot data for investigators planning microarray experiments (http://www.poweratlas.org). Another popular web-based product, CressExpress (http://www.cressexpress.org), was developed as a **turnkey** tool to study the co-expressive behavior of Arabidopsis specie genes. CressExpresses usage statistics **(Table #2)** has been impressive mainly due to the adoption of the web backbone systems like the Classic 3-Tier architecture, Service-Oriented Architecture (SOA) and the Representative Sytle Architecture (RESTful Web-services). The linkage software library consists of approximately 60+ programs from association to haplotyping to population stratification; the complete list is summarized on our web site at http://www.soph.uab.edu/ssg/linkage/lddac.

Major Equipment:

All the faculty members have access to the Alabama Supercomputer Center (http://www.asc.edu) which is located in the Alabama Supercomputer Authority's 24,000 square foot building in Huntsville, Alabama. In addition to the SGI Altix supercomputer described above, the center houses the Dense Memory Cluster

(DMC), a distributed computing cluster with 1,512 CPUs and 8,224 GB of distributed memory. Scientific workstations provide visualization and interactive graphics capabilities at the center and on the research campuses across the state. Several scientific computing frameworks, tools and software packages are installed and maintained.

In addition and if necessary, through a grant on which we collaborate with the University of Alaska (P20RR016430), we have access to supercomputers at the Arctic Region Supercomputing Center (http://www.arsc.edu/) including two Cray systems.

Currently, across the Beowulf clusters, SGI Altix supercomputer, DMC, and other HPC resources, a total of 2,818 processors are in place and available to SSG investigators.

Information and Data Security:

Along with our primary aim to promote research, we thrive on another important goal, which is to safeguard classified research contents. Although most of our aims are geared around sharing data, annotation results and opening our knowledge hotspots, during the planning and development phase of the individual aims we would like to operate and coordinate between secure sandboxes. All our digitized data from our research will be in PCs, servers, workstations, and storage areas that are safe behind firewalls. Some our information security measures offer solutions like (1) Controlling and partitioning data access to members of different working groups. (2) Assigning different access controls properties *(Public, Private and Protected)*to different target audience and working group members. (3) Implementing or using a sign-on policy system that requires members of an interest group to have authorized log-ins and accounts to access the protected knowledge. All our software codes and other computer instructions will be in a Source Code Management (SCM), which also offers controlled access of its contents to authorized users only. As the specific aims start to formulate into matured end products, we will relax the security constraints imposed on our research contents.

Department of Biostatistics

David Redden, PhD, Chair. The Department of Biostatistics is organized into two cooperating sections, Research Methods and Clinical Trials (RMCT) and the Section on Statistical Genetics (SSG). The Department has 25 faculty members and 51 staff, with research emphases in the broad areas of statistical genetics and the management of large epidemiological studies and clinical trials. Research directed by faculty in the Department of Biostatistics is supported in excess of $14 million annually, and, in addition to operating multiple Statistical Coordinating Centers, includes investigations in diverse areas such as the methodological development of techniques in statistical genetics; understanding the causes of the excess stroke mortality in the southeastern US; epidemiology and treatment of multiple sclerosis; and advancing techniques to determine the number of patients needed in randomized clinical trials using data from nested pilot studies.

Office: In addition to standard faculty/staff office space in the Departments of Biostatistics and Epidemiology the REGARDS Operations Office is approximately 1,200 square feet in the SOPH that is arranged for the high-volume operations implied for the study (i.e., 7 PC-based data verification stations, large sorting and preparation area, etc). The Survey Research Unit has allocated approximately 1,500 square feet of space (23 networked and functioning CATI stations plus supervisor space) to the REGARDS project. Approximately 1,400 square feet has been allocated for the REGARDS Outcomes Unit which retrieves processes and prepares medical records for adjudication. All offices are within easy access to each other, favoring a collaborative environment. All investigators and staff have easy access to phone, fax, copier, and campus library services.

Other: Approximately 600 square feet of off-site storage is supported for a forms and data archival location.

Office: Offices for the primary faculty and staff participating in the proposal are included in the academic space for the Departments of Epidemiology and Biostatistics on the 2nd, 3rd and 4th floors of the Ryals Building, respectively.

Other: The coordination of the laboratory, statistical and clinical trial management activities associated with the proposed study are located within the UAB School of Public Health across the departments of Epidemiology, Biostatistics, and the Computer Resource Lab. The institution has a strong track record of managing other NHLBI- funded clinical trials and epidemiologic studies such as REGARDS and SPS3 and provides adequate support. Adequate office space is available to serve as the Statistical Analysis Center including access to computers, printers, telephones, FAX machines etc.

Laboratory: Not Applicable

Clinical: Not Applicable

Animal: Not Applicable.

List of Referees

1. Jose M. Ordovas, PhD
   Senior Scientist and Director of the Nutrition and Genomics Laboratory, Chair of the Functional Genomics Core Scientific Advisory Committee, Jean Mayer USDA Human Nutrition Research Center on Aging
   Professor, Nutrition and Genetics, Gerald J. and Dorothy R. Friedman School of Nutrition Science and Policy at Tufts University

2. Ana Baylin, MD, DrPH
   Associate Professor of Epidemiology and Nutritional Sciences
   University of Michigan School of Public Health

3. Bert B. Boyer, PhD
   Professor of Biochemistry and Molecular Biology
   Associate Director of Human Health—Institute of Arctic Biology
   Director, Center for Alaska Native Health Research
   University of Alaska at Fairbanks

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

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Project Role*: PD/PI Other Project Role Category:

Degree Type: PhD Degree Year: 2011

	File Name
Attach Biographical Sketch*:	1254-Aslibekyan_K01 biosketch.pdf
Attach Current & Pending Support:	

Tracking Number: GRANT12188650 Funding Opportunity Number: PA-16-190 . Received Date: 2016-06-09T16:27:00.000-04:00

PROFILE - Senior/Key Person

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Degree Type: PhD Degree Year: 1986

	File Name
Attach Biographical Sketch*:	1255-Tiwari_Biosketch_for_Stella_5_31_16.pdf
Attach Current & Pending Support:	1256-Tiwari_Other_Support_05_16_2016.pdf

PROFILE - Senior/Key Person

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Degree Type: PhD Degree Year: 1992

	File Name
Attach Biographical Sketch*:	1257-DKA Biosketch.pdf
Attach Current & Pending Support:	1258-Other_Support_Arnett.pdf

PROFILE - Senior/Key Person

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Project Role*: Other (Specify) Other Project Role Category: Co-Mentor

Degree Type: MD Degree Year: 1981

	File Name
Attach Biographical Sketch*:	1259-Garvey Biosketch 5.20.2016.pdf
Attach Current & Pending Support:	1260-Garvey ORS 5.10.2016 REVISED.pdf

PROFILE - Senior/Key Person

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Degree Type: DPhil Degree Year: 2001

	File Name
Attach Biographical Sketch*:	1261-Biosketch_Abecasis 0316.pdf
Attach Current & Pending Support:	

PROFILE - Senior/Key Person

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Project Role*: Other (Specify) Other Project Role Category: Other Significant Contributor

Degree Type: PhD Degree Year: 1987

	File Name
Attach Biographical Sketch*:	1262-Mitchell_Bio_VerD_May 2016.pdf
Attach Current & Pending Support:	

PROFILE - Senior/Key Person

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Project Role*: Other (Specify) Other Project Role Category: Other Significant Contributor

Degree Type: PhD Degree Year: 2000

	File Name
Attach Biographical Sketch*:	1263-Stella_Biosketch_Absher_20160525_AES.pdf
Attach Current & Pending Support:	

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Aslibekyan, Stella

eRA COMMONS USER NAME (credential, e.g., agency login): saslibek

POSITION TITLE: Assistant Professor of Epidemiology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Stanford University, Stanford, CA	B.A. (Honors)	06/05	Human Biology
Harvard School of Public Health, Boston, MA	S.M.	06/08	Epidemiology
Brown University, Providence, RI	Ph.D	05/11	Epidemiology
University of Alabama at Birmingham	Postdoctoral	02/13	Genetic Epidemiology

A. Personal Statement

I am a genetic epidemiologist with a long-held interest in cardiometabolic traits. The goal of this Mentored Career Development Award application is to build my skill set in statistical genetics, specifically in whole genome sequence and integrative –omics methods, and foster my research independence in this rapidly evolving field. My background to date includes solid training in epidemiologic methods and experience with candidate gene and low-resolution genome-wide association studies. Inspired by the advent of readily available high-dimensional data on population cohorts, I propose a significant methodologic shift for my career, focusing on cutting-edge analytic approaches that synthesize evidence across multiple genotypic and phenotypic layers. This K award will allow me to facilitate discovery of novel genetic and epigenetic variants implicated in lipid metabolism, and to position myself as an independent research scientist poised to harness the promise of 'big data' to inform personalized medical efforts.

a. Aslibekyan S, Demerath EW, Mendelson M, Zhi D, Guan W, Liang L, Sha J, Pankow JS, Liu C, Irvin MR, Fornage M, Hidalgo B, Lin LA, Thibeault KS, Bressler J, Tsai MY, Grove ML, Hopkins PN, Boerwinkle E, Borecki IB, Ordovas JM, Levy D, Tiwari HK, Absher DM, Arnett DK. Epigenome-wide study identifies novel methylation loci associated with body mass index and waist circumference. Obesity 2015;23(7):1493-1501. PMCID: PMC4482015
b. Aslibekyan S, Vaughan LK, Wiener HW, Lemas DJ, Klimentidis YC, Havel PJ, Stanhope KL, O'Brien DM, Hopkins SE, Boyer BB, Tiwari HK. Evidence for novel genetic loci associated with metabolic traits in Yup'ik people. Am J Hum Biol 2013; 25(5):673-680. PMCID: PMC3785243
c. Aslibekyan S, Goodarzi MO, Frazier-Wood AC, Yan X, Irvin MR, Kim E, Tiwari HK, Guo X, Straka RJ, Taylor KD, Tsai MY, Hopkins PN, Korenman SG, Borecki IB, Chen YD, Ordovas JM, Rotter JI, Arnett DK. Variants identified in a GWAS meta-analysis for blood lipids are associated with the lipid response to fenofibrate. PLoS One 2012;7(10):e48663. PMCID: PMC3485381
d. Aslibekyan S, Irvin MR, Hidalgo B, Perry R, Jeyarajah E, Garcia E, Shalaurova I, Hopkins P, Province M, Tiwari HK, Ordovas JM, Absher DM, Arnett DK. Genome- and epigenome-wide study of circulating trimethylamine-N-oxide. Eur J Clin Nutr, under review.

B. Positions and Honors

Positions and Employment

2013- Assistant Professor, Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL
2011-2013 Postdoctoral Fellow, Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL

Other Experience and Professional Memberships

2014- Member, International Genetic Epidemiology Society
2008- Member, Human Biology Association
2007- Member, Society of Epidemiologic Research
2006- Member and Ad Hoc Peer Reviewer, American Heart Association

Selected Honors

2014 Finalist for the Young Investigator Award, American Heart Association
2013 Best Paper in Nutrition or Obesity Award, Science Unbound Foundation
2010 Reginald D. Archambault Award for Teaching Excellence, Brown University
2008 Sidney E. Frank Graduate Fellowship, Brown University
2005 Departmental Honors, Stanford University

C. Contributions to Science

1. I have an extensive record of publications documenting the association between genetic or epigenetic variation and complex traits. I have conducted several low-resolution genome- and epigenome-wide studies of validated disease markers such as body mass index, inflammatory cytokines, and lipid phenotypes. Moreover, I have discovered novel pharmacogenetic variants associated with response to lipid-lowering interventions (fenofibrate therapy). Many of my findings have been successfully validated in independent populations and represent potential diagnostic and therapeutic targets.
   a. Aslibekyan S, Kabagambe EK, Irvin MR, Straka RJ, Borecki IB, Tiwari HK, Tsai MY, Hopkins PN, Ordovas JM, Arnett DK. A genome-wide association study of inflammatory marker changes in response to fenofibrate treatment in Genetics of Lipid Lowering and Diet Network. Pharmacogenet Genomics 2012;22(3):191-197. PMCID: PMC3275691
   b. Frazier-Wood AC, Aslibekyan S, Absher DM, Hopkins PN, Sha J, Tsai MY, Tiwari HK, Waite L, Zhi D, Arnett DK. Methylation at CPT1A locus is associated with lipoprotein subfraction profiles. J Lipid Res 2014;55(7):1324-1330. PMCID: PMC4076093
   c. Irvin MR, Zhi D, Aslibekyan S, Claas SA, Absher DM, Ordovas JM, Tiwari HK, Watkins SM, Arnett DK. Genomics of post-prandial lipidomic phenotypes in the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study. PLoS ONE 2014;9(6):e99509. PMCID: PMC4048279
   d. Aslibekyan S, Irvin MR, Hidalgo B, Perry R, Jeyarajah E, Garcia E, Shalaurova I, Hopkins P, Province M, Tiwari HK, Ordovas JM, Absher DM, Arnett DK. Genome- and epigenome-wide study of circulating trimethylamine-N-oxide. Eur J Clin Nutr, under review.

2. In addition to contributions in genetic epidemiology of cardiometabolic traits, I have made methodological advances in DNA sequence analysis. Using cutting-edge Bayesian approaches, we have established that rare and very rare variants explain a higher percentage of the variance in blood pressure than common variants, and that the number of contributing rare alleles plays an important role in the genetic architecture of chronic disease traits. My other methodological contributions lay in the area of pathway analysis, a promising technique for modeling complex traits that is currently facing several challenges to the validity and interpretation of findings, and in exploring overlap between genomic and epigenomic data via methylation quantitative trait loci (meQTL) analysis.
   a. Aslibekyan S, Almeida M, Tintle N. Pathway analysis approaches for rare and common variants: insights from genetic analysis workshop 18. Genet Epidemiol 2014;38 Suppl 1:S86-91. PMCID: PMC4221731
   b. Aslibekyan S, Wiener HW, Wu G, Zhi D, Shrestha S, de los Campos G, Vazquez AI. Estimating proportions of explained variance: a comparison of whole genome subsets. BMC Proc 2014;8 Suppl 1 Genetic Analysis Workshop 18:S102. PMCID: PMC4143698

c. Zhi D, Aslibekyan S, Irvin MR, Claas SA, Borecki IB, Ordovas JM, Absher DM, Arnett DK. CpG-changing SNPs modulate genome-epigenome interaction. Epigenetics 2013;8(8):802-806. PMCID: PMC3883783

3. Finally, throughout my career I have investigated relationships between nutrition (particularly fatty acid intake), genomics, and epigenomics in diverse populations. Specifically, I led the first comprehensive study of epigenomic patterns and omega-3 fatty acid intake in an Alaska Native population, establishing distinct methylation signatures for this dietary exposure. Furthermore, using data from a large case-control study of myocardial infarction conducted in Costa Rica, I have investigated interactions between diet and variants in genes that encode enzymes in the fatty acid biosynthesis pathway.

a. Aslibekyan S, Wiener HW, Havel PJ, Stanhope KL, O'Brien DM, Hopkins SE, Absher DM, Tiwari HK, Boyer BB. DNA methylation patterns are associated with n-3 fatty acid intake in Yup'ik people. J Nutr 2014;144(4):425-430. PMCID: PMC3952620

b. Aslibekyan S, Jensen MK, Campos H, Loucks EB, Linkletter CD, Ordovas JM, Deka R, Rimm EB, Baylin A. Fatty acid elongase gene variants are not associated with serum blood lipids, inflammation, or the risk of nonfatal myocardial infarction. Eur J Clin Nutr 2012;66(3):353-359. PMCID: PMC3806713

c. Aslibekyan S, Jensen MK, Campos H, Loucks EB, Linkletter CD, Ordovas JM, Deka R, Rimm EB, Baylin A. Fatty acid desaturase polymorphisms and the risk of nonfatal myocardial infarction in the Costa Rica Study. Front Genet 2012;3:72. PMCID: PMC3342508

Complete List of Published Work: http://www.ncbi.nlm.nih.gov/pubmed/?term=aslibekyan

D. Research Support

Ongoing Research Support

P60 AR064172 Redden (PI) 09/16/13 – 07/31/18
UAB Multidisciplinary Clinical Research Center Methodology Core
This program provides methodological support for projects aimed at understanding the role of genetic variation in the etiology and response to treatment in autoimmune disease.
Role: Co-Investigator

R01 HL55673 Arnett (PI) 08/10/96 – 04/30/17
HyperGEN: Genetics of Left Ventricular Hypertrophy
This project extends the genetic analysis of previously collected hypertension pedigrees with echocardiographic measures. We are conducting a genome-wide association study to identify genomic regions contributing to variation in cardiac size and structure.
Role: Co-Investigator

American Heart Association CVGPS Pathway Arnett (PI) 02/01/15 – 01/31/17
Epigenetic Determinants of Left Ventricular and Function in Hypertensive African-Americans
Left ventricular hypertrophy (a thickening of heart walls that can reduce the heart's ability to pump effectively) is common in African Americans, and it contributes more to the risk of cardiovascular death in African Americans than it does in other race groups. This project is designed to determine which non-coding genetic factors (that is, epigenetic factors) may play a role in the development of left ventricular hypertrophy in African Americans.
Role: Co-Investigator

Completed Research Support

American Heart Association 14CRP18060003 Aslibekyan (PI) 01/01/14 – 12/31/15
Genetic and Epigenetic Determinants of Trimethylamine-N-oxide
This project investigated the role of genetic and epigenetic variation in determining the levels of trimethylamine-N-oxide (TMAO), an emerging disease risk factor, as well as associations between TMAO and intermediate chronic disease phenotypes such as blood lipids and inflammatory markers.

Role: PI

R01 HL104135 Arnett (PI) 08/15/10 – 05/31/16
Epigenetic Determinants of Lipids Response to Dietary Fat and Fenofibrate
This project aims to identify epigenetic loci that determine gene-environment interactions that predict lipid response to two interventions, one to raise triglycerides (intake of a high-fat meal), and one to lower triglycerides (treatment with fenofibrate).
Role: Co-Investigator

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Tiwari, Hemant K.

eRA COMMONS USER NAME (credential, e.g., agency login): htiwari

POSITION TITLE: Professor and Head of the Section on Statistical Genetics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Kanpur, Kanpur, UP, India	B.Sc.	08/76	Math, Physics, Statistics
Indian Institute of Technology, Kanpur, UP, India	M.Sc.	08/78	Mathematics
University of Notre Dame, Indiana	M.S.	12/83	Mathematics
University of Notre Dame, Indiana	Ph.D.	08/86	Mathematics
LSU Medical Center, New Orleans, Louisiana	Post-Doc	05/93-06/95	Statistical Genetics
Case Western Reserve University, Cleveland, Ohio	Post-Doc	06/96	Statistical Genetics

A. Personal Statement

Dr. Tiwari has extensive experience in both developing statistical methods and their application to biomedical research. He has unique expertise in quantitative and applied research having PhD in mathematics, teaching and doing research in theoretical statistics, and collaborations with biomedical community. In particular, his research interests include Genetic Linkage Analysis, Disequilibrium Mapping, Genome-Wide Association Studies, Structural variations, Epigenetics, Pharmacogenetics/Pharmacogenomics, Gene expression, Exome sequencing, Pathway and network analysis, Bioinformatics, Metabolomics, and Population Genetics. He was lead statistician from UAB to perform data analyses in a Genome-wide Association to conduct a multi-stage GWAS in HyperGEN: Genetics of Left Ventricular Hypertrophy study and is currently investigator in recently renewed HyperGEN grant to perform 1200 exome sequences (R01HL055673 (PI: Arnett)). He was also lead statistical investigator in a recently completed *Genome-Wide Association Study in African-Americans with Rheumatoid Arthritis* (PI: Bridges). Currently, he is an investigator in an epigenetics study: Epigenetic Determinants of Lipid Response to Fenofibrate and Dietary Fat R01HL091357 (PI: Arnett)). Dr. Tiwari possesses deep expertise in statistical genetics software programs, bioinformatics, and developing new methods for genomics data. In addition, he is interested in developing methods for next gen sequencing technology including Structural variations, Exome sequencing, genome-wide methylation, microbiome, metabolome, and transcriptome data types and integration of different data domains. In addition, he is a PI of funded educational programs, R25, to deliver national short courses in statistical genetics/genomics (R25 GM093044 (Tiwari)) and short courses on Next-Generation Sequencing Technology and Statistical Methods (R25HG006110 (Tiwari)) and co-PI on "UAB Metabolomics Workshop: From Design To Decision" (PI: Barnes; R25GM103798). Drs. Tiwari and Aslibekyan have long standing collaborations in several funded grants. Drs. Aslibekyan and Tiwari have been co-investigators in funded R01 on “Epigenetic Determinants of Lipid Response to Fenofibrate and Dietary Fat” (R01HL091357, PI: Arnett). With his experience in research in GWAS, WGS, harmonization of different data sets and track record of mentoring and collaborating with Dr. Aslibekyan, he is well qualified and highly enthusiastic to be a primary mentor for Dr. Aslibekyan **"An Integrative -Omics Study of Postprandial Lipoprotein Phenotypes"**.

B. Positions and Honors

Positions and Employment

1986 - 1988	Visiting Assistant Professor of Mathematics, University of Notre Dame, Indiana
1988 - 1990	Visiting Assistant Professor of mathematics, Loyola University of Chicago, Chicago, Illinois
1990 - 1993	Asst. Prof. of Mathematics and Computer Science, University of Maine, Fort Kent, Maine
1993 - 1995	Post-Doc, LSU Medical Center, New Orleans, LA
1995 - 1996	Post-doc, Case Western Reserve University, Cleveland, OH
1996 - 1999	Senior Instructor, Department of Epi and Biostatistics, CWRU, Cleveland, Ohio
1999 - 2001	Asst. Prof., Department of Epi and Biostatistics, CWRU, Cleveland, Ohio
2002 - 2006	Assistant Professor, Section on Statistical Genetics, Department Biostatistics, & Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama
2006 - 2011	Associate Professor, Section on Statistical Genetics, Department Biostatistics, University of Alabama at Birmingham, Birmingham, Alabama
2010 -	William “Student: Sealy Gosset Professor in Biostatistics in the School of Public Health, University of Alabama at Birmingham, Birmingham, Alabama
2011- 2015	Professor and Head of Section on Statistical Genetics, UAB

Other Experience

2002 – 2006	Charter Member of NAME Study Section (formally known as ECDA), CSR,NIH
2010 – 2013	Member of CIDR Study Section NIH/NHGRI

Honors

1993-1995	NIH Postdoctoral Fellowship, Louisiana State University Medical School
1995	NIH Postdoctoral fellowship, Case Western Reserve University
2010	Graduate Dean’s Excellence in Mentoring Award, School of Public Health, UAB

C. Contribution to Science

I have published more than 100 peer-reviewed papers including methodological work, collaborative work, and review work. A complete listing can be found in my bibliography at: http://www.ncbi.nlm.nih.gov/sites/myncbi/1bq3yXt-b-tAd/bibliography/47568868/public/?sort=date&direction=ascending.

Statistical Genetics Methods Development. Since 1995, I have had privilege to work on most challenging problems in statistical genetics. For example, in 1998, I developed a new simple method to derive the theoretical expectations of variance components in multilocus epistatic models. Using simple matrix algebra and calculus, I derived a formulation of any n-dimensional multilocus variance components using only n-1 variance components recursively. The purpose of this paper was to give a simple general formulation to derive the additive, dominant, and epistatic effects, and hence the corresponding variance components, for any multilocus model. This manuscript was published in Theoretical Population Biology, a premier journal of mathematical population biology. This formulation also helped in developing GxG interaction extension to Haseman-Elston’s seminal paper for non-parametric linkage analysis. I also developed new joint covariance- and marginal-based tests of association and linkage for quantitative traits for random and non-random-sampling. These joint tests of linkage and association utilized information in both the covariance (and more generally, dependency) between genotype and phenotype and the marginal distribution of genotype and are powerful tests for linkage and association. Calculating power is an essential part of any genetic study to determine whether any meaningful results will be obtained with a given sample size and other parameters. There are many tools available to calculate power. However, some situations may require study-specific simulations using given parameters such as sample size, mode of inheritance, allele frequency of the disease and marker, etc. The simulations could be computationally extensive as well as time consuming and could take several weeks to months depending on the nature of the study. We developed a simple method to rapidly estimate power based on asymptotic theory using other available studies similar to the study of interest to the investigator. Recently, we published on multivariate data analysis with his student (Yan *et al*., 2015). Currently, I have been developing new optimal association test for methylation data correcting for cell purity with a trainee

and have developed an optimal method of association in gene mapping for the count data as outcome, specifically when the count data follows zero-inflated negative binomial distribution (in press).

- **Tiwari HK**, Holt J, George V, Beasley TM, Amos CI, Allison DB (2005): New Joint Covariance- and Marginal-based Tests for Association & Linkage for Quantitative Traits for random and non-random sampling. Genet Epidemiol 28(1): 48-57. PMID: 15558568
- **Tiwari HK**, Birkner T, Moondan A, Zhang S, Page GP, Patki A, Allison DB (2011). Accurate and Flexible Power: Calculations on the Spot: Applications to Genomic Research. *Statistics and Its Interface*. Volume 4 (2011) 353-358. PMCID: PMC3196559.
- Yan Q, Weeks DE, Celedón JC, **Tiwari HK**, Li B, Wang X, Lin WY, Lou XY, Gao G, Chen W, Liu N. Associating Multivariate Quantitative Phenotypes with Genetic Variants in Family Samples with a Novel Kernel Machine Regression Method. Genetics. 2015 Dec;201(4):1329-39. doi: 10.1534/genetics.115.178590. Epub 2015 Oct 19. PubMed PMID: 26482791; PubMed Central PMCID: PMC4676518.
- Waite LL, Weaver B, Day K, Li X, Roberts K, Gibson AW, Edberg JC, Kimberly RP, Absher DM, **Tiwari HK**. Estimation of Cell-Type Composition Including T and B Cell Subtypes for Whole Blood Methylation Microarray Data. *Front Genet*. 2016 Feb 18;7:23. doi: 10.3389/fgene.2016.00023. eCollection 2016. PMID: 26925097; PMCID: 4757643

Population Genetics. I published very first paper on population genetics to start my career in statistical genetics. I have taught courses in population genetics, bioinformatics, and molecular evolution. He had developed a course in population genetics pertaining to gene discovery in diseases or traits while at Case Western Reserve University. Here are few examples of publications using population genetics methodology.

- Knight A, Batzer MA, Stoneking M, **Tiwari HK**, Scheer WD, Herrera RJ, Deininger PL (1996): DNA Sequences of Alu Elements Indicate a Recent, Single Origin for Modern Humans. *Proc Nat Acad Sci* USA 93:4360-4364. PMCID: PMC39542
- Makowsky R, Yan Q, Wiener HW, Sandel M, Aissani B, **Tiwari HK**, Shrestha S. The utility of mitochondrial and Y chromosome phylogenetic data to improve correction for population stratification. Front Genet. 2012;3:301. doi: 10.3389/fgene.2012.00301. Epub 2012 Dec 21. PMCID: PMC3527715
- Vaughan LK, Divers J, Padilla M, Redden DT, **Tiwari HK**, Pomp D, Allison DB. The use of plasmodes as a supplement to simulations: A simple example evaluating individual admixture estimation methodologies. Computational Statistics and Data Analysis. 2009. 53(5):1755-1766. PMCID: PMC2678733
- Hill AE, Plyler ZE, **Tiwari H**, Patki A, Tully JP, McAtee CW, Moseley LA, Sorscher EJ. Longevity and plasticity of CFTR provide an argument for noncanonical SNP organization in hominid DNA. PLoS One. 2014 Oct 28;9(10):e109186. doi: 10.1371/journal.pone.0109186. eCollection 2014. PMCID: PMC4211684

Collaborative Research. I have had extensive record of productive collaborations in searching for genes for obesity, cardiovascular diseases, Rheumatoid Arthritis, SLE, Stroke, and Multiple Sclerosis, to name few. I have served as a lead statistical geneticist in several collaborative projects. My role has been as collaborative scientist to design the study and if funded use most optimal method of analysis. I always test a method through simulations for validity and power before using it for the analysis. Some of the long collaborations have been very productive and have resulted in several papers. Below are few examples of my collaborative publications with Dr. Aslibekyan.

- Aslibekyan S, An P, Frazier-Wood AC, Kabagambe EK, Irvin MR, Straka RJ, **Tiwari HK**, Tsai MY, Hopkins PN, Borecki IB, Ordovas JM, Arnett DK. Preliminary evidence of genetic determinants of adiponectin response to fenofibrate in the Genetics of Lipid Lowering Drugs and Diet Network. Nutr Metab Cardiovasc Dis. 2013 Oct;23(10):987-94. doi: 10.1016/j.numecd.2012.07.010. Epub 2012 Nov 11. PubMed PMID: 23149075; PubMed Central PMCID: PMC3578131.
- Aslibekyan S, Vaughan LK, Wiener HW, Lemas DJ, Klimentidis YC, Havel PJ, Stanhope KL, O'brien DM, Hopkins SE, Boyer BB, **Tiwari HK**. Evidence for novel genetic loci associated with metabolic traits in Yup'ik people. Am J Hum Biol. 2013 Sep-Oct;25(5):673-80. doi:

10.1002/ajhb.22429. Epub 2013 Aug 1. PubMed PMID: 23907821; PubMed Central PMCID: PMC3785243.

- Aslibekyan S, Wiener HW, Havel PJ, Stanhope KL, O'Brien DM, Hopkins SE, Absher DM, **Tiwari HK**, Boyer BB. DNA methylation patterns are associated with n-3 fatty acid intake in Yup'ik people. J Nutr. 2014 Apr;144(4):425-30. doi: 10.3945/jn.113.187203. Epub 2014 Jan 29. PubMed PMID: 24477300; PubMed Central PMCID: PMC3952620.
- Aslibekyan S, Demerath EW, Mendelson M, Zhi D, Guan W, Liang L, Sha J, Pankow JS, Liu C, Irvin MR, Fornage M, Hidalgo B, Lin LA, Thibeault KS, Bressler J, Tsai MY, Grove ML, Hopkins PN, Boerwinkle E, Borecki IB, Ordovas JM, Levy D, **Tiwari HK**, Absher DM, Arnett DK. Epigenome-wide study identifies novel methylation loci associated with body mass index and waist circumference. Obesity (Silver Spring). 2015 Jul;23(7):1493-501. doi: 10.1002/oby.21111. PubMed PMID: 26110892; PubMed Central PMCID: PMC4482015.

Reviews of current topics. Reviews are most time consuming manuscripts to write, but they provide all the information in one place and are great service to scientific community. Of course, they require vast knowledge of the topic in question and an author's ability to summarize the large body of work by others in succinct form. Thus, reviews are also very important as methodological work. Here we provide two examples of reviews, one I as a first author and other with my student as a first author.

After publication of a seminal manuscript by Spielman *et al.* (1995) on Transmission Disequilibrium Tests (TDT) for linkage in the presence of association, there have been ~225 published extensions and variations of the original TDT. In this review article, we summarized this large body of work based mainly on four categories: (1) relaxing the requirement of only two alleles at the marker locus; (2) relaxing the requirement of the trait to be dichotomous; (3) relaxing the requirement of a parent/offspring trio design and (4) extension to using genotype information from the X-chromosome (X-linked TDT). Other extensions to the TDT included multiple loci, Bayesian TDT, multiple phenotypes, parent of origin/imprinting effects, inbreeding, TDT for haplotypes, censored data, simultaneous and separately modeling of the linkage and association parameters, and other variations to increase power; we chose to focus this review mostly on the four main categories with some discussion of the other extensions.

- **Tiwari HK**, Barnholtz-Sloan J, Wineinger N, Padilla MA, Vaughan LK, Allison DB. Review and evaluation of methods correcting for population stratification with a focus on underlying statistical principles. *Hum Hered*. 2009; 66(2):67-86. PMCID: PMC2803696

As with any genetic association analysis, the goal of a CNV association analysis is to find structural genetic variants that affect the disease phenotype of interest. While the technology exists for CNV genotyping, a further understanding and discussion of how to use the CNV data for association analyses was warranted. In this invited review with my past PhD student as a first author, we presented the options available for processing and analyzing CNV data. We partitioned the manuscript into choice of genotyping platform, normalization of the array data, calling algorithm, and statistical analysis.

- Wineinger N, Kennedy R, Erickson S, Wojcynski M, Bruder C, **Tiwari HK** (2008): Statistical Issues in the Analysis of DNA Copy Number Variations Data. *Int J Computational Biology and Drug Design* 1(4): 368-395. PMCID: PMC2747762

D. Research Support

Ongoing Research Support

NIH R25 GM093044 (Tiwari) 08/01/10 – 07/31/15
NIH/NIGMS
Short Course on Statistical Genetics and Genomics
To offer an annual statistical genetics short course to be focused on applying advanced quantitative approaches to the search for genes that predispose complex human disorders and quantitative traits.
Role: Principal investigator

NIH R25HG006110 (Tiwari) 04/01/11 – 03/31/17
NIH/NHGRI
Short Course on Next-Generation Sequencing Technology and Statistical Methods
To offer an annual short course focused on technological and statistical approaches pertaining to next-generation sequencing applied to complex human disorders and quantitative traits.

Role: Principal investigator

NIH R25GM103798 (Barnes) 09/18/12 – 08/31/17
NIH/NIGMS
UAB Metabolomics workshop: From decision to design
To offer an annual 4 day metabolomics workshop to prepare investigators to advance the use of metabolomics in translational research and to direct highly interdisciplinary teams or collaborations in metabolomic studies.
Role: Co-Principal investigator

NIH 2R01HL055673-15A1 (Arnett) 08/10/96 – 04/30/17
NIH/NHLBI
HyperGEN: Genetics of left ventricular hypertrophy
Conduct Whole exome sequence (WES) 1,200 AA unrelated hypertensives with extreme values for echocardiographic LV mass/hgt2.7 to identify rare and low-frequency variants contributing to LV mass and related structural and functional phenotypes.
Role: Co-Investigator

R01HL104135 (Arnett) 08/15/10-05/31/16
NIH/NHLBI
Epigenetic Determinants of Lipid Response to Dietary Fat and Fenofibrate
This study aims to discover the epigenetic factors that cause people's bodies to respond so differently to diet and drugs with the belief that such knowledge could ultimately help lower people's risk for cardiovascular disease.
Role: Co-investigator

NIH R01 (Brown) 07/01/14 – 06/30/19
NIH/NIAMS
Association of genetic and autoantibody signatures with SLE clinical course
The purpose of this study is to characterize complex interactions between variation in DNA sequence and autoantibody profiles with the rate of progression and severity of lupus-associated nephritis and severe organ damage, which are more common among ethnic minorities. The knowledge gained from this study may help us to lower the risk of lupus-related clinical manifestations and to manage and treat it more effectively.

Role: Co-Investigator

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

NAME: **Donna K. Arnett, PhD**

eRA COMMONS USER NAME: darnett

POSITION TITLE: Professor and Dean, College of Public Health

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of South Florida, Tampa FL	BSN	03/1981	Nursing
University of South Florida, Tampa FL	MSPH	12/1987	Epidemiology
University of North Carolina at Chapel Hill, Chapel Hill, NC	PhD	05/1992	Epidemiology
University of North Carolina at Chapel Hill, Chapel Hill, NC	Postdoctoral	06/1994	Epidemiology

A. Personal Statement

I am a cardiovascular genetic epidemiologist with more than 20 years of continuous NIH funding in this area. I developed a keen interest in understanding the variable phenotypic expression of severe target organ damage from hypertension. This provided the nidus for my first R01, The Genetics of Left Ventricular Hypertrophy: The HyperGEN Study. I am also PI of the Genetics of Hypertension Associated Treatments (GenHAT) study (an ancillary study of ALLHAT, Antihypertensive and Lipid Lowering Heart Attack Trial) which is determining whether genetic variation within BP-regulating genes interacts with type of antihypertensive therapy (diuretic, ACE inhibitor, calcium antagonist, or alpha blocker) to modify the occurrence of fatal and non-fatal MI in over 40,000 high-risk hypertensive participants followed for over six years. GenHAT remains the largest pharmacogenetic study of antihypertensive agents to date and includes the largest number of African Americans (~35%). I am PI of the large NIH-sponsored clinical study, the Genetics of Lipid Lowering and Diet Network (GOLDN, both a U01 and R01). This is a gene-environmental interaction study conducted in families where two interventions, one to raise lipids and one to lower lipids, were performed. Genome-wide association, whole-exome sequencing, epigenetic, and metabolomic phenotype studies are currently underway in this cohort as well. I have over 400 peer-reviewed publications. I have served as Chair of the NIH Cardiovascular and Sleep Epidemiology study section, and I have served as Editor for the American Journal of Epidemiology. I am a past president of the American Heart Association (AHA), and have led the AHA's Research Committee and Scientific Publishing Committee. I am an elected fellow of the American College of Epidemiology, the American Epidemiological Society, and the AHA.

1. Ma Y, Smith CE, Lai CQ, Irvin MR, Parnell LD, Lee YC, Pham LD, Aslibekyan S, Claas SA, Tsai MY, Borecki IB, Kabagambe EK, Ordovás JM, Absher DM, **Arnett DK**. The effects of omega-3 polyunsaturated fatty acids and genetic variants on methylation levels of the interleukin-6 gene promoter. Mol Nutr Food Res 60:410-9, 2016. PMCID: PMC4844557
2. Das M, Irvin MR, Sha J, Aslibekyan S, Hidalgo B, Perry RT, Zhi D, Tiwari HK, Absher D, Ordovas JM, **Arnett DK**. Lipid changes due to fenofibrate treatment are not associated with changes in DNA methylation patterns in the GOLDN study. Front Genet 6:304, 2015. PMCID: PMC4586504
3. Tran NT, Aslibekyan S, Tiwari HK, Zhi D, Sung YJ, Hunt SC, Rao DC, Broeckel U, Judd SE, Muntner P, Kent ST, **Arnett DK**, Irvin MR. PCSK9 variation and association with blood pressure in African Americans: preliminary findings from the HyperGEN and REGARDS studies. Front Genet 6:136, 2015. PMCID: PMC4389541
4. **Arnett DK**. Plugging the leaking pipeline: why men have a stake in the recruitment and retention of women in cardiovascular medicine and research. Circ Cardiovasc Qual Outcomes ;8:S63-4, 2015.

B. Positions and Honors

Employment

1994-1998	Assistant Professor, Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, MN
1998-2003	Associate Professor (tenured), Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, MN
2003-2004	Mayo Professor, Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, MN
2004-2015	Chair and Professor, Department of Epidemiology, School of Public Health, University of Alabama at Birmingham
2014-2015	Associate Dean of Academic and Strategic Programs, School of Public Health, University of Alabama at Birmingham
2016-present	Dean and Professor, College of Public Health, University of Kentucky

Other Experience and Professional Memberships

1996-1997	Planning Committee, National Heart, Lung, and Blood Institute (NHLBI) Conference on Electrocardiography in Epidemiologic Studies
1997-1999	Executive Committee, American Heart Association (AHA) Council on Epidemiology and Prevention
1997-present	Program Project Reviewer, NHLBI
1998	Special Emphasis Panel, NHLBI Workshop on Genetic Basis of Variability of Progression and Outcome in Heart, Lung, and Blood Diseases
1998-2000	Vice-chair, AHA Behavioral Science, Epidemiology and Prevention Peer Review Committee
1998-2000t	Vice-chair, Chair (2001-2004), Member (present), AHA Council on Epidemiology and Prevention, Program Committee
1999-2000	Member, AHA Affiliate Behavioral Science, Epidemiology and Prevention Research Committee
2001	Chair, AHA Behavioral Science, Epidemiology and Prevention Peer Review Committee
2001-2004	Chair, AHA Council on Epidemiology and Prevention, Program Committee
2001-present	Member, AHA Council on Epidemiology and Prevention, Program Committee
2002-present	Chartered Member, National Institutes of Health (NIH) CASE Study Section
2002-present	Chair, AHA Functional Genomics Interdisciplinary Working Group
2003-2006	Member, AHA Committee of Scientific Sessions Program
2003-present	Member, AHA Scientific Advisory Committee
2004-present	Senior Scientist, Clinical Nutrition Research Center, Comprehensive Cancer Center, Center for AIDS Research, University of Alabama at Birmingham
2004-present	Editor, American Journal of Epidemiology
2006-present	Member, AHA Board of Directors, Greater Southeast Affiliate
2007-2009	Chair, AHA Research Committee
2007-present	Member, AHA National Board of Directors
2007-2009	Chair, NIH, CASE Study Section
2009-present	Associate Editor-in-Chief, International Journal of Molecular Epidemiology and Genetics
2009-present	Board of Directors, American College of Epidemiology
2009-2011	Chair, AHA Scientific Publishing Committee
2010-present	President, AHA, Greater Southeast Affiliate
2010-present	NIH Center for Scientific Review College of Reviewers
2011-2014	President Elect, President, and Immediate-Past-President, AHA

Honors

1981	Graduated magna cum laude
1992-present	Delta Omega, Honor Society for Public Health, Theta Chapter
1999	Fellow, American Heart Association, Council on Epidemiology and Prevention
2006-2007	Fellow, Executive Leadership in Academic Medicine
2008	Distinguished Faculty Investigator, University of Alabama School of Public Health
2009	Outstanding Woman University of Alabama Faculty Member
2010	H.A. Tyroler Distinguished Alumni Award
2010	American Heart Association Distinguished Achievement Award

C. Contribution to Science

1. From early population-based studies on arterial stiffness to my more recent research on other cardiovascular disease (CVD) risk factors, a significant portion of my career has been spent advancing our understanding of cardiovascular health and disease. CVD is the leading cause of death globally, responsible for 17.3 million deaths in 2013. Research studies for which I have served as principal investigator or co-investigator have not only characterized risk of CVD in specific populations (e.g., Minnesotans, African Americans), they have also refined our understanding of risk factors such as hypertension, and dyslipidemia, and other constituents of the metabolic syndrome. My epidemiological research has directed leadership roles in cardiovascular public health, culminating in my 2012-2013 Presidency of the American Heart Association and continuing with public health agenda-setting initiatives, both national and global.

    a. Do AN, Irvin MR, Lynch AI, Claas SA, Boerwinkle E, Davis BR, Ford CE, Eckfeldt JH, Tiwari HK, Limdi NA, **Arnett DK**. The effects of angiotensinogen gene polymorphisms on cardiovascular disease outcomes during antihypertensive treatment in the GenHAT study. Front Pharmacol 5:210, 2014. PMCID: PMC4165277
    b. Aggarwal P, Turner A, Matter A, Kattman SJ, Stoddard A, Lorier R, Swanson BJ, **Arnett DK**, Broeckel U. RNA expression profiling of human iPSC-derived cardiomyocytes in a cardiac hypertrophy model. PLoS One 9:e108051, 2014. PMCID: PMC4177883
    c. Lynch AI, Irvin MR, Boerwinkle E, Davis BR, Vaughan LK, Ford CE, Aissani B, Eckfeldt JH, **Arnett DK**, Shrestha S. RYR3 gene polymorphisms and cardiovascular disease outcomes in the context of antihypertensive treatment. Pharmacogenomics J 13:330-4, 2013. PMCID: PMC3435442
    d. Ahmed A, Fonarow GC, Zhang Y, Sanders PW, Allman RM, **Arnett DK**, Feller MA, Love TE, Aban IB, Levesque R, Ekundayo OJ, Dell'Italia LJ, Bakris GL, Rich MW. Renin-angiotensin inhibition in systolic heart failure and chronic kidney disease. Am J Med 125:399-410, 2012. PMCID: PMC3324926

2. The bulk of my research has examined the influence of genetic and genomic factors on CVD-related phenotypes. Although environmental factors play a critical role in the development of CVD, most CVD phenotypes (including risk factors, disease markers, and responses to drug therapies) have a heritable component. Family-based studies have been integral to knowledge discovery in this domain; these studies place special demands on investigators, particularly in the areas of participant recruitment and data analysis. I have been principal investigator and co-investigator for numerous family-based studies, including the HyperGEN: Genetics of Left Ventricular Hypertrophy Study (HyperGEN LVH), the Genetics of Lipid-lowering Drugs and Diet Network Study (GOLDN), the MESA Family Study, and others. From early linkage to current sequencing studies, this work has identified genetic loci associated with important CVD phenotypes.

    a. **Arnett DK**, Hong Y, Bella JN, et al. Sibling correlation of left ventricular mass and geometry in hypertensive African Americans and whites: the HyperGEN study. Hypertension Genetic Epidemiology Network. Am J Hypertens 14:1226-30, 2001.
    b. Tang W, Devereux RB, Rao DC, Oberman A, Hopkins PN, Kitzman DW, **Arnett DK**. Associations between angiotensinogen gene variants and left ventricular mass and function in the HyperGEN study. Am Heart J 143:854-60, 2002.
    c. Rasmussen-Torvik LJ, Pankow JS, Peacock JM, Borecki IB, Hixson JE, Tsai MY, Kabagambe EK, **Arnett DK.** Suggestion for linkage of chromosome 1p35.2 and 3q28 to plasma adiponectin concentrations in the GOLDN Study. BMC Med Genet 10:39, 2009. PMCID: PMC2691741.
    d. **Arnett DK**, McClelland RL, Bank A, et al. Biomarkers of inflammation and hemostasis associated with left ventricular mass: The Multiethnic Study of Atherosclerosis (MESA). Int J Mol Epidemiol Genet 2:391-400, 2011. PMCID: PMC3243453

3. Genome-wide association studies (GWAS) were conceived to test the "common disease, common variant" hypothesis. Both my HyperGEN LVH and GOLDN studies have GWAS components, and both have made significant contributions to their respective fields. For example, in HyperGEN we discovered associations between echocardiographic phenotypes and variants in the NCAM1 gene, a finding that has (in part) motivated further functional studies of this gene in the context of hypertrophy and cardiomyopathies.

a. **Arnett DK**, Li N, Tang W, et al. Genome-wide association study identifies single-nucleotide polymorphism in KCNB1 associated with left ventricular mass in humans: the HyperGEN Study. BMC Med Genet 10:43, 2009. PMCID: PMC2692849
b. **Arnett DK**, Meyers KJ, Devereux RB, et al. Genetic variation in NCAM1 contributes to left ventricular wall thickness in hypertensive families. Circ Res 108:279-83, 2011. PMCID: PMC3328104
c. Aslibekyan S, Goodarzi MO, Frazier-Wood AC, Yan X, Irvin MR, Kim E, Tiwari HK, Guo X, Straka RJ, Taylor KD, Tsai MY, Hopkins PN, Korenman SG, Borecki IB, Chen YD, Ordovas JM, Rotter JI, **Arnett DK**. Variants identified in a GWAS meta-analysis for blood lipids are associated with the lipid response to fenofibrate. PLoS One 7:e48663, 2012. PMCID: PMC3485381
d. Irvin MR, Zhi D, Aslibekyan, Claas SA, Absher DM, Ordovas JM, Tiwari HK, Watkins S, **Arnett DK**. Genomics of post-prandial lipidomic phenotypes in the Genetics of Lipid lowering Drugs and Diet Network (GOLDN) study. PLoS One 9:e99509, 2014. PMCID: PMC4048279

4. My research group's continuing work now includes whole-exome sequencing studies in both GOLDN and HyperGEN LVH. This research scans the coding regions of the genome for common and rare variant associations with phenotypes of interest. In HyperGEN we have combined exome-sequencing with functional validation in stem cells and novel gene-prioritization strategies that have been commended as broadly applicable to other phenotypes.

   a. Irvin MR, Zhi D, Aslibekyan S, Claas SA, Absher DM, Ordovas JM, Tiwari HK, Watkins S, **Arnett DK**. Genomics of post-prandial lipidomic phenotypes in the Genetics of Lipid lowering Drugs and Diet Network (GOLDN) study. PLoS One 9:e99509, 2014. PMCID: PMC4048279.
   b. Irvin MR, Zhi D, Joehanes R, Mendelson M, Aslibekyan S, Claas SA, Thibeault KS, Patel N, Day K, Jones LW, Liang L, Chen BH, Yao C, Tiwari HK, Ordovas JM, Levy D, Absher D, **Arnett DK**. Epigenome-wide association study of fasting blood lipids in the Genetics of Lipid-lowering Drugs and Diet Network study. Circulation 130:565-72, 2014. PMCID: PMC4209699.
   c. Hidalgo B, Irvin MR, Sha J, Zhi D, Aslibekyan S, Absher D, Tiwari HK, Kabagambe EK, Ordovas JM, **Arnett DK**. Epigenome-wide association study of fasting measures of glucose, insulin, and HOMA-IR in the Genetics of Lipid Lowering Drugs and Diet Network study. Diabetes 63:801-7, 2014. PMCID: PMC3968438.
   d. Aslibekyan S, Demerath EW, Mendelson M, Zhi D, Guan W, Liang L, Sha J, Pankow JS, Liu C, Irvin MR, Fornage M, Hidalgo B, Lin LA, Thibeault KS, Bressler J, Tsai MY, Grove ML, Hopkins PN, Boerwinkle E, Borecki IB, Ordovas JM, Levy D, Tiwari HK, Absher DM, **Arnett DK**. Epigenome-wide study identifies novel methylation loci associated with body mass index and waist circumference. Obesity (Silver Spring) 23:1493-501, 2015. PMCID: PMC4482015.

Complete list of published work can be found at: http://www.ncbi.nlm.nih.gov/sites/myncbi/donna.arnett.1/collections/49852747/public/

D. Research Support

Pending University of Kentucky-originated grant
Kentucky Center for Clinical and Translational Science
NIH/CTSA ULITR000117 07/01/2016-06/30/2021
The University of Kentucky (UK) Center for Clinical and Translational Science (CCTS) has created an integrated home for clinical and translational research to promote scientific progress and discoveries at every phase of the translational continuum. Our overarching goal as a CTSA hub is to continue to champion innovation in the full spectrum of clinical and translational research while educating the workforce of the future, engaging our communities in biomedical science and working with the national network to advance cohesive multi-center clinical trials, which will ultimately elevate the health and quality of life of the populace of Central Appalachia.

Pending grant transfers to University of Kentucky
HyperGEN: Genetics of Left Ventricular Hypertrophy
NIH/NHLBI 2 R01 HL055673-17 01/01/16-04/30/17

This project extends the genetic analysis of previously collected hypertension pedigrees with echocardiographic measures. We are conducting an exome sequencing study identify rare variants contributing to variation in cardiac size and structure and testing functionality of these variants in iPSC derived cardiomyocytes.

Epigenetic Determinants of Lipid Response to Dietary Fat and Fenofibrate

NIH/NHLB 1R01HL104135-04 01/01/16-05/31/16 NCE

This study aims to discover the epigenetic factors that cause people’s bodies to respond so differently to diet and drugs with the belief that such knowledge could ultimately help lower people’s risk for cardiovascular disease

Epigenetic Determinants of Left Ventricular and Function in Hypertensive African Americans

American Heart Association CVGPS Pathway 01/01/16-01/31/17

Left ventricular hypertrophy (a thickening of heart walls that can reduce the heart's ability to pump effectively) is common in African Americans, and it contributes more to the risk of cardiovascular death in African Americans than it does in other race groups. This project is designed to determine which non-coding genetic factors (that is, epigenetic factors) may play a role in the development of left ventricular hypertrophy in African Americans.

Genomewide Association: Triglyceride Response to Fenofibrate Therapy and Dietary Fat

NIH/NHLBI 2R01HL091357-05 01/01/16-02/28/19

Health officials have long recognized the important role fat and cholesterol play in conditions and diseases such as obesity, diabetes, and heart disease. However, how people's genes interact with their consumption of dietary fat or their treatment with drugs to reduce blood fats is poorly understood. This study aims to identify genetic variants that influence fat and cholesterol’s response to diet and drugs; this knowledge may someday help doctors tailor prevention efforts and treatments based on individual’s genetic endowment.

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME:	W. Timothy Garvey, MD
eRA COMMONS USER NAME:	GARVEYT
POSITION TITLE:	Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Washington University, St. Louis, MO	B.A.	1974	Biology
St. Louis University, St. Louis MO	M.D.	1978	Medicine
Washington University/Barnes Hospital	Residency	1981	Internal Medicine
U of Colorado and U of California San Diego	Fellowship	1984	Endocrinology & Metab

A. Personal Statement

Dr. Garvey is an internationally recognized expert in insulin resistance, adipocyte and muscle cell biology, obesity, Metabolic Syndrome, and Type 2 Diabetes, bringing basic technologies to the study of humans. His work has advanced our understanding of cardiometabolic disease, the role of the glucose transport system in insulin resistance, and effective strategies for diabetes prevention.

Dr. Garvey is a dedicated mentor for our next generation of clinicians, basic scientists, and physician scientists. He has mentored 13 junior faculty with NIH K01, NIH K23, RWJF, Fogarty, and COBRE awards; 15 post-doctoral fellows on NIH T32 and other training grants; 9 clinical fellows pursuing research careers; two MD/PhD students in the Medical Scientist Training Programs; 20 graduate students as primary mentor in PhD Degree programs. All of the junior faculty members and many of the pre-doctoral and postdoctoral fellows have gone on to become successful independent researchers. As PI of the NIH-funded Diabetes Research Center at UAB, he has helped enhance the intellectual environment at UAB for junior scientists and trainees alike.

B. Positions and Honors

Positions and Employment

1984 - 1989 Instructor & Assistant Professor, Department of Medicine, University of California, San Diego
1989 - 1993 Associate Professor of Medicine, Physiology and Biophysics, Indiana University
1993 - 1994 Professor of Medicine, Physiology and Biophysics, Indiana University School of Medicine, and Chief, Section of Endocrinology, Indianapolis VAMC, Indianapolis, IN
1994 - 2003 Director, Division of Endocrinology, Diabetes, and Medical Genetics, Medical University of South Carolina, and Staff Physician at Charleston VAMC
2003 -present Chairman and Professor, Department of Nutrition Sciences, University of Alabama at Birmingham, and Staff Physician/GRECC investigator at Birmingham VAMC
2008 -present Director, UAB Diabetes Research Center (DRC)

Other Experience and Professional Memberships

Member: ADA; Endocrine Society; TOS, AACE, FASEB, ASCI; AAP. Study Sections: ADA 1992-1995 and 2005-2008; JDRF 1994-1997; American Federation for Aging Research 2004-2012; VA Merit Review Endocrine Section 1996-2000; NIH Metabolism Study Section 1998-2002; member and chairman of multiple NIH ad hoc; Chairman, DSMB for NHLBI Vascular SCCOR 2005-2015; Chair ADA Sci & Med Mtgs Oversight Com 2006-8; AACE Board of Directors 2013-2016; Chair AACE Obesity Scientific Committee 2013-present

Honors and Awards

Alpha Omega Alpha Honor Medical Society, 1977; Alpha Sigma Nu Jesuit Honor Society, 1978; Wendell Griffith Prize in Biochemistry, St. Louis U., 1978; Pfizer Postdoctoral Fellowship Award, 1984; Pfizer Scholars Award, 1987; 1988; American Society for Clinical Investigation, 1994; Pfizer Visiting Professor, 1999-2000, Association of American Physicians, 2002. Charles E. Butterworth, Jr.,MD, Professorship at UAB, 2006. UAB Excellence in Mentoring Award, 2011; FACE designation from the Amer Assoc Clin Endocrinologists, 2014.

C. Contribution to Science (selections from over 200 publications) http://www.ncbi.nlm.nih.gov/sites/myncbi/1j7GfQ1m69q5w/bibliography/40306423/public/?sort=date&direction=descending

I. Glucose Transport

By studying molecular parameters in muscle and fat tissue from metabolically characterized individuals, the Garvey laboratory has made important observations regarding the pathogenesis of human insulin resistance. He has been a principle contributor to our understanding of the role of the glucose transport system and glucose transporter proteins in human insulin resistance. In cultured cell and rodent models, and in human muscle and adipose biopsies, he has elucidated defects in glucose transporter expression and in GLUT4 vesicle trafficking and translocation as causes for insulin resistance.

Garvey WT, Hueckstead TP, Birnbaum MJ. Suppression of an insulin-responsive glucose transporter gene in diabetes mellitus. Science 125-2341-2349, 1989.

Garvey, W.T., L. Maianu, T.P. Hueckstead, M.J. Birnbaum, J.M. Molina, and T.P. Ciaraldi. Pretranslational suppression of a glucose transporter protein causes cellular insulin resistance in non-insulin-dependent diabetes mellitus and obesity. J Clinical Investigation. 87:1072-1081, 1991.

Garvey WT, Maianu L, Zhu J-H, Brechtel-Hook G, Wallace P, Baron AD. Evidence for defects in the trafficking and translocation of GLUT4 glucose transporters in skeletal muscle as a cause of human insulin resistance. J Clin Investigation 101: 2377-86, 1998. PMCID:PMC508827

Fu Y, Luo L, Luo N, Zhu X, **Garvey WT**. NR4A Orphan Nuclear Receptors Modulate Insulin Action and the Glucose Transport System: Potential Role in Insulin Resistance. J Biol Chem 282:31525-31533, 2007.

Lara-Castro C, Newcomer BR, Rowell J, Wallace P, Shaughnessy SM, Munoz AJ, Shiflett AM, Rigsby DY, Lawrence JC, Bohning DE, Buchthal S, **Garvey WT**. Effects of short-term very low calorie diet on intramyocellular lipid and insulin sensitivity in nondiabetic and type 2 diabetics. Metabolism 57:1-8, 2008

Ingram KH, Hill HS, Moellering DR, Lara-Castro C, Hill BG, Newcomer B, Brandon LJ, Ingalls CP, Penumetcha M, Rupp JC, **Garvey WT**. Skeletal muscle lipid peroxidation and insulin resistance in humans. Journal of Clinical Endocrinology and Metabolism, 97:E1182-E1186, 2012 PMCID:PMC3387404

II. Glucose-Induced Insulin Resistance and Role of Tribbles Homolog 3

The Garvey lab pioneered in the demonstration that high glucose induces insulin resistance in human patients and in cultured cell models. Working with Dr. Steve Marshall, there was the demonstration that glucose-induced insulin resistance required glucose metabolism via the hexosamine biosynthetic pathway; however, until recently the mechanisms by which flux through this pathway mediated insulin resistance were unknown. More recently the lab identified TRIB3 in microarray analyses as differentially expressed in human muscle and that levels of this pseudokinase, which binds and blocks phosphorylation of AKT, are correlated with fasting glucose and insulin resistance. In cultured cells and mice, TRIB3 is induced by glucose with dependency on the hexosamine pathway, impairs insulin-stimulated glucose transport, and modulates glucose toxicity in STZ-induced diabetic mice.

Liu J*, Wu X*, Franklin JL, Messina JL, Martin M, **Garvey WT**. Mammalian Tribbles Homolog TRB3 Impairs Insulin Action in Skeletal Muscle: Possible Role in Glucose-Induced Insulin Resistance. American Journal of Physiology, 298:E565-E576, 2010 PMCID:PMC2838520

Liu J, Zhang W, Chuang GC, Hill HS, Tian L, Fu Y, Moellering DR, **Garvey WT**. Role of TRIB3 in Regulation of Insulin Sensitivity and Nutrient Metabolism during Short-term Fasting and Nutrient Excess. American Journal of Physiology, 303:E908-E916, 2012 PMCID: PMC3469620

Zhang W, Liu J, Tian L, Liu Q, Fu Y, **Garvey WT**. TRIB3 Mediates Glucose-Induced Insulin Resistance Via a Mechanism that Requires the Hexosamine Biosynthetic Pathway. Diabetes. 62:4192-4200, 2013

Zhang W, Wu M, Kim T, Jariwala RH, Garvey WJ, Luo N, Kang M, Ma E, Tian L, Steverson D, Yang Q, Fu Y, Garvey WT. Skeletal Muscle TRIB3 Mediates Glucose Toxicity in Diabetes and High Fat Diet-Induced Insulin Resistance. **Diabetes.** In Press, 2016 E-pub May 10, 2016

III. Role of Adiponectin in Cardiometabolic Disease

The Garvey lab has elucidated the role of adiponectin in both the metabolic and vascular components of cardiometabolic disease. The lab first discovered that it was the large molecular weight complex of adiponectin (duodecamer) rather that the smaller complexes (hexamers and trimers) that was most highly correlated with insulin resistance, lipids, and abdominal fat in humans. In cultured cells and genetically-manipulated mice, the lab proved that adiponectin functions as an autocrine/paracrine factor in adipose tissue to modulate insulin-sensitive glucose transport, lipid storage capability, and inflammatory status. Dr. Fu and Dr. Garvey showed that adiponectin also impaired macrophage foam cell formation by inducing genes that promote lipid efflux and suppressing genes that mediate lipid uptake. In mice, augmentation of adiponectin action in macrophages, by macrophage-specific overexpression of adiponectin R1 receptors, produced a lean, diabetes-resistant, atherosclerosis-resistant model with diminished macrophage infiltration in adipose. The data indicate that adiponectin action in macrophages links metabolic and vascular disease in insulin resistant patients.

Lara-Castro C, Luo N, Wallace P, Klein RL, **Garvey WT**. Adiponectin multimeric complexes and the metabolic syndrome trait cluster. Diabetes 55:249-259, 2006. PMID:16380500

Fu Y, Luo N, Klein RL, **Garvey WT**. Adiponectin Promotes Adipocyte Differentiation, Insulin Sensitivity, and Lipid Accumulation: Potential Role in Auto-Regulation of Adipocyte Metabolism and Adipose Mass. J Lipid Res 46:1369-1379, 2005. PMID:15834118

Tian L, Luo N, Klein RL, Chung BH, **Garvey WT**, Fu Y. Adiponectin Reduces Lipid Accumulation by in Macrophage Foam Cells. Atherosclerosis, 202:152-161, 2009. PMCID:PMC2630479

Luo N, Chung B-H, Wang X, Klein RL, Tang C-K, **Garvey WT**, Fu Y. Enhanced adiponectin actions by overexpression of adiponectin receptor 1 in macrophages. Atherosclerosis,228:124-135,2013 PMC3640696

IV. Genetics of Diabetes and the UCP3 Gene Mutation Affecting Substrate Metabolism

Dr. Garvey has participated in genetic studies of diabetes, obesity, and cardiovascular disease risk in the Pima Indians, T1DM patients in the DCCT, and in Gullah-Speaking African Americans lining on the Sea Islands of South Carolina. In the Gullahs, he led Project SuGAR, and demonstrated extremely low Caucasian admixture, and went on to identify chromosomal markers linked to diabetes, obesity, and lipid/lipoprotein subclasses measured by NMR spectroscopy. He discovered a UCP3 polymorphism present in 10% of Gullahs that altered fuel preference towards carbohydrate and away from fat as a metabolite for resting energy expenditure. This polymorphism would predictably promote fat storage under conditions of a high fat diet, and was associated with severe obesity in the Gullahs. The Garvey lab has also examined differential gene expression in muscle using cDNA microarrays in comparing insulin sensitive and resistant humans.

Argyropoulos G, Brown AM, Willi SM, Zhu J-H, He Y, Reitman M, Gevao SM, Spruill I, **Garvey WT**. Effects of mutations in the human uncoupling protein 3 gene on the respiratory quotient and fax oxidation in severe obesity and type 2 Diabetes. J Clin Invest 102: 1345-51, 1998. PMCID:PMC508981

Sale MM, Lu L, Spruill I, Fernandes J, Lok KH, Divers J, Langefeld CD, **Garvey WT.** A genome-wide linkage scan in Gullah-speaking African American families with type 2 diabetes: The Sea Islands Genetic African American Registry. Diabetes, 58:260-267, 2009 PMCID:PMC2606883

Divers J, Sale MM, Lu L, Chen WM[3,6], Lok KH, Spruill IJ[8], Fernandes JK, Langefeld CD, **Garvey WT**. The genetic architecture of lipoprotein subclasses in Gullah-speaking African American families enriched for type 2 diabetes: The Sea Islands genetic African American registry (project SuGAR). Journal of Lipid Research, 51:586-597, 2010

Klein RL, McHenry MB, Lok KH, Hunter SJ, Le N-A, Jenkins AJ, Zheng D, Brown WV, Lyons TJ, **Garvey WT**, and DCCT/EDIC Research Group. Apolipoprotein C-III Protein Concentrations and Gene Polymorphisms in Type 1 Diabetes: Associations with Lipoprotein Subclasses. Metabolism 53:1296-1304, 2004.

V. Diabetes Prevention and Medical Models of Obesity Management.

Dr. Garvey has conducted clinical trials involving recently approved weight loss medications, and this has led to an appreciation that these new tools now enable a more robust medical model for obesity management. Dr. Garvey was a leading contributor and author in the AACE Position Statement designating Obesity as a disease and the proposition to the AMA which designated Obesity as a disease in May, 2013. Dr. Garvey was the chief architect of the Complications-Centric Model for Care of the Overweight/Obese Patient, an algorithm that emphasizes the use of weight loss therapy to treat obesity-related complications as the primary goal of treatment, as opposed to the BMI as the main determinant of treatment indications and success. Dr. Garvey developed Cardiometabolic Disease Staging, which allows clinicians to quantitatively assign risk for Type 2 Diabetes and

cardiovascular disease mortality as a guide for intensity of weight loss therapy, within the context of a complications-centric approach. This work is widely applicable and relevant to policy-making regarding the prevention of diabetes. Thus, Dr. Garvey is a national leader in the development of medical models for the management of obesity and diabetes prevention.

Garvey WT, Ryan DH, Henry R, Bohannon NJ, Toplak H, Schwiers M, Troupin B, Day WW. Prevention of Type 2 Diabetes in Subjects With Prediabetes and Metabolic Syndrome Treated with Phentermine and Topiramate Extended-Release. Diabetes Care, 37:912-921, 2014

Guo F, Moellering DR, **Garvey WT.** The Progression of Cardiometabolic Disease: Validation of a New Cardiometabolic Disease Staging System Applicable to Obesity. Obesity, 22:110-118, 2014 PMC3866217

Garvey WT, Garber AJ, Mechanick JI, Bray GA, Dagogo-Jack S, Einhorn D, Grunberger G, Handelsman Y, Hennekens CH, Hurley DL, McGill J, Palumbo P, Umpierrez G, On Behalf Of The AACE Obesity Scientific Committee. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the 2014 advanced framework for a new diagnosis of obesity as a chronic disease. Endocrine Practice. 20:977-989, 2014

Garvey WT, Ryan DH, Bohannon NJ, Kushner RF, Rueger M, Dvorak RV, Troupin B. Weight-loss therapy in type 2 diabetes: effects of phentermine and topiramate extended release. Diabetes Care 37:3309-16, 2014

D. Research Support **ACTIVE**

Merit Review Research Grant, Garvey (PI) 04/01/15 to 03/31/19
Department of Veterans Affairs
"Mechanisms of Insulin Resistance in Diabetes"
This proposal assesses molecular mechanisms contributing to glucose-induced insulin resistance in diabetes with an emphasis of the role of tribbels homolog 3 in insulin action and systemic metabolism

R01DK096388-01A1 Gower (PI) 09/19/13 to 06/30/18
NIH/NIDDK "Race Adiposity Interactions Regulate Mechanism Determining Insulin Sensitivity"
This study explores mechanisms underlying race/ethnicity differences in metabolism including differences in hepatic insulin sensitivity and mitochondrial function. Role: Garvey is Co-Investigator

P60 DK-079626, Garvey (PI) 03/01/13 to 02/28/18
NIH/NIDDK "UAB Diabetes Research Center"
This center grant enhances infrastructure for diabetes related research by funding core facilities and pilot projects, through programs in community based research and disease prevention and control, and by promoting enrichment activities and training programs relevant to diabetes.

P30 DK-56336, Allison (PI) 06/01/12 to 05/31/17
NIH/NIDDK "Nutrition and Obesity Research Center"
This center grant enhances infrastructure for nutrition related research by funding core facilities and pilot projects. Dr. Garvey does not receive funds that directly support his individual research from this center grant.
Role: Dr. Garvey is Associate Director of the center.

U01 DK098246 George Washington U, Lachin (PI), Garvey (site PI) 04/01/12 to 03/31/20
The Glycemia Reduction Approaches for Diabetes: A Comparative Effectiveness (GRADE) Study.
This is a multi-center, NIDDK-sponsored clinical trial with Dr. Garvey as PI at the UAB site

Duke University (DCRI)/Astra Zeneca , Garvey (PI). 7/27/10 to 07/26/16
BCB109. EXCSEL Study. A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes After Treatment with Exenatide Once Weekly in Patients with Type 2 Diabetes Mellitus.
This is an industry-initiated clinical trial. Role: Garvey is PI at the UAB site.

Pfizer/Merck B1521021, Garvey (PI) 01/22/15 to 01/21/20
Randomized, Double-Blind, Placebo-Controlled. Parallel-Group Study to Assess Cardiovascular Outcomes Following Treatment with Ertugliflozin (MK-8835/PF-04971729) in Subjects With Type 2 Diabetes Mellitus and Established Vascular Disease. This is an industry-initiated clinical trial. Role: Garvey is PI at UAB site.

Lexicon LX4211-1-309-T1DM, Garvey (PI) 07/13/15 – 07/12/17
Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parralel-Group, Multicenter Study to Evaluate Efficacy, Safety, and Tolerability of LX4211 as Adjunct Therapy in Adult Patients with Type 1 Diabetes"

Novo Nordisk NN9535-4101, Garvey (PI) 08/12/15 to 09/20/17
Dose-Finding of Semaglutide Administered Subcutaneously Once Daily Versus Placebo and Liraglutide in Subjects with Type 2 Diabetes". This is an industry-initiated trial with Dr. Garvey as site PI.

Elcelyx Therapeutics, Inc. LCRM112, Garvey (PI) 12/10/15 to 12/09/16

A Randomized Double-Blind Parallel Group Multicenter Placebo-Controlled Dose-Ranging Study to Evaluate Glycemic Effects, Safety, and Tolerability of Metformin Delayed Release in Subjects with Type 2 Diabetes.

COMPLETED

RO1 DK083562, Garvey (PI). 08/01/09 – 07/31/13
NIH/NIDDK "NR4A Orphan Receptors and Insulin Resistance"
This proposal will examine the role of NR4A orphan nuclear receptors in modulating insulin sensitivity in cultured cells, transgenic mice, and humans, and will develop rationale for NR4A3 as a novel target for treatment of insulin resistance, Metabolic Syndrome, and Type 2 Diabetes.

R01 DK38765, Garvey (PI) 07/01/06-06/30/12
NIH/NIDDK "Mechanisms of Human Insulin Resistance"
This porposal studies the functional and molecular defects in mitochondria from skeletal muscle that contribute to defects in lipid metabolism and insulin resistance in the Metabolic Syndrome, obesity, T2DM

RO1 DK-078328, NIH/NIDDK. S. Adams (PI). 8/4/09 - 9/30/2012
NIH/NIDDK "Identification of Muscle Specific Biomarkers of Fatty Acid Beta Oxidation".
This project examines metabolomic profiles of lipids in insulin resistance and after exercise in subjects carrying a slice donor polymorphism for the UCP3 gene. Role: Garvey is PI of the subcontract from USDA.

Sanofi (Garvey) 4/1/14 to 8/1/15
"A Randomized, 30-Week, Active-Controlled, Open Label, 2- Treatment Arm, Parallel-Group, Multicenter Study Comparing the Efficacy and Safety of the Insulin Glargine/Lixisenatide Fixed Ratio Combination to Insulin Glargine With or Without Metformin in Patients with T2DM"
This is an industry-initiated clinical trial.
Role: Garvey is PI at the UAB site.

OVERLAP

The current funding and pending grant applications do not constitute any scientific or budgetary overlap.

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Abecasis, Goncalo R.

eRA COMMONS USER NAME (credential, e.g., agency login): goncalo

POSITION TITLE: Department Chair and Felix Moore Collegiate Professor of Biostatistics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Leeds, England	BSc (Honours)	07/1997	Genetics
University of Oxford, England	DPhil	06/2001	Human Genetics

A. Personal Statement

My research focuses on using human genetics to improve our understanding of human health and disease. To advance human genetic studies, my group develops statistical and computational methods that enable geneticists to apply emerging high-throughput technologies to studies of human health and disease. Over the past 15 years, I have developed computational tools, analytical models and study designs that have facilitated the widespread deployment of array-based genotyping and short read sequencing technologies in human genetic studies. My research is highly collaborative and benefits from interactions with experts in statistics and biostatistics, biology and human genetics, computer science and mathematics. I have mentored 12 doctoral students and 14 postdoctoral research fellows, of whom 16 are now on the faculty at major research universities in the United States.

B. Positions and Honors

Positions and Employment

2001-2002	Assistant Research Scientist, University of Michigan, Ann Arbor
2002-2005	Assistant Professor, University of Michigan, Ann Arbor
2005-2009	Associate Professor, University of Michigan, Ann Arbor
2009-	Felix Moore Collegiate Professor, University of Michigan, Ann Arbor
2010-	Director, University of Michigan Genomics Initiative, Ann Arbor
2014-	Chair, Department of Biostatistics, University of Michigan, Ann Arbor

Honors

1987,1991,1993	Macao Governor's Award for top student in Prep, Intermediate and High School Student
1996	Leeds University Crab Tree Award
1997-2001	Welcome Trust Prize Studentship, University of Oxford
2001	Fulker Award for Best Paper in *Behavior Genetics*
2005-2009	Pew Scholar for the Biomedical Sciences
2008	University of Michigan School of Public Health Excellent in Research Award
2009, 2011-2012	Thomson-Reuters "Hot Scientist List" (based on number of highly cited publications)
2010	Invited to White House for Recovery Act Innovation Report
2013	Overton Prize from the International Society for Computational Biology
2014	Curt Stern Award from the American Society of Human Genetics

Service

2005-2007	Associate Editor, American Journal of Human Genetics
2005-2009	Center for Inherited Disease Research (CIDR) Genotyping Access Committee
2005-2009	NCRR / Broad Institute Genotyping Center Steering Committee
2005-	Associate Editor, PLoS Genetics
2007-2012	GCAT Study Section (Member)
2007-2012	Associate Editor, Genome Research
2008-	University of Southern California Epigenomics Center, Scientific Advisory Board
2011-2013	American Society of Human Genetics Awards Committee
2014-	Regeneron Genetics Center, Scientific Advisory Board

C. Contribution to Science

1. **Methods that Enable Large Scale Genetic Association Studies.** One of my research group's major contributions has been the development and implementation of statistical methods that enable powerful genetic association studies of complex traits. We have developed widely used software for genotype imputation, for meta-analysis and visualization of association study results, and – more recently – for the analysis and meta-analysis of rare variants. These developments have often been motivated by the challenges we encounter in our own studies – for example, we were the first to use imputation in a genomewide association study (in 2007) and to carry out a meta-analysis of genomewide association study data (in 2008). I am a senior author and leader or co-leader for each of the exemplar studies listed below. Studies (ii), (iii) and (iv) each have >500 citations.

(i) Liu DJ, Peloso GM, Zhan X, Holmen OL, Zawistowski M, Feng S, Nikpay M, Auer PL, Goel A, Zhang H, Peters U, Farrall M, Orho-Melander M, Kooperberg C, McPherson R, Watkins H, Willer CJ, Hveem K, Melander O, Kathiresan S, **Abecasis GR** (2014) Meta-analysis of gene-level tests for rare variant association. *Nat Genet*. **46**:200-4. PubMed Central PMCID: PMC3939031.

(ii) Pruim RJ, Welch RP, Sanna S, Teslovich TM, Chines PS, Gliedt TP, Boehnke M, **Abecasis GR**, Willer CJ (2010) LocusZoom: regional visualization of genome-wide association scan results. *Bioinformatics*. **26**:2336-7. PubMed Central PMCID: PMC2935401.

(iii) Li Y, Willer CJ, Ding J, Scheet P, **Abecasis GR** (2010) MaCH: using sequence and genotype data to estimate haplotypes and unobserved genotypes. *Genet Epidemiol*. **34**:816-34. PubMed Central PMCID: PMC3175618.

(iv) Willer CJ, Li Y, **Abecasis GR** (2010) METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics*. **26**:2190-1. Pubmed Central PMCID: PMC2922887.

2. **Development of Computationally Efficient Methods for Genetic Analysis.** Since early this century, the number of genotypes in state-of-the-art complex trait studies has grown ~4x each year. The growing size and complexity of these genetic datasets constantly challenges analysis methods and their implementations. We have regularly developed new algorithms for genetic analysis that enable scientists to analyze increasingly complex datasets and realize the benefits of new high-throughput technologies. Examples range from methods for analysis of SNP data in families, to rapid genetic association tests for family samples, to improved methods for genotype imputation, to the ability to rapidly estimate ancestry for sequenced samples and match sequenced cases to potential controls. I am a leader of each of the exemplar studies listed below. Studies (ii), (iii) and (iv) each have 100s to 1000s of citations.

(i) Wang C, Zhan X, Bragg-Gresham J, Kang HM, Stambolian D, Chew EY, Branham KE, Heckenlively J; FUSION Study, Fulton R, Wilson RK, Mardis ER, Lin X, Swaroop A, Zöllner S, **Abecasis GR** (2014) Ancestry estimation and control of population stratification for sequence-based association studies. *Nat Genet*. **46**:409-15. PubMed Central PMCID: PMC4084909.

(ii) Howie B, Fuchsberger C, Stephens M, Marchini J, **Abecasis GR** (2012) Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. *Nat Genet.* **44**:955-9. PubMed Central PMCID: PMC3696580.

(iii) Chen WM, **Abecasis GR** (2007) Family-based association tests for genomewide association scans. *Am J Hum Genet*. **81**:913-26. PubMed Central PMCID: PMC2265659.

(iv) **Abecasis GR**, Cherny SS, Cookson WO, Cardon LR (2002) Merlin--rapid analysis of dense genetic maps using sparse gene flow trees. *Nat Genet.* **30**:97-101. PubMed PMID: 11731797.

3. **Methods for Analysis of Short Read Sequence Data.** A recent research area has been the development of methods for the analysis of short read sequence data. I originally proposed low-pass sequencing as a cost-effective strategy for reconstructing the genomes of thousands of individuals; a strategy that was adopted by the 1000 Genomes Project (where I co-lead the analysis team) and by several ongoing complex trait association studies. As part of my role in the project, I co-led the development of the widely used VCF and BAM formats for storing genetic variants and short-read sequence data, respectively. I have also developed methods for estimating ancestry from short-read sequence data, for analyzing sequence data in families, and – in ongoing work – to automate the analysis of 1,000s – 10,000s of sequenced samples through our GotCloud analysis pipeline (for details on GotCloud, see http://genome.sph.umich.edu/wiki/GotCloud).

(i) Chen W, Li B, Zeng Z, Sanna S, Sidore C, Busonero F, Kang HM, Li Y, **Abecasis GR** (2013) Genotype calling and haplotyping in parent-offspring trios. *Genome Res.* **23**:142-51. PubMed Central PMCID: PMC3530674.

(ii) Li B, Chen W, Zhan X, Busonero F, Sanna S, Sidore C, Cucca F, Kang HM, **Abecasis GR** (2012) A likelihood-based framework for variant calling and de novo mutation detection in families. *PLoS Genet*. **8**:e1002944. PubMed Central PMCID: PMC3464213.

(iii) Li Y, Sidore C, Kang HM, Boehnke M, **Abecasis GR** (2011) Low-coverage sequencing: implications for design of complex trait association studies. *Genome Res*. **21**:940-51. PubMed Central PMCID: PMC3106327.

(iv) Li H, Handsaker B, Wysoker A, Fennell T, Ruan J, Homer N, Marth G, **Abecasis G,** Durbin R; 1000 Genome Project Data Processing Subgroup (2009) The Sequence Alignment/Map format and SAMtools. *Bioinformatics*. **25**:2078-9. PubMed Central PMCID: PMC2723002.

4. **The Genetic Mapping of Quantitative Traits in Humans** is a long-standing interest of mine, with a particular focus on the genetic dissection of blood lipid levels. I currently co-lead the Global Lipids Genetics Consortium, with Sekar Kathiresan (Broad) and Cristen Willer (Michigan). Over the years, I have led investigations of varied quantitative traits – including cardiovascular disease risk factors such as blood glucose levels, blood pressure and blood lipids. An important focus has been the translation of genetic association signals into biological and mechanistic insights. Our studies have not only identified >100 loci regulating medically important quantitative traits in humans but also helped dissect the relationship between these traits and human disease. Using Mendelian randomization, we have shown that LDL cholesterol and triglycerides, but not HDL cholesterol, appears to be causally related to heart disease risk in humans. We have also suggested a connection between HDL cholesterol levels and age-related macular degeneration. I am principal investigator and led or co-led each of the studies listed below, which have 100s to 1000s of citations.

(i) Global Lipids Genetics Consortium, Willer CJ, Schmidt EM, Sengupta S, Peloso GM, (… 251 others …) Kathiresan S, Mohlke KL, Ingelsson E, **Abecasis GR** (2013) Discovery and refinement of loci associated with lipid levels. *Nat Genet*. **45**:1274-83. PubMed Central PMCID: PMC3838666.

(ii) Sanna S, Li B, Mulas A, Sidore C, Kang HM, Jackson AU, Piras MG, Usala G, Maninchedda G, Sassu A, Serra F, Palmas MA, Wood WH 3rd, Njølstad I, Laakso M, Hveem K, Tuomilehto J, Lakka

TA, Rauramaa R, Boehnke M, Cucca F, Uda M, Schlessinger D, Nagaraja R, **Abecasis GR** (2011) Fine mapping of five loci associated with low-density lipoprotein cholesterol detects variants that double the explained heritability. *PLoS Genet*. **7**:e1002198. PubMed Central PMCID: PMC3145627.

(iii) Prokopenko I, Langenberg C, Florez JC, Saxena R, (… 100 others …) McCarthy MI, Wareham NJ, Meigs JB, **Abecasis GR** (2009) Variants in MTNR1B influence fasting glucose levels. *Nat Genet*. **41**:77-81. PubMed Central PMCID: PMC2682768.

(iv) Willer CJ, Sanna S, Jackson AU, Scuteri A, Bonnycastle LL, Clarke R, Heath SC, Timpson NJ, Najjar SS, Stringham HM, Strait J, Duren WL, Maschio A, Busonero F, Mulas A, Albai G, Swift AJ, Morken MA, Narisu N, Bennett D, Parish S, Shen H, Galan P, Meneton P, Hercberg S, Zelenika D, Chen WM, Li Y, Scott LJ, Scheet PA, Sundvall J, Watanabe RM, Nagaraja R, Ebrahim S, Lawlor DA, Ben-Shlomo Y, Davey-Smith G, Shuldiner AR, Collins R, Bergman RN, Uda M, Tuomilehto J, Cao A, Collins FS, Lakatta E, Lathrop GM, Boehnke M, Schlessinger D, Mohlke KL, **Abecasis GR** (2007) Newly identified loci that influence lipid concentrations and risk of coronary artery disease. *Nat Genet*. **40**:161-9. PubMed PMID: 18193043.

5. Genetic Dissection of Age Related Macular Degeneration. Another important set of contributions has been to the genetic dissection of age-related macular degeneration. Studies that I have led have resulted in the identification of about half of the known age-related macular degeneration susceptibility loci. We have used fine-mapping and sequence based studies of rare variation to try and understand how genetic variants in the identified loci contribute to disease – showing, for example, that increased C3 activity appears to increase the risk of age-related macular degeneration and that non-coding variation in CFH may be as important a determinant of disease risk as coding variation.

(i) Zhan X, Larson DE, Wang C, Koboldt DC, (… 52 others …) Stambolian D, Mardis ER, Swaroop A, **Abecasis GR** (2013) Identification of a rare coding variant in complement 3 associated with age-related macular degeneration. *Nat Genet.* **45**:1375-9. PubMed Central PMCID: PMC3812337.

(ii) Fritsche LG, Chen W, Schu M, Yaspan BL, (… 148 others …) Haines JL, Farrer LA, Heid IM, **Abecasis GR**; AMD Gene Consortium (2013) Seven new loci associated with age-related macular degeneration (2013) *Nat Genet.* **45**:433-9. PubMed Central PMCID: PMC3739472.

(iii) Chen W, Stambolian D, Edwards AO, Branham KE, (… 58 others …) Haines JL, Gorin MB, **Abecasis GR**, Swaroop A (2010) Genetic variants near TIMP3 and high-density lipoprotein-associated loci influence susceptibility to age-related macular degeneration. *Proc Natl Acad Sci U S A.* PubMed Central PMCID: PMC2867722.

(iv) Li M, Atmaca-Sonmez P, Othman M, Branham KE, Khanna R, Wade MS, Li Y, Liang L, Zareparsi S, Swaroop A, **Abecasis GR** (2006) CFH haplotypes without the Y402H coding variant show strong association with susceptibility to age-related macular degeneration. *Nat Genet*. **38**:1049-54. PubMed Central PMCID: PMC1941700.

For a complete list of published work, see:
https://scholar.google.com/citations?user=t53jWtYAAAAJ

D. Research Support

Ongoing Research Support

R01HL117626 (Abecasis, PI) 01/01/13 - 12/31/17
NIH
Studies of Rare Genetic Variation in the Isolated Population of Sardinia
These studies will result in experimental strategies and analysis tools that will be readily deployable by many laboratories to study the genomes of many other individuals and further our understanding of the genetics and biology of many different traits and conditions.

A supplement to this award enables high-quality analysis and processing of sequence data for the National Heart Lung and Blood Institutes TopMed Program.

R01HG007002-01 (Abecasis, PI) 07/18/12 - 04/30/17
NIH
Computational and Statistical Models for Human Genetics
Develop computational and statistical methods that will enable studies of complex traits in humans to effectively exploit new sequencing and genotyping technologies.

Completed Research Support

U01HG006513 (Abecasis, PI) 12/31/12 - 12/31/15
NIH
Robust Software Tools for Variant Identification and Functional Assessment
Dr. Abecasis and the Ann Arbor group will work with Dr. Marth and his team to deliver a documented, validated set of tools for the analysis of next generation sequencing data. These will implement state of the art methods and will allow analysis to proceed from short read sequence data, to read mapping, to variant identification and genotype calling, to variant annotation and downstream association analyses.

R01 EY022005 (Abecasis, PI) 09/30/11 - 09/30/15
NIH
More Complete Assessment of DNA Variation in Age-Related Macular Degeneration
The goal of this to project is to apply cost effective whole genome sequencing approaches to 2,000 carefully selected individuals and use the results to study the genetics of age-related macular degeneration.

U01DK085584 (Abecasis/Boehnke, PIs) 09/20/09 - 07/31/15
NIH
Identifying T2D Variants by DNA Sequencing in Multiethnic Samples
Improved understanding of the genetic basis of type 2 diabetes has the potential to reduce the impact of the diabetes epidemic by supporting identification of novel drugs and therapies, enabling better targeting of preventive and therapeutic approaches, and providing more accurate risk prediction.

OMB No. 0925-0001/0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Mitchell Jr., Braxton Dallam

eRA COMMONS USER NAME (credential, e.g., agency login): bmitchel

POSITION TITLE: Professor of Medicine and Epidemiology; Vice Division Chief, Endocrinol, Diabetes & Nutr

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Princeton University, Princeton, NJ	B.A.	06/78	Psychology
University of Michigan, Ann Arbor, MI	M.P.H.	12/82	Epidemiology
University of Michigan, Ann Arbor, MI	Ph.D.	09/87	Epidemiology
University of Texas Health Science Center	Postdoctoral	10/87-03/91	Epidemiology

A. Personal Statement

Dr. Mitchell is a genetic epidemiologist with a long track record of NIH funding in complex genetic diseases. His current research focuses on type 2 diabetes mellitus, cardiovascular disease, stroke, osteoporosis, osteoarthritis, and obesity. As a campus leader in genomics, Dr. Mitchell interacts with investigators across the University of Maryland campus. He directs the Genomics Cores for the Baltimore Diabetes Research and Training Center and the Mid-Atlantic Nutrition Obesity Research Center, where he provides support to investigators in their diabetes, obesity, and nutrition-related research. Many of Dr. Mitchell's research projects are multidisciplinary and include basic researchers, clinicians, and translational research. He is also a core investigator in the Amish Complex Disease Genetics program, in which he has worked extensively for the past 15 years. He is the PI of the Amish ancillary study funded by NHLBI to obtain whole genome sequencing of 1,100 Amish. Relevant to this application, he has been an active participant in the International Stroke Genetics Consortium since its inception over 10 years ago, and for the past 5 years he has led the Analysis Committee for the Stroke Genetics Network (SiGN) Consortium, whose goal is to map genes for ischemic stroke and its subtypes utilizing over 17,000 stroke cases. For the proposed project, Dr. Mitchell will direct the analyses proposed in this application. For the proposed project, Dr. Mitchell will support Dr. Xu on analysis of the SiGN data for replication and extension of associations observed in WHI

B. Positions and Honors

Positions and Employment

1991 - 1994 Assistant Professor, University of Texas Health Science Center, San Antonio, TX
1994 - 1995 Staff Scientist, Southwest Foundation for Biomedical Research, San Antonio, TX
1996 - 1998 Associate Scientist, Southwest Foundation for Biomedical Research, San Antonio, TX
1999 - 2000 Scientist, Southwest Foundation for Biomedical Research, San Antonio, TX
1999 - 2000 Adjunct Professor of Medicine, University of Texas Health Science Center, San Antonio, TX
2000 - Professor of Medicine, University of Maryland School of Medicine, Baltimore, MD
2000 - Professor of Epidemiology & Public Health, Univ of Maryland School of Medicine.
2005 - 2013 Track Leader, Graduate Program in Human Genetics and Genomic Medicine. Univ of Maryland, Baltimore.

2014 - Vice Division Chief (Research), Division of Endocrinol, Diabetes & Nutrition, Dept. of Medicine, Univ of Maryland School of Medicine.

Awards and Activities

1984 - 1987 Diabetes Epidemiology Training Grant, University of Michigan.
1999 - 2000 Editorial Board, *Diabetes Care*
2001 – 2002 Scientific Sessions Planning Committee, American Diabetes Association
2001 - present NIH Study Section, ad hoc grant reviewer
2001 - 2006 NIH Study Section (Chartered Member): Cardiovascular and Sleep Epidemiology
2002 - 2014 Co-Editor, *Diabetes/Metabolism Research and Reviews*
2006 Outstanding Mentor Award. Dept of Epidemiology and Preventive Medicine, University of Maryland School of Medicine.
2006 - 2009 Editorial Board, *Diabetes*
2008 Harry and Jeanette Weinberg Foundation Research Award. Awarded for American Heart Assoc Grant-in-Aid award "Genes Influencing Susceptibility to Young Onset Stroke."
2009 - present Associate Editor, *Diabetes*
2011 Outstanding Alumnus Award. St. Paul's School. Brooklandville, MD.
2011 Faculty Mentor Award. Program in Epidemiology and Human Genetics. University of Maryland School of Medicine.
2011 - 2014 Editorial Board, *Diabetes Management*
2011 - present Faculty mentor, Young Investigator Initiative (YII) program, US Bone and Joint Decade
2012 Research Faculty Teacher of the Year Award. Division of Endocrinology, Diabetes, & Nutrition, Dept of Medicine, University of Maryland School of Medicine.
2013 - 2014 External Scientific Review Board, Cardiac Health Project (ICHP), Walter Reed National Military Medical Center, Bethesda, MD
2013 - present NIH Study Section (Chartered Member): Kidney, Obesity, Nutrition, and Diabetes
2014 - present Center for Inherited Disease Research (CIDR) Access Committee, NHGRI
2014 - present Vice Division Chief, Endocrinology, Diabetes and Nutrition, Dept of Medicine

C. Contributions to Science

1. In the 1990's I played leading roles in developing two large population-based family studies, the San Antonio Family Diabetes Study and the San Antonio Family Heart Study. My publications from these studies focused on quantifying the genetic architecture of diabetes and cardiovascular risk using quantitative genetic methods. This work broadened understanding of how common sets of genes influence joint variation across multiple traits simultaneously.
    a. Mitchell BD, Kammerer CM, Reinhart LJ, Stern MP. (1994). NIDDM in Mexican American families: heterogeneity by age of onset. Diab Care 17:567-73. PMID: 8082526
    b. Mitchell BD, Kammerer CM, Blangero J, Mahaney MC, Rainwater DL, Dyke B, Hixson JE, Henkel RD, Sharp MR, Comuzzie AG, VandeBerg JL, Stern MP, MacCluer JW. (1996). Genetic and environmental contributions to cardiovascular risk factors in Mexican Americans: The San Antonio Family Heart Study. Circulation 94:2159-2170. PMID: 8901667.
    c. Mitchell BD, Kammerer CM, Mahaney MC, Blangero J, Comuzzie AG, Atwood LD, Haffner SM, Stern MP, MacCluer JW. (1996). Genetic analysis of the IRS: pleiotropic effects of genes influencing insulin levels on lipoprotein and obesity measures. Arterioscler Thromb Vasc Biol 16:281-288. PMID: 620344.
    d. Mitchell BD, Almasy LA, Schneider JL, Blangero J, Rainwater DL, Stern MP, MacCluer JW. (1999). Diabetes and hypertension in Mexican American families: relation to cardiovascular risk. Am J Epidemiol 149:1047-1056. PMID: 10355381.
2. I have worked extensively on studies of the Old Order Amish in Lancaster County for nearly 20 years. From this work, I have made substantial contributions on the epidemiology and genetics of vascular calcification. For example, we identified dyslipidemia as a more important risk factor for coronary artery calcification (CAC) than for carotid wall thickness, and hypertension a more important risk factor for carotid wall

thickness. We identified a mutation in *APOB* that is highly enriched in the Amish and documented its strong effect not only on LDL-C levels, but also on CAC. More broadly, we have contrasted cardiometabolic risk factors between Amish and non-Amish, showing lower overall mortality in Amish despite greater dyslipidemia.

a. Bielak LF, Yu PF, Ryan KA, Rumberger JA, Sheedy, II PF, Turner ST, Shuldiner AR, Mitchell BD, Peyser PA. (2008). Differences in prevalence and severity of coronary artery calcification between two European American populations with diverse lifestyles. Atherosclerosis 196:888-95. PMC2277512.

b. Rampersaud E, Bielak LF, Parsa A, Shen H, Post W, Ryan KA, Rumberger JA, Sheedy II PF, Peyser PA, Shuldiner AR, Mitchell BD. (2008). The association of coronary artery calcification and carotid intima-media thickness with distinct, traditional coronary artery disease risk factors in asymptomatic adults. Am J Epidemiol 168:1016-1023. PMC2720772.

c. Shen H, Bielak LF, Ferguson JF, . . ., Mitchell BD. (2010). Association of the vitamin D metabolism gene *CYP24A1* with coronary artery calcium. Arterioscl Thromb Vasc Biol 30:2648-2654. PMC2988112.

d. Shen H, Damcott CM, Rampersaud E, Pollin TI, Horenstein R, McArdle PF, Peyser PA, O'Connell JR, Bielak LF, Post W, Chang Y-P C, Ryan KA, Miller M, Shelton J, Shuldiner AR, Mitchell BD. Familial defective apolipoprotein B-100 and increased low-density lipoprotein cholesterol and coronary artery calcification in the Old Order Amish. (2010). Arch Intern Med 170:1850-1855. PMC3587042.

3. I have led and/or participated in a number of follow-up studies from our Amish program designed to follow-up observed genetic associations. In one of these we showed that a common variant in the FTO gene, previously shown in many different populations to influence body mass index (BMI) and obesity, was also present in the Amish. But we extended this work and were the first to show that the effect of the BMI-increasing allele was apparent only in the least active subset of Amish; in the most active Amish the risk allele was not associated with BMI. This result has enormous public health significance in demonstrating that lifestyle can offset the deleterious effects of many disease susceptibility genes. In addition to FTO, I have performed follow-up studies of various rare large effect variants we have identified in the Amish to further characterize effects of the variant on other phenotypes and to test new hypotheses. For example, we demonstrated that carriers of the *APOB* R3500Q mutation, who have isolated hyperlipidemia in the absence of non-lipid metabolic abnormalities, also have lower bone mineral density, providing for the first time epidemiologic evidence linking hyperlipidemia to osteoporosis risk.

a. Rampersaud E, Mitchell BD, Pollin TI, Fu M, Shen H, O'Connell JR, Ducharme JL, Hines S, Sack P, Naglieri R, Shuldiner AR, Snitker S. (2008). Physical activity and the association of common *FTO* gene variants with body mass index and obesity. Arch Intern Med 168(16):1791-1797. PMC3635949.

b. Horenstein RB, Mitchell BD, Post WS, Leutjohann D, von Bergmann K, Ryan KA, Terrin M, Shuldiner AR, Steinle NI. (2013). The *ABCG8* G574R variant, serum plant sterol levels, and cardiovascular disease risk in the Old Order Amish. Arterioscl Thromb Vasc Biol 33:413-9. PMC3817740.

c. Yerges-Armstrong LM, Shen H, Streeten EA, Shuldiner AR, Mitchell BD. Decreased bone mineral density in subjects carrying familial defective Apolipoprotein B-100. (2013). J Clin Endocrinol Metab 12:E1999-2005. PMC3849668.

4. In addition to my research in the Amish, I also have a major research focus in the genetics of ischemic stroke. For over 12 years I have worked closely with Dr. Steven Kittner, a neurologist at the University of Maryland on the genetics of young onset stroke. I have been involved in the International Stroke Genetics Consortium since its inception in 2007 and chair the Analysis Committee for the large NINDS-sponsored Stroke Genetics Network (SiGN), in which we have just completed GWAS analysis of ~17,000 stroke cases

a. Mitchell BD, Fornage M, McArdle PF, Cheng YC, Pulit SL, . . ., de Bakker PIW, on behalf of the Stroke Genetics Network (SiGN). (2014). Using previously genotyped controls in genome-wide association studies (GWAS): application to the Stroke Genetics Network (SiGN). Front Genet 5:95. PMC4010766.

b. Cheng Y-C, Cole JW, Kittner SJ, Mitchell BD. The genetics of ischemic stroke in young adults. Circ Cardiovasc Genet 7(3):383-92, 2014. PMC4231871.
c. Pulit S, McArdle PF, Wong Q, Malik R, Gwinn K, . . . , Mitchell BD*, Rosand J*. Loci associated with ischaemic stroke and its subtypes (SiGN): a genome-wide association study. Lancet Neurol 15:174-184, 2016. PMC in progress
d. Cheng YC, Stanne TM, Giese AK, …, Mitchell BD. Genome-wide association analysis of young onset stroke identifies a locus on 10q25 near *HABP2*. Stroke 47:307-16, 2016. PMC in progress

I have published over 350 papers in peer-reviewed journals. A complete listing of my published work is available in **MyBibliography:**

http://www.ncbi.nlm.nih.gov/sites/myncbi/braxton.mitchell.1/bibliography/43946410/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

R01 HL121007-01 (Mitchell) 01/15/14-11/30/17
NIH
Identification and Functional Characterization of a Gene Influencing LDL-C on 5q
This project seeks to identify and characterize a gene influencing levels of LDL cholesterol levels in the Amish using multiple genetic and functional approaches.

R01 HL121007-01 Suppl (Mitchell) 01/15/14-11/30/17
NIH
Identification and Functional Characterization of a Gene Influencing LDL-C on 5q
This supplement is to whole genome sequence 1100 Amish, to impute sequence in subjects previously GWASed, and to detect associations of sequenced variants with cardiovascular risk factors.

P30 DK072488-06 (Taylor & Mitchell, MPI) 09/01/15 - 08/31/20
NIH
Mid-Atlantic Nutrition Obesity Research Center
The NORC will focus on the influence of nutrition and exercise on risk for age-related chronic diseases, including obesity, type 2 diabetes, hypertension, cardiovascular disease (CVD), sleep disordered breathing, and osteoporosis.

Regeneron Genetics Center (Mitchell & Pollin) 5/01/2015-4/30/20
Gene Discovery in the Amish
This project is to obtain whole exome sequencing in the Amish and identify large effect variants segregating in the Amish.

P60DK079637-02 (Mehboob, Site PI) 03/05/13 – 01/31/18
NIH
Baltimore Diabetes Research Center
The overall goal of the Baltimore DRC is to provide services in selected areas to diabetes researchers the Johns Hopkins Medical Institution and the University of Maryland that will lead to rational interventions for the effective treatment and prevention of diabetes and related diseases.

R01 DK088231-01 (Mitchell subcontract) 12/01/10 – 2/29/16
NIH
Genetic Determinants of Weight Loss and Resolution of Co-Morbidities
The goal of this project is to identify common and rare gene variants that are associated with weight loss and improvement in metabolic traits following bariatric surgery.

R01 AR052873-07 (Mitchell subcontract) 07/01/12-06/30/17
NIH
Leukocyte Gene Expression and Genetic Biomarkers of OA Incidence and Progression
This project seeks to identify inflammation-related genetic, proteomic, and lipidomic biomarkers that predict progression of osteoarthritis in symptomatic patients.

R01 NS073346 (Mitchell, subcontract) 03/15/11 – 02/28/16
NIH
Secondary Prevention of Subcortical Stroke Prevention Genetic Substudy Timing
The goal of this project is to identify genetic determinants of recurrent stroke, including those mediated by response to clopidogrel and other antiplatelet agents.

R01 NS086905-01 (Mitchell, sub PI) 07/01/15-06/30/20
NIH (sub with Mass General)
MRI-GENetics Interface Exploration (MRI-GENIE) Study
The goal of this study is to develop and validate automated methods for extracting brain lesion phenotypes from MRI data and then applying these methods to MRIs collected from subjects in the SiGN Neuroimaging Repository to examine their association with stroke outcome and to map genes associated with variation in these traits.

U01 HL105198-06 (Shuldiner) 04/10/10 – 03/31/16
NIH
Pharmacogenomics of Anti-platelet Intervention-2 (PAPI-2) Study
The major goal of this randomized clinical trial is to provide evidence base for translation of genotype-directed anti-platelet therapy into clinical practice.

U01 NS069208 (Kittner) 07/01/10 - 06/30/16
NIH
The NINDS Ischemic Stroke Genetics Consortium
The major goal of this project is to establish a consortium to perform a large sample size genome-wide association study for ischemic stroke using both previously genotyped and samples that need genotyping and to replicate and extend findings from discovery sample through international collaboration with other genome-wide association studies.

P30 NR014129-01 (Dorsey) 09/27/12 – 08/31/17
NIH
Center for Genomics of Pain
This center provides support for investigators at the University of Maryland seeking to use genomic approaches to understand the etiology and treatment of pain.

U01 MH108148 (Hong) 09/10/15 - 06/30/19
NIH
Amish Connectome Project on Mental Illness
The Amish Connectome Project will collect data from large, multi-generational Old Order Amish families with high prevalence of mental disorders. The project aims to extend the ongoing Human Connectome Project with state of the art cerebral connectomics and whole genome sequencing data to study the underpinning of heritable mental disorders.

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Absher, Devin Michael

eRA COMMONS USER NAME (credential, e.g., agency login): DEVINABSHER

POSITION TITLE: Faculty Investigator

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
U.C. San Diego, San Diego, CA	BS	06/1991	Molecular Biology
Emory University, Atlanta, GA	PHD	05/2000	Biochem. & Mol. Biol.
Stanford University, Stanford, CA	Postdoctoral Fellow	10/2005	Human Genetics

A. PERSONAL STATEMENT

I am a Faculty Investigator at the HudsonAlpha Institute for Biotechnology with more than 15 years of experience in human genetics and genomics research. For the past decade, I have led a genomics laboratory using high-throughput technologies to study the genetics of common diseases and traits. These studies include genome-wide association studies for a broad spectrum of chronic diseases, including cardiovascular disease, bipolar disorder, lupus, and rheumatoid arthritis. I have also performed a variety of studies on natural genetic variation in human populations that have enabled more detailed association studies. My laboratory has contributed to The Cancer Genome Atlas project, studying copy number variation in three types of cancer. We also study the epigenetics of complex diseases, using both microarrays and next-generation sequencing to assay DNA methylation patterns genome-wide. I am currently a member of the UAB Comprehensive Cancer Center and I play a key role in the UAB Center for Clinical and Translational Science and the UAB-HudsonAlpha Center for Genomic Medicine. Dr. Aslibekyan and I have productively collaborated on multiple genetic and epigenetic studies, and my laboratory will again contribute, to the fullest extent possible, our expertise in genomics.

1. Irvin MR, Zhi D, Joehanes R, Mendelson M, Aslibekyan S, et al. Epigenome-wide association study of fasting blood lipids in the Genetics of Lipid-lowering Drugs and Diet Network study. Circulation. 2014 Aug 12;130(7):565-72. PubMed PMID: 24920721; PubMed Central PMCID: PMC4209699.
2. Day K., Song J., Absher, D.M. (2014) Targeted Sequencing of Large Genomic Regions in CATCH-Seq. PLoS One. 9(10):e111756. PMCID:PMC4214737.
3. Brunner, A.L., Johnson DS, Kim SW, Valouev A, Reddy TE, Neff NF, Anton E, Medina C, Nguyen L, Chiao E, Oyolu CB, Schroth GP, Absher DM, Baker JC, Myers RM. (2009). Distinct DNA methylation patterns characterize differentiated human embryonic stem cells and developing human fetal liver. Genome Res. 19:1044-56. PMCID: 2694474
4. Li JZ, Absher DM, Tang H, Southwick AM, Casto AM, et al. Worldwide human relationships inferred from genome-wide patterns of variation. Science. 2008 Feb 22;319(5866):1100-4. PubMed PMID: 18292342.

B. POSITIONS AND HONORS

Positions and Employment

1991 - 1993	Staff Research Associate I, Department of Medicine, Kenneth R. Chien Laboratory, University of California, San Diego, CA
1993 - 2000	Graduate Student, Stephen T. Warren Laboratory, Emory University, Atlanta, GA
2001 - 2005	Postdoctoral Fellow, Richard M. Myers Laboratory, Stanford University, Stanford, CA
2005 - 2008	Senior Scientist, Stanford Human Genome Center, Stanford University, Stanford, CA
2008 -	Faculty Investigator, HudsonAlpha Institute for Biotechnology, Huntsville, AL
2009 -	Adjunct Faculty, University of Alabama at Birmingham, Birmingham, AL
2009 -	Adjunct Faculty, University of Alabama in Huntsville, Huntsville, AL
2015 -	Co-leader of the Cancer control & Population Sciences Program, University of Alabama at Birmingham, Comprehensive Cancer Center, Birmingham, AL

Other Experience and Professional Memberships

2011 - 2013	Teaching, Molecular Epidemiology, University of Alabama, Birmingham
2012 - 2014	Teaching, NHGRI Short Course in Next Generation Sequencing
2013 - 2014	Teaching, Epigenetics, University of Alabama, Birmingham
2013 - 2014	Teaching, Genomics, University of Alabama, Birmingham
2014 -	Teaching, Genomics, HudsonAlpha Institute for Biotechnology

Honors

1987	Provost's Honors , University of California, San Diego
1988	Provost's Honors , University of California, San Diego
1989	Provost's Honors , University of California, San Diego
1993	NIH Predoctoral Training Grant , Emory University
2002	NIH Postdoctoral Training Grant , Stanford University

C. CONTRIBUTIONS TO SCIENCE

1. Genomic and epigenomic analysis of cancer - My laboratory has been a contributor to The Cancer Genome Atlas project, studying copy number variation in Glioblastoma, Lung and Ovarian cancers. Recently, we revealed novel biomarkers in renal cell carcinoma and prostate cancer, using DNA methylation profiling.
   a. McLendon R, et al, (Absher DM, 39th of 100 authors). Cancer Genome Atlas Research Network. (2008) Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature. 455: 1061-8. PMCID: 2671642
   b. Integrated genomic analyses of ovarian carcinoma. Nature. 2011 Jun 29;474(7353):609-15. PubMed PMID: 21720365; PubMed Central PMCID: PMC3163504.
   c. Kobayashi Y, Absher DM, Gulzar ZG, Young SR, McKenney JK, et al. DNA methylation profiling reveals novel biomarkers and important roles for DNA methyltransferases in prostate cancer. Genome Res. 2011 Jul;21(7):1017-27. PubMed PMID: 21521786; PubMed Central PMCID: PMC3129245.
   d. Lasseigne BN, Burwell TC, Patil MA, Absher DM, Brooks JD, et al. DNA methylation profiling reveals novel diagnostic biomarkers in renal cell carcinoma. BMC Med. 2014 Dec 4;12(1):235. PubMed PMID: 25472429; PubMed Central PMCID: PMC4265327.

2. Genetic and epigenetic studies of autoimmune diseases – My laboratory has performed genome-wide and epigenome-wide association studies for systemic lupus erythematosus (SLE), rheumatoid arthritis, and other autoimmune diseases.
   a. Absher DM, Li X, Waite LL, Gibson A, Roberts K, et al. Genome-wide DNA methylation analysis of systemic lupus erythematosus reveals persistent hypomethylation of interferon genes and compositional changes to CD4+ T-cell populations. PLoS Genet. 2013;9(8):e1003678. PubMed PMID: 23950730; PubMed Central PMCID: PMC3738443.

b. Julià A, Domènech E, Ricart E, Tortosa R, García-Sánchez V, et al. A genome-wide association study on a southern European population identifies a new Crohn's disease susceptibility locus at RBX1-EP300. Gut. 2013 Oct;62(10):1440-5. PubMed PMID: 22936669.

c. Alonso A, Domènech E, Julià A, Panés J, García-Sánchez V, et al. Identification of Risk Loci for Crohn's Disease Phenotypes Using a Genome-Wide Association Study. Gastroenterology. 2014 Dec 31;PubMed PMID: 25557950.

3. Genetic studies of cardiovascular risk factors and lipid metabolism - To provide insights into the etiology of coronary artery disease and its risk factors we have performed genome-wide and epigenome-wide association analysis that has identified novel risk factors for CAD and for common human traits that influence CAD and type-2 diabetes.
   a. Heid IM, Jackson AU, Randall JC, Winkler TW, Qi L, et al. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. Nat Genet. 2010 Nov;42(11):949-60. PubMed PMID: 20935629; PubMed Central PMCID: PMC3000924.
   b. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet. 2010 Nov;42(11):937-48. PubMed PMID: 20935630; PubMed Central PMCID: PMC3014648.
   c. Schunkert H, König IR, Kathiresan S, Reilly MP, Assimes TL, et al. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. Nat Genet. 2011 Mar 6;43(4):333-8. PubMed PMID: 21378990; PubMed Central PMCID: PMC3119261.
   d. Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, et al. Large-scale association analysis identifies new risk loci for coronary artery disease. Nat Genet. 2013 Jan;45(1):25-33. PubMed PMID: 23202125; PubMed Central PMCID: PMC3679547.

4. Epigenetic studies of cardiovascular risk factors and lipid metabolism - To provide insights into the etiology of coronary artery disease and its risk factors we have performed genome-wide and epigenome-wide association analysis that has identified novel risk factors for CAD and for common human traits that influence CAD and type-2 diabetes.
   a. Hidalgo B, Irvin MR, Sha J, Zhi D, Aslibekyan S, et al. Epigenome-wide association study of fasting measures of glucose, insulin, and HOMA-IR in the Genetics of Lipid Lowering Drugs and Diet Network study. Diabetes. 2014 Feb;63(2):801-7. PubMed PMID: 24170695; PubMed Central PMCID: PMC3968438.
   b. Frazier-Wood AC, Aslibekyan S, Absher DM, Hopkins PN, Sha J, et al. Methylation at CPT1A locus is associated with lipoprotein subfraction profiles. J Lipid Res. 2014 Apr 7;55(7):1324-1330. PubMed PMID: 24711635; PubMed Central PMCID: PMC4076093.
   c. Irvin MR, Zhi D, Joehanes R, Mendelson M, Aslibekyan S, et al. Epigenome-wide association study of fasting blood lipids in the Genetics of Lipid-lowering Drugs and Diet Network study. Circulation. 2014 Aug 12;130(7):565-72. PubMed PMID: 24920721; PubMed Central PMCID: PMC4209699.

5. Epigenetic studies of aging – We have performed analyses of the aging process in various tissues, how the epigenome ages, and the effects of aging on gene expression.
   a. Wheeler HE, Metter EJ, Tanaka T, Absher D, Higgins J, et al. Sequential use of transcriptional profiling, expression quantitative trait mapping, and gene association implicates MMP20 in human kidney aging. PLoS Genet. 2009 Oct;5(10):e1000685. PubMed PMID: 19834535; PubMed Central PMCID: PMC2752811.
   b. Day K, Waite LL, Thalacker-Mercer A, West A, Bamman MM, et al. Differential DNA methylation with age displays both common and dynamic features across human tissues that are influenced by CpG landscape. Genome Biol. 2013;14(9):R102. PubMed PMID: 24034465; PubMed Central PMCID: PMC4053985.

c. Ma Y, Smith CE, Lai CQ, Irvin MR, Parnell LD, et al. Genetic variants modify the effect of age on APOE methylation in the Genetics of Lipid Lowering Drugs and Diet Network study. Aging Cell. 2015 Feb;14(1):49-59. PubMed PMID: 25476875; PubMed Central PMCID: PMC4324456.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/devin.absher.1/bibliography/42522894/public/?sort=date&direction=ascending

D. RESEARCH SUPPORT

Ongoing Research Support

08/18/15 – 03/31/19
UL1TR001417, NIH
Robert Kimberly (PI)
UAB Center for Clinical and Translational Science
HudsonAlpha will, under subcontract to UAB, participate in the Genomic Medicine Module proposed in this Clinical and Translational Science Award.
Role: Co-PI

09/01/12 – 08/31/17
5P30AR048311-14, NIH
John Mountz (PI)
Rheumatic Diseases Core Center
The RDCC provides a variety of core facility services to researchers in the field of rheumatic disease. Dr. Absher serves as co-director of the Transgenic Mouse and Genomics Core.
Role: Co-Investigator

Completed Research Support

03/29/13 – 03/14/16
HHSN268201300006C, NIH
Tsao, Philip (PI)
Integrative genomics and risk of CHD and related phenotypes in the WHI
This project will identify epigenetic biomarkers of adverse cardiovascular events in the Women's Health Initiative.
Role: Subrecipient PI

09/25/09 – 07/31/15
5R01AR057202-05, NIH
Lou Bridges (PI)
Genome Wide Association Study in African-Americans with Rheumatoid Arthritis
Performed a genome-wide genetic association study of rheumatoid arthritis in African Americans.
Role: Co-Investigator

04/01/13 - 06/30/15
5R21CA155951-03, NIH
Elizabeth Brown (PI)
A genome-wide methylation study of epigenetic contributions to multiple myeloma
Performed genome-wide DNA methylation analysis of immune cells from individuals with multiple myeloma.
Role: Subrecipient PI

08/15/10 – 12/31/15
5R01HL104135-04, NIH
Donna Arnett (PI)
Epigenetic Determinants of Lipid Response to Dietary Fat and Fenofibrate
The goal of this project was to identify epigenetic alterations that influence triglyceride levels in response to environmental challenges. We examined the methylation state of CD4 T-cells in individuals prior to a high fat challenge.
Role: Subrecipient PI

08/30/11 - 06/30/14
5R01MH094141-03, NIH
Rick Myers (PI)
Whole Genome and Exome Sequencing for Bipolar Disorder
Preformed a detailed genetic analysis of bipolar disorder. Used ultrahigh-throughput sequencing to determine the deep whole genome sequence of 2,000 bipolar patients and 2,000 controls.
Role: Co-Investigator

OTHER SUPPORT

HEMANT K. TIWARI, PhD

ACTIVE

NIH R25 GM093044 (Tiwari) 08/01/10 – 07/31/16 1.8 months/year
NIH/NIGMS No Cost Extension
Short Course on Statistical Genetics and Genomics
To offer an annual statistical genetics short course to be focused on applying advanced quantitative approaches to the search for genes that predispose complex human disorders and quantitative traits.
Role: Principal investigator

NIH R25HG006110 (Tiwari) 04/01/11 – 03/31/17 .96 months/year
NIH/NHGRI $ 48,584 (Annual direct costs)
Short Course on Next-Generation Sequencing Technology and Statistical Methods
To offer an annual short course focused on technological and statistical approaches pertaining to next-generation sequencing applied to complex human disorders and quantitative traits.

Role: Principal investigator

NIH R25GM103798 (Barnes) 09/18/12 – 08/31/17 0.30 months/year

NIH/NIGMS $ 49,995 (Annual direct costs)

UAB Metabolomics workshop: From decision to design
To offer an annual 4 day metabolomics workshop to prepare investigators to advance the use of metabolomics in translational research and to direct highly interdisciplinary teams or collaborations in metabolomic studies.
Role: Co-Principal investigator

NIH R01 (Brown) 07/01/14 – 06/30/19 0.6 months/year
NIH/NIAMS $548,330 direct costs Yr1
Association of genetic and autoantibody signatures with SLE clinical course
The purpose of this study is to characterize complex interactions between variation in DNA sequence and autoantibody profiles with the rate of progression and severity of lupus-associated nephritis and severe organ damage, which are more common among ethnic minorities. The knowledge gained from this study may help us to lower the risk of lupus-related clinical manifestations and to manage and treat it more effectively.

Role: Co-Investigator

PENDING

NOTE: The four applications listing Dr. Arnett as PI are in the process of being transferred from the University of Alabama at Birmingham to the University of Kentucky, which is the reason they are currently listed as pending.

5R01HL055673-18 (Arnett) 08/10/96 – 04/30/17 1.2 months/year
NIH/NHLBI $1,385,205 direct costs Yr 18
HyperGEN: Genetics of left ventricular hypertrophy
Left ventricular (LV) remodeling and hypertrophy occurs frequently in the general population and is a strong predictor of myocardial infarction, heart failure, and stroke. The research will continue the success of HyperGEN and GENOA in identifying novel genes contributing to LV hypertrophy, and evaluate their relevance in a cell-based system to identify new pathways for future treatment. This study seeks to discover which

genetic factors may cause an enlarged heart; this may ultimately lead to new diagnoses and treatments to help lower cardiovascular disease risk in blacks.
Role: Co-Investigator

R01HL104135-04 (Arnett) 08/15/10-05/31/15 1.2 months/year
NIH/NHLBI No-Cost Extension Transfer
Epigenetic Determinants of Lipid Response to Dietary Fat and Fenofibrate
This study aims to discover the epigenetic factors that cause people's bodies to respond so differently to diet and drugs with the belief that such knowledge could ultimately help lower people's risk for cardiovascular disease.
Role: Co-investigator

2R01HL091357-05 (Arnett) 08/01/2015 – 07/31/2019 0.6 months/year
NIH/NHLBI $699,304 direct costs Yr5
Genomewide Association Study of Lipid Response to Fenofibrate and Dietary Fat
This study aims to identify genetic variants that influence fat and cholesterol's response to diet and drugs; this knowledge may someday help doctors tailor prevention efforts and treatments based on individual's genetic endowment.
Role: Co-investigator

15GPSPG23890000 (Arnett) 02/01/15 – 01/31/17 .36 calendar
American Heart Association $90,309 (Year 2 direct costs)
Epigenetic Determinants of Left Ventricular Structure and Function in Hypertensive African Americans
Left ventricular hypertrophy (a thickening of heart walls that can reduce the heart's ability to pump effectively) is common in African Americans, and it contributes more to the risk of cardiovascular death in African Americans than it does in other race groups. This project is designed to determine which non-coding genetic factors (that is, epigenetic factors) may play a role in the development of left ventricular hypertrophy in African Americans.

1R01 HL123782-01A (Irvin) 07/01/2016-06/30/2021 0.6 months/year
(beginning year 2)
NIH/NHLBI $499,791direct costs Yr 1
Genomic Background of Blood Pressure Response to Thiazide Diuretic in African Americans.
Research shows that better blood pressure control produces cardiovascular benefits in African Americans. This study seeks to discover genetic variants that influence how blood pressure can be controlled in African Americans on a frequently used medication class (thiazide diuretics). In the future, such knowledge could help improve the care of African Americans with high blood pressure.
Role: Co-Investigator

NIH R01DK074842 (Boyer) 12/01/16 – 11/30/20 1.32 months/year
NIH/NIDDK $106,081 direct costs Yr1
Epigenome modification by a dietary pattern rich in polyunsaturated fatty acids
The overall goal of the proposed research is to identify epigenetic factors underlying the relationship between metabolic health and the traditional Yup'ik Alaska Native diet, rich in n-3 polyunsaturated fatty acids (PUFAs) from marine mammals, fish, and other wild country (subsistence) foods.
Role: MPI

OVERLAP

If all of the pending applications were funded, Dr. Tiwari's percent effort might exceed 100%. In that event, his percent effort on certain projects would be reduced and compensated for by an increase in percent effort by other qualified personnel.

For New and Competing Applications (PHS 398) – DO NOT SUBMIT UNLESS REQUESTED
For Non-competing Progress Reports (PHS 2590) – Submit only Active Support for Key Personnel

PHS 398/2590 OTHER SUPPORT

DONNA K. ARNETT, Ph.D.

PENDING

2 R01 HL055673-17 (PI: Arnett) **01/01/16-04/30/17** **1.20 calendar**
NIH/NHLBI **$1,385,205**
Hypergen: Genetics of Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH) is a common phenotype, occurring in up to 60% of hypertensives that is associated with significant cardiovascular mortality. Ancillary to the Hypertension Genetic Epidemiology Network (HyperGEN) of the Family Blood Pressure Program (FBPP). The study will further refine our linkage results by conducting linkage analyses that include the offspring of the hypertensive siblings who were recently genotyped by the Mammalian Genotyping Service. Finally, we will implement novel statistical methods for association studies.

1R01HL104135-04 (PI: Arnett) **01/01/16-05/31/16** **1.20 calendar**
NIH/NHLBI **NCE**
Epigenetic Determinants of Lipid Response to Dietary Fat and Fenofibrate

This study aims to discover the epigenetic factors that cause people's bodies to respond so differently to diet and drugs with the belief that such knowledge could ultimately help lower people's risk for cardiovascular disease.

CVGPS Pathway (PI: Arnett) **01/01/16-01/31/17** **0.60 calendar**
American Heart Association **$227,273**
Epigenetic Determinants of Left Ventricular and Function in Hypertensive African Americans

Left ventricular hypertrophy (a thickening of heart walls that can reduce the heart's ability to pump effectively) is common in African Americans, and it contributes more to the risk of cardiovascular death in African Americans than it does in other race groups. This project is designed to determine which non-coding genetic factors (that is, epigenetic factors) may play a role in the development of left ventricular hypertrophy in African Americans.

2R01HL091357-05 (PI: Arnett) **01/01/16-02/28/19** **1.20 calendar**
NIH/NHLBI **$699,303**
Genomewide Association: Triglyceride Response to Fenofibrate Therapy and Dietary Fat

Health officials have long recognized the important role fat and cholesterol play in conditions and diseases such as obesity, diabetes, and heart disease. However, how people's genes interact with their consumption of dietary fat or their treatment with drugs to reduce blood fats is poorly understood. This study aims to identify genetic variants that influence fat and cholesterol's response to diet and drugs; this knowledge may someday help doctors tailor prevention efforts and treatments based on individual's genetic endowment.

ULITR000117 (PI: Kern) **07/01/2016-06/30/2021** **0.6 calendar**
NIH/CTSA **$3,777,970**
Kentucky Center for Clinical and Translational Science

The University of Kentucky (UK) Center for Clinical and Translational Science (CCTS) has created an integrated home for clinical and translational research to promote scientific progress and discoveries at every phase of the translational continuum. Our overarching goal as a CTSA hub is to continue to champion innovation in the full spectrum of clinical and translational research while educating the workforce of the future, engaging our communities in biomedical science and working with the national network to advance cohesive multi-center clinical trials, which will ultimately elevate the health and quality of life of the populace of Central Appalachia.

OVERLAP:
n/a

PHS 398 OTHER SUPPORT

GARVEY, W. TIMOTHY, MD

ACTIVE/NEW

LCRM112 (Garvey) 12/10/15 – 12/09/16 0.12 calendar UAB time
Elcelyx Therapeutics, Inc. $21,251
"A Randomized, Double-Blind, Parallel-Group, Multicenter, Placebo-Controlled, Dose-Ranging Study to Evaluate the Glycemic Effects, Safety and Tolerability of Metformin Delayed Release in Subjects"
This is an industry-initiated clinical trial.
Role: Garvey is PI at the UAB site

LX4211-1-309-T1DM (Garvey) 07/13/15 – 07/12/17 0.12 calendar UAB time
Lexicon $1,075
"A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety and Tolerability of LX4211 as Adjunct Therapy in Adult Patients with Type 1"
This is an industry-initiated clinical trial.

NN9535-4191 (Garvey) 08/12/15 – 09/20/17 0.24 calendar UAB time
Novo Nordisk $3,570
"Dose-Finding of Semaglutide Administered Subcutaneously Once Daily Versus Placebo and Liraglutide in Subjects with Type 2 Diabetes"
This is an industry-initiated clinical trial.

ACTIVE

Merit Review Research Grant, (Garvey) 04/01/15-03/31/19 2.4 calendar VA time
Department of Veterans Affairs $150,000
"Mechanisms of Insulin Resistance in Diabetes"
This proposal assesses molecular mechanisms contributing to glucose-induced insulin resistance in diabetes with an emphasis of the role of tribbels homolog 3 in insulin action and systemic metabolism

R01DK096388-01A1 (Gower) **0**9/19/13 – 06/30/18 2.4 calendar UAB time
NIH/NIDDK $410,160
"Race Adiposity Interactions Regulate Mechanism Determining Insulin Sensitivity"
This study explores mechanisms underlying race/ethnicity differences in metabolism including differences in hepatic insulin sensitivity and mitochondrial function
Role: Garvey is Co-Investigator

P60 DK-079626, (Garvey) 03/01/13 – 02/28/18 2.4 calendar UAB time
NIH/NIDDK $784,247
"UAB Diabetes Research Center"
This center grant enhances infrastructure for diabetes related research by funding core facilities and pilot projects, through programs in community based research and disease prevention and control, and by promoting enrichment activities and training programs relevant to diabetes.
Note: this is a center grant and does not provide funds to the PI for his research.

P30 DK-56336, (Allison) 06/01/12 to 05/31/17 0.96 calendar UAB time
NIH/NIDDK $750,000
"Nutrition and Obesity Research Center"
This center grant enhances infrastructure for nutrition-related and obesity research by funding core facilities and pilot projects.

Role: Associate Center Director for Administrative Core, Note: this is a center grant and does not provide funds to the PI for his research

NIH/George Washington University (Lachin) 01/01/13 – 07/31/18 1.5 calendar UAB time
NIH/NIDDK $244,412
"The Glycemia Reduction Approaches for Diabetes: A Comparative Effectiveness (GRADE) Study." This is a multi-center, NIDDK-sponsored clinical trial.
Role: Garvey is PI at the UAB site

BCB 109 (Garvey) 07/27/10 to 07/26/16 0.24 calendar UAB time
Duke University (DCRI)/Astra Zeneca $71,683
"EXSCEL Trial"
Phase III, A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Exenatide Once Weekly in Patients with Type 2 Diabetes Mellitus.
This is an industry-initiated multi-site clinical trial.
Role: Garvey is PI at the UAB site

B1521021 (Garvey) **0**1/22/15 to 01/21/20 0.12 calendar UAB time
Pfizer/Merck Parexel International Corp $2,520
"Randomized, Double-Blind, Placebo-Controlled. Parallel-Group Study to Assess Cardiovascular Outcomes Following Treatment with Ertugliflozin (MK-8835/PF-04971729) in Subjects with Type 2 Diabetes Mellitus and Established Vascular Disease"
This is an industry-initiated multi-site clinical trial.

INACTIVE

(Garvey) 4/1/14 to 8/1/15
Sanofi
"A Randomized, 30-Week, Active-Controlled, Open Label, 2- Treatment Arm, Parallel-Group, Multicenter Study Comparing the Efficacy and Safety of the Insulin Glargine/Lixisenatide Fixed Ratio Combination to Insulin Glargine With or Without Metformin in Patients with T2DM"
This is an industry-initiated clinical trial.
Role: Garvey is PI at the UAB site.

OVERLAP

The current funding and pending grant applications do not constitute any scientific or budgetary overlap.

BUDGET JUSTIFICATION
K01 Mentored Research Scientist Development Award

Institutional base salaries listed are current. The fringe rates at UAB are 30.8% for faculty and 34.1% for staff.

A. Personnel

Stella Aslibekyan, PhD (Principal Investigator): Dr. Aslibekyan is an assistant professor in the Department of Epidemiology, School of Public Health, University of Alabama at Birmingham. She is a genetic epidemiologist with solid experience in genetic and epigenetic studies of complex diseases, as well as a proven record of published research (44 papers, 21 of them as a first author). The proposed Mentored Research Scientist Development Award will enable her to expand her toolkit to include integrative, "big data" methods, and become an independent investigator at the cutting edge of –omics science. *Salary support is being requested for 9 calendar months (75% effort) in years 1-4.*

Vinodh Srinivasasainagendra, MS (Information Systems Manager, Section on Statistical Genetics): Mr. Srinivasasainagendra is an experienced information technology professional with deep knowledge of "big data", which is essential to the success of this multidimensional proposal. He will assist Dr. Aslibekyan with 1) large scale data storage solutions, 2) efficient use of high-performance computing facilities, and 3) identifying and implementing state-of-the-art software solutions. *Salary support is being requested for 1.2 calendar months (10% effort) year 1, 1.3 calendar months (11% effort), 1.2 calendar months (10% effort), and 2.3 calendar months (19% effort) in year 4.*

B. Travel

Funds are requested in the amount of $4,000 per year in years 1-4 to cover travel to scientific meetings, short courses, and training locations, including Dr. Abecasis' group in Ann Arbor, MI and TOPMed investigator meetings in Bethesda, MD. An additional $1,500 is requested in year 3 to cover travel to the K awardee meeting in or near Bethesda, MD.

C. Other Expenses

Bisulfite sequencing: $10,000 per year in years 1-3 are requested to cover the cost of bisulfite sequencing on 5 genomic regions on 100 GOLDN participants. The work will be conducted by Dr. Devin Absher's laboratory at the Hudson Alpha Institute for Biotechnology and will include sample processing, DNA isolation, bisulfite sequencing and quality control.

Publication costs: $1,000 (year 2), $760 (year 3), and $1,000 (year 4) are requested to cover costs associated with publication of abstracts and manuscripts.

High-performance computer cluster: $1,000 per year in years 1-4 is requested for use of the UAB high performance computer cluster, Cheaha. Cheaha is a campus resource dedicated to enhancing research computing productivity at UAB. It is sponsored by UAB Information Technology (UAB IT) and is available to members of the UAB community in need of increased computational capacity. Cheaha supports high-performance computing and high-throughput computing paradigms and is the primary interface for leveraging computational resources on UABgrid, the campus distributed research support infrastructure. Dr. Aslibekyan will use Cheaha to perform WGS analysis jobs with various R packages.

Computer and software for PI: $2,260 in year 1 is requested to purchase an up-to-date personal computer capable of running state-of-the art "big data" analyses, as well as for any necessary software licenses not currently covered by UAB.

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 10/31/2018

1. Human Subjects Section

Clinical Trial? ○ Yes ● No

*Agency-Defined Phase III Clinical Trial? ○ Yes ○ No

2. Vertebrate Animals Section

Are vertebrate animals euthanized? ○ Yes ● No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

○ Yes ○ No

If "No" to AVMA guidelines, describe method and proved scientific justification

3. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount ($)	*Source(s)

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4. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ○ Yes ● No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

5. Inventions and Patents Section (RENEWAL)

*Inventions and Patents: ○ Yes ○ No

If the answer is "Yes" then please answer the following:

*Previously Reported: ○ Yes ○ No

6. Change of Investigator / Change of Institution Section

☐ Change of Project Director / Principal Investigator

Name of former Project Director / Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

☐ Change of Grantee Institution

*Name of former institution:

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OMB Number: 0925-0001
Expiration Date: 10/31/2018

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Citizenship*:

U.S. Citizen or Non-Citizen National?* ❑ Yes ☑ No

If no, select most appropriate Non-U.S. Citizen option

- ☑ With a Permanent U.S. Resident Visa
- ❑ With a Temporary U.S. Visa
- ❑ Not Residing in the U.S.

If with a temporary U.S. visa who has applied for permanent resident status and expect to hold a permanent resident visa by the earliest possible start date of the award, also check here: ❑

Candidate Background

My academic background provides a solid foundation for growth as a **multidisciplinary –omics scientist**. As an undergraduate in the interdepartmental Human Biology program at Stanford University, I developed a strong passion for what the late Oliver Sacks called "the special vicissitudes of constitution or culture or environment, which predispose a population to a specific disease." Since the beginning of my academic journey, I have been especially interested in how these predispositions work in the setting of **cardiovascular** pathologies. Working in a cardiothoracic surgery laboratory at the Stanford School of Medicine, I focused on the "constitution" part of disease risk, investigating the contributions of inflammatory cytokines to pulmonary arteriovenous malformations in animal models. While my findings were null, this work culminated in a successfully defended honors project and instilled qualities that still imbue my research approach: resilience, scientific integrity, and a strong desire to understand the interconnectivity of biological systems.

To expand my emerging focus on cardiovascular disease to the population level, I subsequently completed a Master's degree in Epidemiology at the Harvard School of Public Health. Working with Dr. Murray Mittleman, I used publicly available nationwide data to estimate cross-sectional associations of cocaine use and the risk of myocardial infarction. This work resulted in my first publication as a first author and, together with didactic experiences at Harvard, developed my proficiency with epidemiologic methods. Eager to merge this methodological knowledge with my interest in the more 'constitutional' determinants of disease risk, I sought out a doctoral dissertation project rooted in genetic epidemiology of cardiovascular traits. I found such an opportunity at Brown University under the tutelage of Dr. Ana Baylin, who mentored me as we investigated effects of candidate gene variants, biomarkers of fatty acid intake, and their interactions in a large-scale study of myocardial infarction. This work resulted in four first-author publications, multiple conference presentations, and a pilot grant I received last year to further characterize our study population using metabolomics. Additionally, as Dr. Baylin left Brown University to take a new academic position, I took full advantage of 'academic cross-pollination,' following her to the University of Michigan as a visiting student and acquiring new skills from local genomics experts.

Once I completed my doctoral work in 2011, I took a postdoctoral position with Dr. Donna Arnett's genetic epidemiology group at the University of Alabama at Birmingham (UAB). During that training period, I learned to perform genome-wide association studies (GWAS) of cardiovascular and autoimmune disease traits, including lipids, inflammatory markers, and drug response phenotypes. As my first postdoctoral project, I led the first GWAS publication from the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN), implicating several biologically relevant loci (e.g. polymorphisms near the gene encoding interleukin-2 receptor alpha) in baseline systemic inflammation. Impressed by prior evidence of pathways shared between inflammatory markers, I used principal component analysis to derive two distinct patterns of inflammation, identifying novel genetic determinants for each. These findings immeasurably raised my awareness of the **elegant complexity of biological processes** and determination to continually add to my genetic epidemiology toolbox. During that period, I also started working with the Consortium for Heart and Aging Research in Genetic Epidemiology, contributing analyses to large-scale GWAS of cardiometabolic disease traits. That experience taught me the intricacies of meta-analysis and the fruitful potential of cross-institutional collaborations. Finally, during my postdoctoral training I led a team of UAB epidemiologists and statisticians in exploring Genetic Analysis Workshop 18 data, to which we applied a novel Bayesian method to estimate relative contributions of whole genome subsets to trait variance. Our findings lent support for the 'common disease, rare variant' view of blood pressure and inspired me to continue working with **next-generation sequencing data**. During the Genetic Analysis Workshop itself, I also compiled data from multiple research groups for a broad look at best practices and challenges of pathway analysis. Overall, my work with the Genetic Analysis Workshop data resulted in two first-author publications and kindled my passion for –omics approaches to cardiovascular traits.

My postdoctoral training and subsequent transition to junior faculty coincided with the advent of the 'big data' era in genetic epidemiology. Although I was well-aware of the beneficial aspects of changing institutions from my previous experience at Brown and Michigan, I chose to stay with my UAB team because of the unique opportunity to stay at the vanguard of –omics research. Specifically, in 2013 the GOLDN study became one of the first cohorts to measure DNA methylation at ~470,000 loci across the genome, and I was keen to **integrate both genetic and environmental contributions to disease through epigenetic mechanisms**. At that time, other institutions that extended me offers did not have access to such cutting-edge data. Working with Drs. Hemant Tiwari and Degui Zhi at UAB, I learned statistical approaches to analyzing epigenomic evidence and published an epigenome-wide study of obesity traits. As a result of this study, which

discovered and replicated associations between methylation loci in *CPT1A* and obesity indices, I was chosen as a finalist in the American Heart Association Young Investigator competition through the Council on Functional Genomics and Translational Biology. Our further work on GOLDN epigenetic data resulted in a manuscript compellingly linking DNA sequence and methylation variation in our cohort. Observing the strong relationships between genetic mutations and methylation status, I was once again struck by the **imperative to creatively model complexity, synthesizing evidence from multiple –omics domains** to yield the most relevant insights into disease etiology.

Since joining my department as a tenure-earning faculty member in 2013, I have witnessed a rapid expansion of high-dimensional data that have yet to be fully exploited to understand complex traits. GOLDN remains a unique resource in the cardiovascular –omics field because it recently added or is in process of adding the following: ~350 sterols and fatty acids (**lipidomics**), exome chip and exome sequencing data, **whole genome sequencing data through the NHLBI TOPMed program** on the entire cohort, and shotgun **transcriptomics** (RNASeq) on a subset of participants. The methods for analyzing such multilevel data are constantly developed and updated, and I anticipate that my future success in –omics research is contingent on mastering the cutting-edge approaches. This career development award will provide a valuable opportunity to enhance my methodological expertise in **statistical genetics**—a field in which I have tremendous interest and some experience, but **very limited formal training**. Additionally, it will leverage my strong background in human biology to incorporate the most current knowledge of **lipid metabolism**. My current publication record (**43 total papers, including 20 as first author**) testifies to my work ethic and productivity, which I am eager to bring to this K01 opportunity. Building on my scientific experience to date, this 'big data' career development proposal is a natural and necessary step in my evolution into an independent cardiovascular –omics investigator.

Career Goals and Objectives

My overarching professional goal is **to become an interdisciplinary leader in cardiovascular –omics research**. Through the research and training proposed in this career development award application, I will be well-prepared to **take on the central challenge** that the field faces today: harnessing the available 'big data' to characterize individual variability in complex traits, specifically lipid metabolism, and generating evidence that could guide future prevention and treatment efforts.

As I work towards attaining research independence as a 'big data' scientist, I have identified three major areas for building expertise**:**

1) Analysis of next-generation sequencing data;

2) Lipid metabolism in cardiovascular disease;

3) Statistical and bioinformatic methods for integrating multiple –omics layers.

These areas represent a natural extension of my previous training in genetic epidemiology. First, while I have considerable experience with conducting and publishing genome-wide association studies of complex traits, next-generation sequencing data (such as WGS) pose unique analytic challenges, necessitating statistical approaches (e.g. burden tests) that I have yet to learn. Second, my current understanding of lipids metabolism and its relation to cardiovascular disease risk, while solid, would strongly benefit from incorporating the most up-to-date insights, particularly those from lipidomic studies. Third, the methods for integrating –omics layers are emerging at a rapid pace, and staying at the cutting edge of these developments will be critical in my work with multidimensional data. The specific aims of my proposed project arise organically from the three focus areas defined above, providing me with the opportunity to obtain mentorship, knowledge, and hands-on experience to develop valuable research competencies.

In my current tenure-earning Assistant Professor position at the University of Alabama at Birmingham, I have excellent support for the proposed career development activities. My mentorship plan builds on existing, highly productive collaborations with senior investigators across institutions and enables access to expert knowledge in statistical genetics, lipid biochemistry, and bioinformatics. During the four-year award period, I will have at least 75% of my time devoted to mastering the aforementioned competencies and completing my research aims. As a result of this commitment, I will annually publish at least 2 first-author manuscripts in years 2-4, disseminating my findings and laying the groundwork for future independent research. Using the skills, data, and collaborations made possible by the requested K01 award, **I will develop an R01 application that would 1) integrate novel –omics levels (e.g. microRNA transcriptomics, metagenomics, and others) with existing data and 2) introduce a longitudinal component to –omics analysis of cardiovascular traits**. Successful completion of the proposed training and research program will ensure my readiness to complete for external funding of –omics projects, empower my transition to independence, and grow the ranks of female quantitative experts in the scientific community.

Career Development and Training Activities During Award Period

As a postdoctoral fellow and then a junior faculty member at UAB, I have made initial progress towards my career goals in cardiovascular –omics research. Specifically, I have conducted several genome- and methylome-wide association studies of complex traits (e.g. inflammatory markers, adiponectin, obesity traits, among others), investigated gene-drug interactions, and gained valuable experience with genome-wide linkage studies and pathway analysis. However, as the field of genetic epidemiology evolves to accommodate high-dimensional –omics data, I need to obtain additional training to complete my own evolution to independent 'big data' investigator. Below I describe a multipronged approach to career development that includes classroom learning, one-on-one mentoring by several renowned experts, and hands-on research training at UAB and beyond.

1. Training plan. I propose a comprehensive training plan for this award period, focusing on my unexplored topics in statistical genetics, bioinformatics, and lipid metabolism. This plan, summarized in *Table 1*, bridges the gap between my current experience in genetic epidemiology and my goal of becoming a cardiovascular –omics scientist.

Table 1. Comprehensive Training Plan for the Career Development Award Period.

Activity	Description	Location
1. Analysis of Next-Generation Sequencing Data		
Introduction to Scientific Computing (CB2-101)	This course lays the foundation for big data analysis, ensuring proficiency with Linux, Python, R, and Bioconductor. CB2-101 is a prerequisite for other bioinformatics and computational biology offerings included in this proposal: CB2-201 and GBS787.	UAB
Computational Genomics (GBS 787)	This course provides hands-on training in computational skills required to perform sequence analysis, with emphasis on high-throughput data.	UAB
Computational Biology and Bioinformatics (CB2-201)	This two-week 'immersive learning' opportunity offers hands-on training on a variety of computational tools (e.g. BLAST, IGV, RSEM, Samtools) in the next generation sequencing context.	UAB
Hands-on Training with Dr. Gonçalo Abecasis	I will spend 2 weeks working with Dr. Abecasis, who heads the Informatics Research Center for NHLBI-WGS-TOPMed, to master the specific challenges of analyzing TOPMed data.	University of Michigan
2. Lipid Metabolism in Cardiovascular Disease		
Advanced Special Topics Course in Metabolomics (GBSC 724)	Applying the –omics framework to lipids and other metabolites, this course covers biological and statistical approaches to small molecule phenotypes.	UAB
Lipid Lovers Journal Club	This is a monthly forum for discussion of noteworthy scientific reports related to lipids in biology and disease.	UAB
3. Statistical and Bioinformatic Methods for Integrating –Omics Layers		
Introduction to Integrative –Omics	This is a unique week-long course on best practices for integrating –omics layers and the capstone of my proposed training. Upon completion, I will be able to apply cutting-edge approaches to big data synthesis, analysis, and visualization.	European Bioinformatics Institute*
Genomic Epidemiology Analysis Group Meetings	This group, including Drs. Hemant Tiwari (statistical genetics), Dr. Degui Zhi (bioinformatics), and Dr. Donna Arnett (genetic epidemiology) meets biweekly to discuss ongoing analyses of multiple –omics layers available in GOLDN.	UAB; Dr. Arnett attends by Skype
Journal Clubs: 1) Section on Statistical Genetics and 2) Computational Biology and Bionformatics	These seminars offer methods-focused lectures, discussions, and hands-on tutorial sessions on a wide range of analytic topics, including integrative –omics analysis.	UAB

*If a similar course with an integrative –omics curriculum becomes available within United States during the award period, I will choose it instead of this offering.

2. Professional skill development. In addition to the substantive offerings described above, I will take advantage of multiple opportunities to hone my professional skills. At UAB, I will take a refresher course on

responsible conduct of research (e.g. GRD 717, Principles of Scientific Integrity) and participate in ongoing career development workshops offered by the Center for Clinical and Translational Science (CCTS). These workshops will offer practical strategies for disseminating research findings, building my leadership and creativity, and applying for research funding. To build on my presentation experience and grow my scientific network, I will biannually submit my findings to prominent conferences, specifically at the meetings of the American Society for Human Genetics. I will also attend the annual South East Lipid Research Conference as well as the annual meetings of TOPMed investigators to foster local and national collaborations. Towards the end of the training period (see *Table 2*), I will focus on sharpening grant writing skills that will be critical to my future R01 application, e.g. by attending the Section on Statistical Genetics monthly grant writing club and participating in the CCTS grant writing retreat.

3. Mentoring team. The career development activities described above were carefully selected to address my training needs and complement the strength of my mentoring team. The primary mentor for this training period will be **Dr. Hemant K. Tiwari**, an internationally recognized statistical geneticist with an impressive history of training junior researchers. He is the Head of the Section on Statistical Genetics, William 'Student' Sealy Gosset Professor in the Department of Biostatistics, and the Director of NHLBI Pre- and Post-Doctoral Training Programs on Statistical Genetics. During my time at UAB, Dr. Tiwari and I have established a strong professional relationship, co-authoring 19 manuscripts (including 15 on GOLDN data) in 5 years. Dr. Tiwari's extensive methodological expertise in statistical genetics, familiarity with GOLDN data, and our history of collaboration make him ideally qualified to serve as my mentor on this proposal. Through weekly one-on-one meetings and biweekly Genomic Epidemiology Group meetings, he will provide feedback on my research progress, advise me of salient methodological developments in the field, and guide my professional development. In addition, he will be available by phone, text, Skype, and in person to address any questions that arise during the course of the proposed training period.

My secondary mentor will be **Dr. Donna K. Arnett**, the principal investigator of the GOLDN study and a globally renowned cardiovascular epidemiologist. Dr. Arnett is the past President of the American Heart Association, the former Chair of the Epidemiology Department at UAB, and the current Dean of the College of Public Health at the University at Kentucky (UK). Since her departure to UK, the robust mentor-mentee relationship we forged during her time at UAB has only grown through our weekly Skype meetings and monthly in-person meetings at UAB, UK, or national conferences. Her uniquely profound knowledge of the GOLDN data, long and decorated history of training junior researchers, and professional network make her an invaluable addition to my mentoring team. Dr. Arnett will advise me on data analysis and interpretation of GOLDN findings, assist with preparation of manuscripts and future grant proposals, and provide strategic inputs pertaining to career development.

My consultants, **Drs. Goncalo R. Abecasis** and **W. Timothy Garvey**, will lend valuable expertise in statistical genetics and lipid metabolism, respectively, to ensure the success of this proposal. Dr. Abecasis heads the Informatics Research Center (IRC) for the NHLBI TOPMed program, providing support for sequence analyses, data harmonization, and follow-up bioinformatics investigations. In this role, Dr. Abecasis is uniquely positioned to mentor me on the analysis and interpretation of TOPMed whole genome sequence (WGS) data (Specific Aim 1). I will travel to the IRC (Ann Arbor, MI) for 1 week during year 1 to receive hands-on training in WGS cross-cohort analysis. Subsequently, I will communicate with Dr. Abecasis by e-mail as well as in person during annual TOPMed investigator meetings. Dr. Garvey is a Professor and Chair of the Department of Nutrition Sciences at UAB and a prolific scholar in the field of lipid metabolism, particularly in the area of NMR lipid phenotypes. He will offer valuable insights into the biological context of the top genetic variants that emerge in the WGS scan of the postprandial lipemia phenotype. During our quarterly in-person meetings, he will assist in data interpretation and planning of follow-up experiments, including my future R01 application.

4. Productivity metrics and timeline. I will dedicate 75% of my total effort in years 1-4 to the research and career development activities outlined in this application, with the remaining 25% dedicated to teaching and service obligations. During years 2-4 of the award period, I will publish at least one manuscript per each specific aim, laying the groundwork for my R01 application submitted in year 4. Continuing my prior record, I will also publish one review article or book chapter on –omics-related topics per year. I will use the Individual Development Plan (IDP) tool offered by the American Association for the Advancement of Science (AAAS) as well as the milestones in *Table 2* to track my progress.

Table 2. Timeline for Training and Research Activities (Excluding Regular Meetings and Seminars).

Year	July-Sept	Oct-Dec	Jan-Mar	Apr-Jun
1 2017-2018	South East Lipid Research Conference Hands-on training with Dr. Abecasis Aim 1 data acquisition and discovery analysis	ASHG meeting CB2-101 Aim 1 discovery analysis Write and submit review article/book chapter	CB2-201 TOPMed meeting Start Aim 3 bisulfite sequencing Aim 1 discovery analysis Revise and resubmit review article/book chapter	GBS 787 Aim 1 replication analysis
2 2018-2019	South East Lipid Research Conference Aim 1 prepare abstract and manuscript Aim 2 data analysis	ASHG meeting Aim 1 finalize manuscript Aim 2 data analysis Write and submit review article/book chapter	GBSC 724 TOPMed meeting Aim 2 data analysis Aim 1 submit manuscript Revise and resubmit review article/book chapter	Integrative –Omics Course Aim 1 revise & resubmit manuscript Aims 2 data analysis
3 2019-2020 (Also in year 3: *K awardee meeting*)	South East Lipid Research Conference Aim 2 prepare abstract and manuscript Complete Aim 3 bisulfite sequencing Aim 3 data analysis	ASHG meeting Aim 3 data analysis Aim 2 finalize manuscript Write and submit review article/book chapter	TOPMed meeting Aim 2 submit manuscript Aim 3 finalize manuscript Revise and resubmit review article/book chapter	Aim 2 revise & resubmit manuscript Aim 3 submit manuscript Identify preliminary data for R01 application
4 2020-2021	South East Lipid Research Conference Aim 3 revise & resubmit manuscript Grant writing retreat Develop R01 application	ASHG meeting Submit R01 application	TOPMed meeting Identify alternative funding and prepare applications Receive R01 score Write and submit review article/book chapter	Develop R01 resubmission if necessary Revise and resubmit review article/book chapter

Specific Aims

Dyslipidemias are a critical determinant of cardiovascular disease (CVD) risk.[1, 2] Although dietary interventions can impact dyslipidemia, there is considerable variation in the lipid response to diet, specifically in postprandial lipemia (PPL). Humans spend most of their waking hours in a non-fasting state, and PPL lipid fluctuations are extremely relevant to disease pathogenesis. Specifically, the ingestion of a high-fat meal leads to shifts in particle size, number, and concentration of high,- low-, and very low-density lipoprotein cholesterol (HDL, LDL, and VLDL), with downstream effects on atherogenesis and CVD risk.[3] Postprandial lipoprotein response is heritable[4, 5] and highly variable between individuals. Previous genomic studies have identified regions associated with the observed PPL variation,[6-8] but these studies have been limited to 1) traditional lipid measures and/or 2) common single nucleotide polymorphisms (SNPs), thus unable to capture the differential atherogenicity of lipoprotein subfractions or their complete genetic architecture.

As part of the Trans –Omics for Precision Medicine (TOPMed) initiative, the National Heart, Lung, and Blood Institute Whole Genome Sequencing (NHLBI-WGS) Project has collected WGS data on 1048 participants of the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN), the largest cohort with nuclear magnetic resonance (NMR) spectroscopy measurements of postprandial lipoproteins. All GOLDN participants were given a standardized high-fat meal, and lipoprotein profiles were assessed at baseline as well as 3.5 and 6 hours after the intervention. TOPMed data offer an exciting opportunity to evaluate genomic contributions to postprandial shifts in lipoprotein subfraction concentrations at an unprecedented resolution. In addition to WGS and NMR lipoprotein phenotypes, GOLDN has data on postprandial changes in ~350 lipidomic features, as well as epigenome-wide blood DNA methylation measurements and shotgun transcriptomics (RNASeq) data. The richly characterized population of GOLDN is ideally suited for investigating the biological context of the genetic variants discovered through WGS, enabling a true 'trans-omics' approach to human metabolic variation.

I propose an integrative -omics study of lipoprotein subfraction response to a standardized high-fat meal, leveraging existing data and adding bisulfite sequencing measurements to describe the functional impact of genomic variation. To accomplish this goal, I will:

(1) Identify and replicate novel genetic variants contributing to the lipoprotein subfraction response to a fat meal in GOLDN (n=1048). Through the NHLBI-WGS program, GOLDN whole genomes are currently being sequenced at ~30X depth, capturing rare variants; however, analysis of WGS data was not funded by the program. I will test for associations of both common and rare variants with the PPL changes in HDL, VLDL, and LDL serum subfraction concentrations, adjusting for age, sex, baseline trait values, ancestry, and family. I will seek replication of the top findings using existing WGS and PPL data from the Heredity and Phenotype Intervention (HAPI) Heart Study (n=766).

***(2) Test for associations between postprandial changes in lipoprotein parameters and small molecule lipids in GOLDN (n=1048)* and HAPI Heart (n=500).** I will fit linear mixed models to evaluate whether PPL changes in lipoprotein subfraction concentrations are associated with postprandial changes in ~350 sterols and fatty acids, adjusting for age, sex, pedigree, and baseline dyslipidemia. For those moieties that show associations with lipoprotein subfractions, I will conduct WGS analysis as described in Aim 1, potentially identifying shared genetic determinants. This analysis will integrate sequence and cutting-edge lipidomics data, generating mechanistic insights.

(3) Define the functional impact of WGS findings using DNA methylation and gene expression data in GOLDN whole blood samples. I hypothesize that sequence variation at PPL-related loci will affect gene expression both directly and by changing the methylation status of the neighboring CpG sites. To test this hypothesis, I will densely map the methylation state of 5 genes containing top WGS PPL hits using targeted bisulfite sequencing, as well as draw upon existing RNASeq data in whole blood samples (n~100). To explore associations between DNA sequence variation, methylation, and expression of the top PPL-related genes, I will use linear mixed models adjusted for age, sex, technical artifacts, ancestry, and family relationships.

Successful completion of this project will deepen current insights into the heritable determinants of lipoprotein response to dietary fat, informing future interventions targeted at reducing dyslipidemias and thus CVD risk. **It will also provide me with the analytical skills and data to develop my subsequent R01 application, focused on integrative –omics analyses of complex traits.**

Research Strategy

1. Significance

1.1 Atherogenic dyslipidemia: A key phenotype in the development and progression of atherosclerosis, dyslipidemia accounts for 49% of the population attributable risk for CVD.[2] Termed the 'lipid triad' or 'atherogenic lipoprotein phenotype,' a common form of dyslipidemia includes elevated triglycerides (TG), reduced HDL cholesterol, and increased number of small LDL particles.[9, 10] Although most clinical efforts to date have targeted overall LDL cholesterol levels, the presence of small, dense LDL particles is an important indicator of residual CVD risk.[11] The prospective associations between LDL size and CVD outcomes are independent of overall LDL cholesterol levels and reflect the increased atherogenicity of small LDL particles, which is in turn conferred by their greater propensity to transfer into the subendothelial space, undergo oxidation, and/or bind to arterial proteoglycans.[12] The atherogenic lipoprotein phenotype is common in the settings of obesity, insulin resistance, type 2 diabetes, and the metabolic syndrome.[13] As the global epidemic of cardiometabolic disease continues to unfold, the public health relevance of atherogenic dyslipidemia will continue to grow, necessitating novel prevention and treatment strategies rooted in deeper understanding of its genetic and environmental contributors.

1.2 Relevance of postprandial lipid measures: Humans spend most of their waking time in the non-fasting state, experiencing continuous fluctuations in postprandial lipemia (PPL) throughout the day.[14] Postprandial lipid response is dynamic, peaking 4-6 hours after a meal, and robust, not only increasing the overall concentrations of LDL, HDL, and VLDL cholesterol, but also impacting lipoprotein particle size and number.[15] Furthermore, PPL response is strikingly (2- to 3-fold) variable between individuals.[5, 16, 17] A more pronounced PPL response, characterized by a sharp increase and delayed clearance[18] of TG-rich lipoproteins, has been shown to promote atherogenesis and predict the presence of CVD.[17, 19-23] The observed differences in CVD risk can be ascribed to specific cardiovascular sequelae of PPL, namely production of atherogenic TG remnant particles, decrease in high-density lipoprotein (HDL) cholesterol levels, formation of small and dense LDL particles, and upregulation of thrombotic processes.[18] Consistent with these plausible mechanisms, a growing body of epidemiologic evidence suggests that non-fasting lipids may be more relevant to CVD risk than fasting measures; e.g., in the Women's Health Study (n=26,509), nonfasting but not fasting TG levels predicted CVD incidence over ~11 years of follow-up.[24]

1.3 Quantitative, precise lipidomic traits: The advent of mass spectrometry (MS)-based profiling techniques across the entire spectrum of lipids ('lipidomics') has enabled further insights into lipid phenotypes, featuring physiologically relevant small-molecule lipids. Lipidomic variation underlies the differential atherogenicity of lipoprotein subclasses; e.g., the ratio of sphingomyelin to phosphatidylcholine in the HDL lipidome determines surface lipid fluidity, thus affecting the antioxidative and antiatherogenic activity of HDL3 (small, dense) particles.[25, 26] In addition to elucidating the biology of lipoprotein subclasses, the lipidomics approach also enables a more nuanced understanding of postprandial traits. For example, a recent crossover trial showed that postprandial changes in several lipidomic phenotypes, but not plasma TG, differed by type of fat ingested during the intervention.[27] Interestingly, the PPL differences were especially notable for plasmalogens and ether lipids,[27] previously implicated in coronary artery disease[28] and diabetes.[28] Another small trial demonstrated that three key metabolites—linoleic acid and palmitoleic acid in the apolipoprotein B fraction of the triacylglycerol lipid class as well as alpha-linolenic acid in the phosphatidylcholine lipid class—exhibited distinct postprandial responses between individuals.[29] While limited by the small sample size of the currently available studies, these findings illustrate the potential of the lipidomics approach to advance the biochemical understanding of human metabolic variation.

1.4 Genetics of postprandial lipemia: Impaired postprandial lipoprotein metabolism has been shown to affect related individuals and to correlate with the familial risk of CVD.[4, 5] Because of their heritability and the large inter-individual variability (e.g., TG levels in the GOLDN study ranged from -27 to +402% over 6 hours post-intervention), PPL phenotypes are well suited for gene discovery. A genome-wide association study (GWAS) of PPL traits identified a common variant near the *APOA1/C3/A4/A5* cluster[6] to be associated with postprandial TG in the GOLDN population, subsequently achieving replication in the HAPI Heart cohort. Candidate gene studies have linked variation in biologically plausible regions including *ABCA1*, *CETP*, *IL6*, *PLIN*, *TCF7L2*, and the cluster encoding lipoproteins to postprandial changes in TG and other lipid phenotypes.[30] More recently, a pilot study conducted on 40 GOLDN participants also suggested genetic determinants for several postprandial lipidomic variables, namely intergenic markers on chromosome 14 as well as polymorphisms in *KCNIP1* and *KCNMB1* for coprostanol, and variants in *MAP6*, *SPACA3*, and intergenic space on chromosome 9 for fatty acids.

Despite these initial successes, existing genetic studies of PPL phenotypes are largely limited to common variants and/or candidate regions, excluding a large portion of human genetic diversity. As evidenced by recent successes from studies of fasting lipids,[31] the WGS approach can augment gene discovery by capturing rare variants, explaining additional missing heritability of PPL traits and generating functional insights into lipid metabolism.

1.5 Genetics of lipoprotein subfractions: In addition to being limited to common variants, existing genetic studies of PPL are largely limited to enzymatic lipid measures, thus failing to account for the differences in atherogenicity between different lipoprotein subfractions. The advent of sophisticated, cost-effective techniques such as NMR has enabled large-scale, physiologically meaningful investigations of genetic inputs into the lipoprotein particle profile. However, published genetic studies of lipoprotein size, concentration, and cholesterol content have only investigated fasting measures. Specifically, genome-wide association studies have identified and replicated several plausible genetic predictors of lipoprotein size, concentration, and cholesterol content, e.g. variants in lipoprotein-encoding genes (*APOC-APOE*), *PCCB* (encoding an enzyme implicated in proprionic acidemia) or *PPP1R3B* (encoding a phosphatase regulating glycogen phosphorylase).[32] Interestingly, associations between common polymorphisms and lipoprotein subclass measures appear to vary by ethnic group.[33] Approximately three-quarters of the genetic findings, mainly in the cholesterol transport pathway, overlap for conventional and NMR-based lipid measures.[34] The remaining markers highlight the distinct genetic etiology of lipoprotein subfractions, holding the potential for mechanistic insights that elude conventional lipid profiles.

1.6 The epigenetic context: In addition to inputs from the DNA sequence, heritable determinants of lipid levels also include epigenetic alterations such as DNA methylation. Prior work from the GOLDN study has compellingly linked the methylation status of an intronic cytosine-guanine-phosphate (CpG) site in *CPT1A* in lymphocytes and fasting lipid levels, particularly TG and very low-density lipoprotein (VLDL) cholesterol[35] as well as fasting VLDL and LDL subfraction parameters.[36] A subsequent analysis of three European cohorts reported robust associations between fasting lipids and several biologically plausible methylation loci in *ABCG1* and *SREBF1*, observed in both whole blood and adipose tissue.[37] The association between differential methylation in *ABCG1* and fasting HDL was shown to be at least partially mediated by gene expression,[37] likely underpinned by methylation-dependent transcription factor binding. While there is substantial evidence correlating DNA methylation patterns with gene expression and fasting lipids, data on epigenetic determinants of PPL traits are sparse. To date, no study has published an epigenome-wide methylation analysis of PPL TG or any cholesterol subtypes. However, a pilot lipidomics investigation in GOLDN revealed strong associations between postprandial changes in circulating fatty acids (namely dihomogammalinoleic and eicosatrienoic) and methylation loci in *EPHB3* and *PRIC285*, respectively,[7] suggesting a role for epigenetic regulation of PPL traits.

1.7 Scientific premise: Postprandial lipemia phenotypes, particularly changes in lipoprotein subfraction profiles, provide unique insights into the pathophysiologic mechanisms underlying cardiovascular and metabolic dysfunction. Like other complex traits, PPL response has numerous genetic and epigenetic underpinnings, many of which are yet to be elucidated. Specifically, no large-scale study to date has investigated: 1) WGS determinants of postprandial lipemia; 2) genomics of postprandial change in NMR-based lipoprotein measures; 3) the interplay between postprandial lipoprotein subfractions and lipidomic traits. While prior research has identified some genetic factors underlying PPL traits,[6] it has been hindered by low-coverage genotyping and/or small sample size[6 38]as well as by the lack of integration between –omics data layers, leaving most of the observed variation unexplained. The unparalleled resources of GOLDN and HAPI Heart, the two largest intervention studies of postprandial traits, offer a unique opportunity to discover novel contributors to high-resolution lipid phenotypes. Specifically, my proposed study would integrate data from WGS, epigenome-wide methylation and transcriptomics, lipidomic profiling, and NMR-based measurements of lipoprotein subfractions. If successful, the findings from this study could inform personalized medical approaches, i.e. development of novel biomarkers to identify individuals at high risk for atherogenic dyslipidemia as well as novel therapeutic strategies.

2. Innovation

2.1 The largest and deepest genetic study of postprandial lipoproteins to date: To the best of our knowledge, GOLDN and HAPI Heart are the largest studies of postprandial lipid traits—particularly postprandial changes in lipoprotein size—with available genomic data. Together, they comprise 1800+ individuals, yielding considerable power for gene discovery and independent replication. Both cohorts either have been or are currently being sequenced at ~30x density through the NHLBI-WGS TOPMed initiative, creating a unique opportunity to explore genetic determinants of postprandial lipids beyond

common variation. The family-based design of GOLDN and HAPI Heart can also enrich for functional rare variants, which may be obscured at the population level.

2.2 High-resolution phenotypes: The phenotypes of the proposed study, namely postprandial changes in a) HDL, LDL, and VLDL subfraction concentrations and b) concentrations of small molecule lipids, offer a powerful discovery platform for genomic studies. Compared to standard lipid measures, both NMR-based measurements of lipoprotein size and lipidomic traits increase precision as well as account for the biochemical, functional, and atherogenic heterogeneity of lipid subclasses. Prior genome-wide studies of quantitative metabolic traits have reported remarkably high effect sizes (explaining as much as 60% of trait variance),[39] which translate to increased power for gene discovery.[40] In addition to their statistical advantages, genomic investigations of granular lipid phenotypes are also well-suited to elucidate the underlying biological mechanisms, informing future translational efforts.

2.3 Biologically informed rare variant analysis: Faced with the formidable multiple testing burden inherent to WGS data, I will implement sequence kernel association (SKAT)-based tests to assess the aggregate contributions of variants within distinct coding and non-coding regions as defined by the freely available Encyclopedia of DNA Elements (ENCODE). The advantage of SKAT-based methods for the analysis of GOLDN WGS data is threefold: first, it accounts for family relatedness using a kinship matrix;[41] second, it allows for allelic effects in opposing directions, accurately representing the underlying biology;[42] third, it enables weighing the contributions of specific variants.[43] In the proposed analysis, I will weigh each variant using a score comprised of predicted effects of gene expression (obtained through eQTL databases), regulatory function (ENCODE), and other bioinformatics criteria (SeattleSeq, http://snp.gs.washington.edu/SeattleSeqAnnotation138/). As a result, the proposed WGS analysis will prioritize functional, and thus more likely causal, disease variants.

2.4 Integrating –omics layers: Lipid traits have a complex genetic architecture, encompassing sequence variation, gene expression, and epigenetic changes. The richness of –omics data available in GOLDN enables a comprehensive interrogation of postprandial lipoproteins, supplying WGS data with epigenomic and transcriptomic annotations. Prior studies, including those of the GOLDN data, have documented cross-talk between the –omics layers, e.g. the influence of neighboring DNA sequence variants on CpG site methylation (cis- methylation quantitative trait loci, or meQTL)[44, 45] or gene expression (eQTL).[46] In addition to such interactions, variation at either DNA sequence or methylation or expression level can independently contribute to postprandial lipoprotein phenotypes, while methylation may impact lipid metabolism by altering gene expression. The cross-sectional associations between methylation or expression patterns with postprandial lipoprotein, however, may alternatively be driven by the phenotype itself (reverse causation) or by an external common predictor (confounding). To disentangle these relationships, I propose a Mendelian randomization approach using meQTL variants as instrumental variables (see section 3.4.4). An integrative approach to –omics data in the context of postprandial lipid phenotypes (**Figure 1**) has several advantages: 1) a more accurate portrayal of the biological complexity underlying the trait; 2) compensation for unreliable or missing information in any given –omic layer; and 3) reducing the likelihood of false positive findings by leveraging multiple domains of evidence.[47]

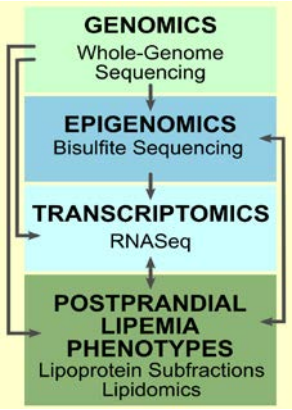

Figure 1. An integrated approach to heritable variation in postprandial lipid traits.

3. Approach

3.1 Study populations

3.1.1 GOLDN study design: GOLDN, designed to identify genetic variants influencing lipid response to dietary and drug interventions, is the largest study of postprandial changes in NMR particle sizes. The standardized meal intervention, administered after discontinuing any lipid lowering drugs for at least 4 weeks, consisted of a flavored milkshake containing 83% fat and 700 calories per m^2.[17] Blood was collected prior to the challenge (fasting) as well as 3.5 and 6 hours after ingesting the milkshake. The high-fat challenge was conducted before and after a 3-week treatment with fenofibrate. For this study, I will only focus on the pre-fenofibrate data. All participants provided written informed consent. The protocol was approved by institutional review boards at all participating sites.

3.1.2. Inclusion and exclusion criteria: GOLDN participants were recruited as extended pedigrees (at least two siblings) at the Minnesota and Utah centers of the Family Heart Study, which was restricted to participants of European descent to balance ethnic diversity across the four studies of the NHLBI Programs in Gene-Environment Interaction (PROGENI). After the initial screening of ~1350 individuals,

the following exclusion criteria were applied: fasting TGs ≥1500 mg/dL; recent history of myocardial infarction or revascularization; history of liver, kidney, pancreas, or gall bladder disease; a history of nutrient malabsorption; current use of insulin; current pregnancy or breastfeeding. Of all initially screened individuals, 1048 (546 of whom are women) had all phenotypes available and consented to future research involving their DNA samples, making them eligible for the TOPMed program and this study.

3.1.3. Postprandial lipoprotein phenotypes in GOLDN: Baseline samples for lipoprotein analysis were collected after an 8-hour fast. Fasting and postprandial VLDL, LDL, and HDL particle diameters were quantified by NMR spectroscopy (LipoScience, Raleigh, NC). Upon exposure to a 400 MHz magnet, NMR detected the signals produced by protons of distinct lipoprotein methyl groups. For each lipid class, average particle diameter was calculated based on the amplitude of the signal and multiplied by the relative mass percentage. Subfractions were defined as follows: VLDL: large (≥65 nm), medium: (35-65 nm) and small (27-35 nm); LDL: large: (23-27 nm), medium-small (21.3 - 23 nm), small (19.8-21.2 nm) and very small (18.3 – 19.7 nm); HDL: large (≥ 8.8-13 nm), medium (8.2-8.8 nm) and small (7.3-8.2 nm).

3.1.4 HAPI Heart study design/ inclusion and exclusion criteria: HAPI Heart, a family-based sister study from the NHLBI PROGENI to GOLDN, recruited ~1000 Old Order Amish participants from the Amish Family Calcification Study. HAPI Heart has a race, gender, and age distribution that is similar to GOLDN (100% European descent, 46% female, mean age 43 years), and in the past has successfully served as a replication cohort for PPL findings.[6] All participants provided written informed consent and the protocol was approved by institutional review boards at all participating sites. HAPI Heart participants had similar exclusion criteria to GOLDN, yielding 766 participants with complete data for this proposal.

3.1.5 Postprandial lipoprotein phenotypes in HAPI Heart: HAPI Heart utilized the same PPL intervention protocol as GOLDN. Lipoprotein subfraction concentrations, namely those of VLDL, LDL, HDL, and IDL, were measured at zero and four hours by Vertical Auto Profile (VAP) technology (Atherotech, Birmingham, AL),[48] roughly corresponding to the baseline and 3.5 hour time points in GOLDN. A recent comparison of subfraction measurement methods[49] confirmed the similarity between NMR- and VAP-based measures, supporting my replication strategy.

3.2 Lipidomic phenotypes

GOLDN has state-of-the-art lipidomics data on all 1048 participants at the 0, 3.5, and 6 hour PPL time points, collected at the West Coast Metabolomics Center (WCMC). Neutral lipids and phospholipids were extracted using ultra performance liquid chromatography coupled to (quadrupole) time-of-flight mass spectrometry (UPLC–QTOFMS). Based on their unique tandem mass spectrometry (MS/MS) fragmentation patterns, lipids were identified using in-house LipidBlast software; this approach quantified 250 lipid species, including ceramides, free fatty acids, and triacylglycerols. Additionally, over 100 sterols and oxysterols were captured using liquid-liquid extractions followed by ULPC-MS/MS. Identical methods were used at WCMC to measure lipidomic species on 500 HAPI Heart participants, 250 from each end of the PPL TG distribution (adjusted for age, sex, and baseline TG), at the 0 and 6 hour time points.

3.3 TOPMed whole genome sequencing

Both GOLDN and HAPI Heart have been selected for whole genome sequencing through the NHLBI TOPMed program. HAPI Heart participants have already been genotyped and that data is currently undergoing variant calling and quality control, while complete data for GOLDN is expected by the end of 2016. All TOPMed samples are sequenced at >30X depth of coverage—sufficient to capture rare variants—at one of the six centers (Northwest Genomics Center for GOLDN, Broad Institute for HAPI Heart). Dr. Gonçalo Abecasis, a consultant on this project and the director of the TOPMed Informatics Resource Center, performs calling of all TOPMed samples jointly. Such harmonized processing ensures consistency across studies and genotyping centers, reducing raw discrepancies between call sets from >7% to <0.5%.[50]

3.4 Statistical analysis

3.4.1. Aim 1—WGS analysis of postprandial lipoprotein changes: Using existing GOLDN data, I will test for associations of both common and rare variants with the PPL changes in HDL, VLDL, and LDL subfraction concentrations. These analyses will be conducted in close collaboration with Dr. Abecasis (please see the letter of support), leveraging his unparalleled expertise and pivotal role in the TOPMed project. In both cohorts, PPL response for each of the subfractions will be defined as the slope of the line connecting the baseline and the postprandial (3.5 hour for GOLDN, 4 hours for HAPI Heart) serum concentration values. To take full advantage of the GOLDN data, I will conduct additional analyses for each phenotype using the area under the curve (AUC) constructed using the 0, 3.5, and 6 hour time points and calculated under the trapezoidal rule, consistent with previous PPL GWAS.[6] Despite the homogeneous ethnic background of study participants, we will generate ancestry principal components using

EIGENSOFT 6.0.1 (https://github.com/DReichLab/EIG) and test for residual stratification. If necessary, resulting principal components will be included in all genetic models. Common variant analysis: In the discovery stage, I will first test for associations between ~10 million common SNPs (minor allele frequency, MAF>1%) and each phenotype using linear mixed models as implemented in the *lmekin* R package,[51] adjusting for family relatedness as a random effect and for age, sex, and ancestry (if needed) as fixed effects. Genome-wide significance will be set at the $2x10^{-8}$ level, assuming 2.5 million independent common SNPs and the correlated nature of the 13 subfraction measurements. Rare variant analysis: For all variants with MAF<5%, I will use a SKAT-based test [43] to assess the cumulative contribution of rare variants across distinct genomic regions, which I will define using a sliding windows approach. This analysis will adjust for family relatedness using a kinship matrix derived from pedigree data.[41] To increase the likelihood of functionally meaningful results, I propose using biological annotations combined into a score as a SKAT weight. The score will additively include one point for each of the annotation criteria, which will be determined using the most up-to-date knowledge at the time of the analysis and may include (but not be limited to) predicted functional effect, conservation score, known clinical associations, and/or mapping to an eQTL or a region containing a regulatory element. For the rare variant analysis, the genome-wide significance rate will be set based at the $5x10^{-7}$ level (0.05/100,000 regions for an expected 23K genes and >50,000 additional regulatory and non-coding regions). Simulated data on 1048 individuals with family structure identical to GOLDN, assuming 5 causally related regions with equal effect size, show that we have excellent statistical power for rare-variant discovery: >80% power to detect at least 3 of 5 causal regions with a 2% effect on PPL traits. Upon completion of the discovery analyses, I will seek replication of the top regions in WGS data from HAPI Heart, using an identical statistical approach. Preliminary data: In GOLDN, we observed linkage peaks for postprandial changes in TG on chromosome 10 and for postprandial changes in HDL cholesterol on chromosome 11 (lodscore>3 for both, unpublished). However, the GOLDN genome-wide study indicated only moderate influence of common variants.[6] Currently ongoing analyses of GOLDN exome sequencing data highlight the potential of rare variants to contribute to PPL phenotypes: e.g. 12 variants in *ITGA7*, a gene whose isoform was previously linked to coronary atherosclerosis,[52] emerged in the analyses of postprandial changes in LDL (unpublished).

3.4.2 Aim 2—integrating lipidomic data with lipoprotein subfractions and WGS: I will test for associations between postprandial changes in lipoprotein subfraction concentrations and ~350 small molecule lipid concentrations using linear mixed models, adjusting for age, sex, baseline TG (as fixed effects) and family relationships (as a random effect). Changes in small molecule lipids will be quantified as the slope of the line connecting the baseline and the 6 hour serum concentration values because these measurements are available in both GOLDN and HAPI Heart. I will take a conservative approach to controlling false positive findings, setting the lipidome-wide significance level at 0.05/350=0.0001 and replicating significant findings in HAPI Heart using identical models. For the moieties that reproducibly associate with lipoprotein subfractions, I will conduct WGS analysis using models described in 3.4.1, estimating genetic variant contributions to postprandial changes in these novel, high-resolution lipid phenotypes. Assuming 5 causal loci with equal effect size and type I error rates defined in Aim 1, statistical power exceeds 80% for at least 3 loci with a 4% effect—a realistic assumption given previously observed robust genetic effects on lipidomic phenotypes.[7] Integrating lipidomic and genomic data, this analysis can identify 1) pleiotropic effects of lipid-related sequence variants and 2) specific heritable determinants of postprandial lipidomic traits. Preliminary data: I contributed to a pilot GOLDN analysis that identified several genomic regions containing both sequence and methylation variants with robust connections to PPL lipidomic traits, e.g. two SNPs in the *SORBS1* gene ($P \leq 4.5*10^{-10}$) as well as highlighted the correlations between PPL changes in saturated fatty acids and those in NMR measures of lipoproteins.[7]

3.4.3 Aim 3—integrating methylation and expression data with WGS: Although most of this proposal makes use of existing rich data in GOLDN and HAPI Heart, for this aim I propose collecting additional data in order to create a detailed epigenetic profile of the top 5 genetic regions that emerge from the WGS analysis of lipoprotein subfractions. To that end, I will build on my long-term collaboration with Dr. Devin Absher (please see the attached letter) at the Hudson Alpha Institute of Biotechnology, drawing upon his expertise with targeted bisulfite sequencing based on multiplex PCR and successfully implemented for other GOLDN findings.[35] This approach generates dense, base-pair resolution methylation data for every cytosine in the region, capturing epigenetic variation that eludes array methods. Bisulfite sequencing will be performed in Dr. Absher's laboratory on ~750bp surrounding the top 5 WGS signals at 20X coverage on whole blood samples from 100 participants with existing gene expression data,

estimating the methylation percentage for each cytosine. To elucidate the functional impact of such methylation variation, I will test for association between each locus and expression of the respective gene, obtained from existing RNASeq data.[35] Specifically, I will use negative binomial models to associate reads per kilobase of exon model per million total reads (RPKM), a measure of transcript abundance currently available in GOLDN whole blood data, with methylation levels at each locus, adjusting for age, sex, and technical covariates (e.g. cell type distribution). The methylation loci that exhibit the strongest association with gene expression will then be carried forward to high-resolution methylation quantitative trait loci (meQTL) analyses. For that, I will fit linear mixed models to WGS data, adjusting for age, sex, and ancestry if needed and accounting for multiple testing using the Bonferroni approach. Any robust meQTL can subsequently be used in a Mendelian randomization analysis to establish the causality of the relationship between expression-related methylation variants and lipoprotein subfraction profiles. Because of the "proximity to the gene," reported effect sizes for methylation phenotypes have been extremely robust (including in GOLDN data),[45] supporting the validity of the genetic instrument. Specifically, I could test for associations between the meQTL genotype and the 13 lipoprotein subfraction response phenotypes in GOLDN, effectively mimicking the randomized trial design and controlling for measured and unmeasured confounders, as well as establishing the direction of the association. These analyses will provide valuable proof of concept for future epigenome-wide, high-resolution integrative analyses. Preliminary data: I coauthored the first epigenome-wide study of lipoprotein subfractions, which used methylation array data and reported a strong ($P<1.1*10^{-12}$) association between fasting profiles and a biologically plausible locus in *CPT1A*. Subsequent studies[35] correlated methylation at locus to *CPT1A* gene expression (r=-0.4, P=0.0003), indicating the functional potential for epigenetic regulation of lipid phenotypes.[36]

3.5 Scientific rigor: Robust—All WGS analyses as well as lipidomics analyses follow the best practices for reducing the chance of false positive findings, namely 1) implementing conservative corrections for multiple testing and 2) replicating all findings in HAPI Heart, an external cohort with remarkably similar experimental design and genotype/lipidomic phenotype data. Further, the Mendelian randomization analyses proposed in Aim 3 enhance the causal interpretation of the findings, as do the functional insights gleaned from incorporating DNA methylation and gene expression data. For further replication and functional follow-up, the wealth of data available through the TOPMed consortium allows for many opportunities. **Unbiased—**I have a longstanding and continuing commitment to transparent and unbiased reporting of findings, including publishing expansive supplemental materials and negative findings.[53-55] I fully intend to uphold this standard in the proposed project.

3.6 Consideration of relevant biological variables: Women comprise approximately half of each study cohort, and all statistical models proposed in this analysis account for age and sex. Where appropriate, the models additionally account for baseline lipid values as they could indicate metabolic variation that could impact postprandial values. Additionally, the genetic models account for ancestry as estimated by principal components to reduce potential confounding by population stratification.

3.7 Potential pitfalls and alternative strategies: Ethnic diversity: Both GOLDN and HAPI Heart are comprised exclusively of European Americans in order to balance out the ethnic diversity across all PROGENI cohorts. For that reason, the findings may not be generalizable to other ethnic groups. At this time, no other cohorts have whole genome sequencing and the primary phenotype of interest: postprandial changes in HDL, LDL, and VLDL subfraction concentrations. However, I have secured support from the Atherosclerosis in Communities study (ARIC, letter of support attached), which offers WGS data on African Americans, to explore our top WGS hits in context of related PPL phenotypes, namely TG-rich lipoprotein triglycerides (which consist predominantly of VLDL) and the apolipoprotein B48 to B100 ratio. As the TOPMed program is extended to more cohorts, I will work closely with the lipids working group to identify further opportunities for replication and meta-analysis. Multiple testing burden in WGS: Although we have adequate power to identify genetic regions associated with postprandial lipoprotein phenotypes, high-resolution genotyping carries an extremely high multiple testing burden. If no loci show genome-wide association (or approach significance by less than one order of magnitude) in Aim 1, hypothesis-driven analysis limited to candidate regions involved in PPL traits, e.g. the *APOA1/C3/A4/A5* cluster.[6] Additionally, as pathway analysis methods develop and overcome the hurdles currently posted by WGS[56] data, I will incorporate these approaches into follow-up analyses, further limiting the multiple testing burden and enhancing the biological interpretability of the findings. Because my proposed training program ensures that I will stay abreast of cutting-edge methodological developments in –omics data analysis (and particularly TOPMed data), I am confident that this proposal will embrace the best-practice approaches that will emerge over the course of the project in this rapidly evolving field.

Training in the Responsible Conduct of Research

1. During my time at UAB, I have completed the initial Collaborative Institutional Training Institute (CITI) training on the protection of human subjects. To satisfy the Department of Epidemiology requirements, I will complete the CITI refresher course every three years to further my understanding of the chief ethical considerations in human subjects research.
2. During year 1 of my proposed award period, I will enroll in GRD 717: Principles of Scientific Integrity, a 3-credit survey course offered by the UAB Graduate School and taught by Dr. Jeffrey Engler. In addition to material on human subjects protection, this course course will cover other pertinent topics such as scientific fraud and other forms of misconduct, ideals of good science, responsibilities of authorship and peer review, the role of scientists in shaping public policy, and potential pitfalls of commercialized research. This course is delivered in a seminar format over approximately 40 hours of in-class instruction.
3. During the entire award period, I will participate in the monthly calls of the Ethical, Social, and Legal Issues (ELSI) and the Steering Committees of the TOPMed program, grappling with novel ethical issues associated with whole genome sequencing data. Examples of issues that have arisen so far and have been discussed on these calls are differential consent levels across studies and the participants' rights to access their genotype data.
4. During the entire award period, I will continue to receive hands-on research conduct training from my mentors (Drs. Tiwari, Arnett, and Garvey) as well as attend relevant conference sessions, e.g. symposia on emerging ethical, legal, and social issues in genomics at the American Society of Human Genetics annual meeting.

UAB SCHOOL OF PUBLIC HEALTH

May 19, 2016

Dear K01 Review Committee members,

I am writing to express my highest level of enthusiasm for Dr. Stella Aslibekyan's application for a K01 Mentored Career Development Award, on which I will serve as the primary mentor. I have had the pleasure of informally mentoring Dr. Aslibekyan since she joined UAB as a post-doctoral fellow in 2011; since then, our collaborations have produced 19 joint publications, with several more currently under review. In addition to her exceptional productivity and unrelenting work ethic, Dr. Aslibekyan has impressed me with her scientific curiosity and fearlessness. I believe this K01 application represents a perfect fit for her intellectual firepower, ambition, and future research plans.

During our five years of working together, Dr. Aslibekyan has repeatedly proven her willingness to tackle the most pressing challenges in genetic epidemiology. She is a voracious reader and a 'big picture' thinker who is deeply cognizant that the issues facing the field now stem from the high-dimensional and multi-layered nature of the data generated by next-generation sequencing and other novel –omics technology. That understanding inspired her current application, which thoughtfully proposes to equip her with the skills to handle these challenges. While her background in genetic epidemiology lays a robust quantitative foundation, **the proposed project is at the cutting edge of our field**, requiring her to get **additional training in analytic methods** that are currently emerging to convert abundant –omics data into useful information. Given the trends in the field and Dr. Aslibekyan's interest in complex pathophysiological traits, she would also benefit from training in computational biology/bioinformatics and lipid biochemistry. This K01 award would enable such training and turbo-charge Dr. Aslibekyan's development into an innovative, independent investigator aligned with the research mission of the NHLBI and specifically the Trans-Omics for Precision Medicine (TOPMed) program.

In my role as her primary mentor, I am well-positioned and excited to guide her training in statistical genetics, focusing on 'big data' methodologies. I have extensive experience developing and applying novel biostatistical methods, including those for analyzing next-generation sequencing data and synthesizing evidence across –omics domains. I have provided statistical support for the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN), the primary cohort involved in Dr. Aslibekyan's proposal, and am currently involved with the TOPMed analysis and population genetics committees. As such, I am knowledgeable in the specifics of the data she will utilize for her training and research, and can provide her with effective, specialized guidance. Additionally, I was head of the Section on Statistical Genetics in the Department of Biostatistics at the University of Alabama at Birmingham. In that role, I enjoyed a special understanding of the support required by junior scientists to transition to independence. Throughout my career, I have mentored or co-mentored 12 pre-doctoral and 11 pos-tdoctoral trainees as well as numerous young faculty, including Dr. Aslibekyan. The overwhelming majority of my mentees have found success as academic or industry scientists, and Dr. Aslibekyan is poised to do the same.

My plan for mentoring Dr. Aslibekyan is as follows. **We will meet in person on a biweekly basis** to discuss ongoing research, latest methodological publications, and Dr. Aslibekyan's professional development activities (e.g. scientific meetings of interest, short courses, and networking opportunities). I will also be available for **additional meetings** as needed to successfully execute the proposed specific aims and training, as well as accessible by phone and e-mail. **Twice a year, we will hold review meetings** including the co-mentors (Drs. Donna Arnett and Tim Garvey), ensuring coordination within our mentoring team and the most effective support for Dr. Aslibekyan's career development. Furthermore, Dr. Aslibekyan and I will continue to **participate in relevant TOPMed conference calls and attend weekly GOLDN research group meetings**, which are also virtually (over Skype or phone) attended by Dr. Donna Arnett—the GOLDN study PI and Dr. Aslibekyan's co-mentor on this application. Dr. Arnett, Dr. Garvey, and I have a fruitful history of collaborating on GOLDN analyses, as evidenced by our publication record. Together, we are committed to the best practices in team science and helping Dr. Aslibekyan realize her remarkable potential. The long-standing relationships between the Department of Epidemiology (Dr. Aslibekyan's primary appointment) and the Section on Statistical Genetics will also ensure that she has the necessary resources to complete the proposed research, including but not limited to programming support, access to a high-performance computer cluster and support staff, and office space. All three mentors on this application are supported by multiple NIH grants.

I would like to highlight that **the proposed K01 research project belongs to Dr. Aslibekyan**, and that she has shown creativity and self-reliance in preparing this proposal. While I and her other mentors have offered some guidance, it was she who posed the questions, developed the research strategy, and prepared the complete application. I was especially impressed with her ability to forge collaborations across cohorts, securing support for replication of her top findings; these skills will serve her well in the era of consortium science. I will fully support her taking the findings and methodological insights from this project and developing her own R01 application during the last two years of the award period.

My enthusiasm for Dr. Aslibekyan's application is underscored by her personal qualities, guaranteed to make her a great role model for other female quantitative scientists. An immigrant who came to this country at 16 years of age to pursue her education, she has jumped through some non-trivial hurdles ranging from immigration red tape to single motherhood. She exhibits standout communication skills, learning agility, and a perennially positive demeanor. She is an exceptionally resilient individual, a collegial collaborator, and overall—true to the etymology of her first name—a rising star. **The NHLBI mentored career development award could not go to a more deserving young investigator**.

Sincerely,

Hemant K. Tiwari, PhD

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May 20, 2016

Dear K01 Review Committee Members,

I am writing to express my highest possible support and enthusiasm for Dr. Stella Aslibekyan's application for an NHLBI K01 Mentored Career Development Award. As her former post-doctoral mentor, department chair, and the PI of the Genetics of Lipid Lowering Drugs and Disease Network (GOLDN), I have come to know her as a researcher of the highest standards, and I am eager to continue our collaboration as her co-mentor on this particular K01. Since the beginning of her post-doctoral fellowship, Dr. Aslibekyan has distinguished herself as a superstar young investigator, quickly earning a promotion to tenure-earning faculty status and passionately working towards independence. The mentorship, training, and research program she proposed in this application comprise the perfect strategy to support her impressive career trajectory.

Throughout my time at UAB, I have found Dr. Aslibekyan to be an exceptionally intelligent, forward-thinking, and focused scientist. These qualities are reflected in her highly innovative research proposal, which integrates the wealth of data currently available in GOLDN to answer a critical question in our field: which heritable factors can explain the tremendous variability observed in the human postprandial lipid response? Her project fully embraces the spirit of the NHLBI Trans-Omics for Precision Medicine (TOPMed) program, and her training plan includes development of key skills for handling the cutting-edge data that GOLDN is receiving through our participation in TOPMed. Through this award opportunity, Dr. Aslibekyan will secure her position at the vanguard of multidimensional data science, leading creative analyses that maximize the potential of the GOLDN and TOPMed resources.

Dr. Aslibekyan possesses several strengths that make her an especially good fit for this project. She is a committed team player with experience on several multi-cohort analyses, exemplified by her 2015 first author publication of an epigenome-wide study of obesity traits. Her collegial nature and superb writing skills make it easy to collaborate across studies—a critical skill for working within a consortium like TOPMed. She is extraordinarily reliable, thoughtfully organized, and goal-oriented. Most importantly, she embodies 'the growth mindset' that is imperative to succeed in science, constantly striving for self-improvement, learning new skills, and reaching for the next big challenge. This mentality is ideal for the K01 award and will serve her well throughout her entire career.

Dr. Aslibekyan and I have an established and prolific mentoring relationship, with dozens of manuscripts published and in progress. Since my departure to the University of Kentucky, we have been meeting biweekly via Skype or phone, in addition to my Skype attendance of weekly

GOLDN team meetings (which include Dr. Hemant Tiwari, Dr. Aslibekyan's primary mentor). I also enjoy offering support and mentorship informally, via regular texts, calls, and instant messaging. During the proposed award period, we will maintain this schedule and add in-person review meetings twice a year. For the latter, I will travel to Birmingham and meet with Dr. Aslibekyan and her other two mentors and my dear colleagues, Drs. Tiwari and Garvey, to facilitate execution of her proposed research program and training plan. I will also continue mentoring Dr. Aslibekyan on issues that are especially germane to women in science, such as balancing a young family and career obligations, leadership training, and networking opportunities. Although I have transitioned to a different institution, I am confident that I can offer effective guidance to Dr. Aslibekyan via the venues described above; after all, we have a successful history of a year-long transcontinental mentorship, necessitated by Dr. Aslibekyan's legal requirement to spend time outside the U.S. in order to become eligible for lawful permanent resident status (granted in 2015).

I am especially excited to mentor Dr. Aslibekyan as she develops her R01 application in years 3 and 4 of the proposed award period. Through the training and research experiences outlined in the current proposal, she will be uniquely prepared to apply integrative –omics approaches to population data available through TOPMed and other consortia. Such large-scale, deeply genotyped and phenotyped studies represent the future of cardiovascular epidemiology, and there is a strong need for investigators who are proficient in 'big data' analyses. I firmly believe that this K01 award can channel Dr. Aslibekyan's high-octane research energy into groundbreaking science. Thus, I offer her my unequivocal recommendation and look forward to following her scientific success.

Sincerely,

Donna K. Arnett

Donna K. Arnett, PhD
Dean and Professor
College of Public Health
University of Kentucky

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

May 20, 2016

National Institutes of Health
Center for Scientific Review
6701 Rockledge Drive MSC 7768
Bethesda MD 20892-7768

Dear Review Committee Members:

It gives me great pleasure to serve as a co-mentor on Dr. Stella Aslibekyan's application for the K01 career development award. She is proposing a truly cutting-edge, integrative analysis of genetic and epigenetic predictors of postprandial changes in lipoprotein subfraction concentrations—a phenotype of considerable interest in my own work. The proposed project offers access to newly generated whole genome sequence data and training in novel analysis methods, putting Dr. Aslibekyan in a position to identify novel heritable contributions to lipoprotein metabolism.

As a physician-scientist with nationally recognized expertise in the molecular and genetic basis of metabolic disorders, I am excited to offer my knowledge and perspective in support of this project. Throughout my career, I have mentored 13 junior faculty with NIH K01, NIH K23, RWJF, Fogarty, and COBRE awards; 15 post-doctoral fellows on NIH T32 and other training grants; 9 clinical fellows pursuing research careers; two MD/PhD students in the Medical Scientist Training Programs; and 20 graduate students as primary mentor in PhD Degree programs. All of the junior faculty members and many of the pre-doctoral and postdoctoral fellows have gone on to become successful independent researchers. As PI of the NIH-funded Diabetes Research Center at UAB, I have strived to enhance the intellectual environment for junior scientists and trainees alike. In my studies of the pathogenesis of insulin resistance and Metabolic Syndrome, I have published work examining the relationship between insulin resistance and lipoprotein subclasses, and initiated Project Sugar which conducted a whole-genome screen for genetic markers associated with diabetes and obesity in Gullah-speaking African Americans living in the low country of South Carolina and Georgia. In fact, Project Sugar has also assessed NMR lipoprotein subclasses as phenotypes in a GWAS study and this could serve to complement Dr. Aslibekyan's observations in GOLDN. On this particular project, I will complement the expertise of Dr. Aslibekyan's other mentors—Drs. Hemant Tiwari and Donna Arnett, by offering clinically informed insights into the primary phenotype of interest, namely NMR-based measurements of lipoprotein subfractions. That includes functional annotation of the top findings from the whole genome sequencing analysis, data interpretation, and generating hypotheses regarding the biological pathway that underlie the observed associations.

I am pleased to note that our prior collaborations with Drs. Tiwari and Arnett on lipoprotein data in GOLDN have paved the way for a smoothly run mentoring experience for Dr. Aslibekyan. I will meet with Dr. Aslibekyan on a quarterly basis to discuss emergent results, her work towards completion of specific aims and the well-thought out training program, and potential follow-up studies. Specifically, in years 3 and 4, I will actively assist Dr. Aslibekyan in preparing her R01 application on integrative –omics of postprandial lipoprotein traits. Additionally, I will join the biannual review meetings with Drs. Tiwari and Arnett to evaluate her overall progress and identify opportunities for further career development.

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Dr. Aslibekyan is a talented, hard-working, passionate young investigator with an outstanding publication history and a keen eye for worthwhile research questions. I firmly believe that integrating data from multiple –omics sources with precise, biologically meaningful phenotypes such as small molecule lipids and lipoprotein subfractions represents the future of metabolic science. Upon successful completion of the proposed K01 project, Dr. Aslibekyan will be able to make critical contributions to understanding individual variation in postprandial lipid metabolism, bringing the promise of personalized medicine closer to fruition. Together with my colleagues, I look forward to mentoring Dr. Aslibekyan in this exciting stage of her career, and I recommend her with the highest level of enthusiasm.

Sincerely,

W Timothy Garvey MD

W. Timothy Garvey, MD
Butterworth Professor and Chair, Department of Nutrition Sciences
Director, UAB Diabetes Research Center
GRECC Investigator and Staff Physician, Birmingham VA Medical Center

UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

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May 21, 2016

RE: Stella Aslibekyan, Ph.D.

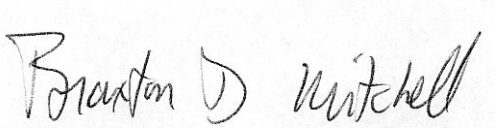
Dear Review Committee Members,

It gives me great pleasure to write this letter in support of Dr. Stella Aslibekyan's application for a K01 Mentored Career Development Award. I am particularly excited about her proposal to use whole genome sequencing data obtained through the NHLBI-WGS TOPMed program, including the Heredity and Phenotype Intervention (HAPI) Heart Study as a replication cohort.

As a senior investigator on the HAPI Heart study and a TOPMed investigator, I will support and guide Dr. Aslibekyan in selecting the best statistical models, oversee replication analyses in the existing HAPI Heart data and provide the summary statistics, and assist her in interpreting the findings. We will monitor progress towards these goals during quarterly Skype meetings as well as regular e-mail contact. Towards the end of the proposed award period, I will also consult her on developing and submitting her first R01 application, exploring further collaborations within TOPMed and beyond.

I have known Dr. Aslibekyan for three years, serving as her mentor in the competitively selected USBJI Young Investigator workshop. She has impressed me with her considerable initiative, dedication, and collaborative approach to science. I believe that the cutting-edge statistical genetics skills she will obtain through the proposed training plan (and honed through application to GOLDN and HAPI Heart data) will be vital for her continued success in the field. Overall, I am very enthusiastic about this K01 application, which holds great promise for Dr. Aslibekyan's development into an independent investigator in the big data era.

Sincerely,



Braxton D. Mitchell, MPH, PhD
Professor of Medicine and of Epidemiology & Public Health
Vice Chair of Research, Division of Endocrinology, Diabetes & Nutrition

UTHealth
The University of Texas
Health Science Center at Houston

School of Public Health

Eric Boerwinkle
Dean
M. David Low Chair in Public Health
Kozmetsky Family Chair in Human Genetics
Professor, Human Genetics Center and Dept. of Epidemiology
Associate Director, Human Genome Sequencing Center at BCM

February 24, 2016

Center for Scientific Review
National Institutes of Health

Dear Review Committee Members,

I am delighted to support Dr. Stella Aslibekyan's timely and novel K01 application, focused on whole genome sequencing (WGS) analysis of postprandial lipemia (PPL) phenotypes. As a principal investigator in the Atherosclerosis Risk in Communities (ARIC) study, I represent one of only three large-scale cohorts with available PPL measurements and strongly agree to provide access to the ARIC resource for the purposes of this project.

Upon successful completion of WGS and quality control in the ARIC study, we will provide access to those participants with PPL measurements. As part of Dr. Aslibekyan's proposed research project, we will perform replication analyses, testing associations between the top 10 genomic regions emerging from the discovery stage, and the PPL phenotypes in the ARIC population.

I believe the proposed analyses of ARIC data will be critical to Dr. Aslibekyan's application for two reasons. First, they will serve to establish reproducibility of her findings, reducing the likelihood of false positive results. Second, because ARIC is the only PPL study that includes minority participants, including these data will increase the diversity of her study population, potentially extending the generalizability of her findings to non-European ethnic groups.

I am genuinely excited for Dr. Aslibekyan's proposal, which takes advantage of the unique WGS resource to considerably advance the current understanding of genetic determinants of postprandial lipid metabolism. I look forward to following the success of this project and Dr. Aslibekyan's career in cardiovascular genomics.

Sincerely,

Eric Boerwinkle, PhD
Dean
M. David Low Chair in Public Health
Kozmetsky Family Chair in Human Genetics
Professor, Human Genetics Center and Dept. of Epidemiology
Associate Director, Human Genome Sequencing Center at BCM

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SCHOOL OF PUBLIC HEALTH
BIOSTATISTICS
UNIVERSITY OF MICHIGAN

June 1, 2016

Dear Review Committee Members:

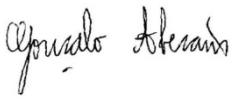
I am pleased to serve as an unpaid consultant on Dr. Stella Aslibekyan's application for a K01 career development award. I strongly believe that her proposed research makes excellent use of the rich Trans-Omics for Precision Medicine (TOPMed) resource, and the proposed training enables her to master cutting-edge skills that would play an essential role in her transition to independence.

In my role as the Director of the NHLBI TOPMed Informatics Resource, I lead a team providing program support for sequence analyses, including cross-cohort harmonization, mapping, calling, and bioinformatics follow-up. As Dr. Aslibekyan undertakes the whole genome sequence analyses described in the first aim of her proposal, my group will provide guidance on the unique opportunities and challenges of the TOPMed data, comprised of deeply sequenced (~30x coverage) genotypes and other –omic layers on an unprecedentedly large number of individuals. We will also facilitate Dr. Aslibekyan's proficiency with the tools we are currently developing to visualize and follow up whole genome sequence findings, including an analysis survey, a rare variant browser, and an imputation server.

To augment Dr. Aslibekyan's training and expand her collaborations in statistical genetics, I have invited her to spend one week with my research group in Ann Arbor in the beginning of her training period. I believe such an intensive hands-on experience will lay the groundwork for truly innovative analyses of TOPMed data, both in the proposed specific aims and in future collaborative research projects. Furthermore, as novel methods for whole genome analysis and/or –omics integration are developed, we would extend Dr. Aslibekyan the opportunity to return for additional interaction to ensure her skills remain on the cutting edge of our field and to provide helpful feedback on the needs of users of IRC-developed tools.

In conclusion, I would like to reiterate my enthusiasm for Dr. Aslibekyan's K01 application. Her proposed research and training plans will arm her with increasingly crucial 'big data' expertise, positioning her for a thriving career as an independent –omics researcher.

Sincerely,



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20 May 2016

To the NHLBI K01 Review Committee:

I am writing to express my enthusiastic support and willingness to contribute to Dr. Stella Aslibekyan's K01 application on integrative –omics of postprandial lipid phenotypes. I have enjoyed a long-standing collaboration with Dr. Aslibekyan and the GOLDN study, and believe her proposal will make a substantial contribution to understanding the role of heritable variation in chronic disease traits.

My primary role as a contributor will be to conduct deep epigenetic phenotyping of 5 candidate regions via bisulfite sequencing on blood samples from 100 individuals. At HudsonAlpha Institute for Biotechnology, my laboratory has the personnel and instrumentation capacity to perform the measurements as described in her proposal, and have done so for other genomic regions of interest in the past using GOLDN samples (Irvin et al., 2014, Circulation). *We will conduct these experiments on a fee-for-service basis at $300/sample, with the total cost of $30,000 evenly split between years 1-3*. I will oversee the handling of the samples, bisulfite sequencing procedures, and all the necessary quality control and cleaning to render these data suitable for analysis.

Dr. Aslibekyan has a sharp and inquisitive mind, an unparalleled drive to succeed, and a personality that lends itself well to research collaborations. I look forward to continuing our work together on this project and wholeheartedly recommend her for this opportunity.

Sincerely,

Devin Absher, PhD
Faculty Investigator
HudsonAlpha Institute for Biotechnology

Institutional Environment

The University of Alabama at Birmingham (UAB) is a doctoral, public research university offering over 140 accredited programs of study leading to bachelor's, master's, doctoral and professional degrees in a wide variety of fields, including health-related fields such as medicine, nutrition, and public health. UAB ranks among the top 15 percent of U.S. colleges and universities by *The Princeton Review*, and is among 96 public and private universities (and the only Alabama university) classified as an institution of "very high research activity" by the Carnegie Foundation. In 2015, UAB researchers received $243 million in NIH grants and contracts, placing UAB 10th in funding among public universities nationwide. The main areas of funding growth include three newly formed research institutes in genomic medicine,
personalized medicine, and informatics—key to Dr. Aslibekyan's proposed research and career development. UAB is also renowned for its supportive workplace environment, as evidenced by its recognition among the Top 5 Best Places to Work in Academia by *The Scientist*.

Resources in genomics research: Dr. Hemant Tiwari, Dr. Aslibekyan's primary mentor, has an appointment in the Section on Statistical Genetics (SSG) in the Department of Biostatistics in the UAB School of Public Health. The SSG, formerly headed by Dr. Tiwari, has a strong commitment to research and methodology development. The SSG sponsors a monthly journal club, grant-writing club and seminar series with presentations by internal and external speakers, often of international renown. The mission of the SSG is to advance knowledge in the field of statistical genetics and in the biological and biomedical sciences through applications of statistical genetics/genomics. To that end, the SSG has developed a cadre of investigators at the faculty, postdoctoral, and graduate student levels that collectively have expertise in several major areas including next-generation sequencing data analysis, bioinformatics, and 'big data' science. The SSG also has a strong track record of integrating individuals with degrees outside of Biostatistics, as well as of collaborating with Dr. Aslibekyan's home department (Epidemiology). The division has a strong commitment to research, with nearly all of the faculty members having at least 80% salary support through extramural funding, providing a rich environment for Dr. Aslibekyan's growth as an investigator.

Computing resources: For distributed computing and parallel programming, Research Computing of UAB offers a Beowulf-style High-Performance Computing (HPC) cluster named Cheaha, which includes compute nodes/cores from four different generation totaling close to 900 computing cores, 3.9TB of RAM, and over 200TB of storage. UAB HPC upgrade has benefits beyond the obvious order-of-magnitude increase in big-memory and storage capability. In particular, because these new nodes are installed as part of the Cheaha cluster and not a completely separate computer, Dr. Aslibekyan will be able to leverage the existing investments in workflow (no change in how tasks/jobs are submitted), storage (no need to painstakingly move data back and forth between different computers), and software (she can continue to rely on the same well-tested, stable version of data analysis programs that she had been using on Cheaha). Additionally, Dr. Aslibekyan will have access to 3 storage 'bricks' of 64TB each, which can accommodate a data back-up solution for the Cheaha resource. Dr. Aslibekyan will be able to use these campus resources to store TOPMed vcf files as well as run memory-intensive data analysis jobs using R software, as she has done in the past; she currently has an account and a home directory on Cheaha that she can use for TOPMed analyses.

Career development resources: UAB has a longstanding commitment to developing junior investigators, including K awardees. For example, the Center for Clinical and Translational Science (CCTS) assists investigators in every aspect of research, from proposal development to data analysis. CCTS also offers monthly seminars and workshops on topics like scientific writing, professional ethics, and career strategies. The CCTS also formed the K-club, bringing together K-awardees across campus in an informal setting to provide them with information on publications, obtaining research funding, and career planning.

The institutional environment at UAB is distinguished by its culture of interdisciplinary collaboration, support for investigators at all levels (and especially junior faculty), and a robust history of federally funded research. Together, these elements provide an exceptional context for Dr. Aslibekyan's research and training plans, ensuring her opportunities to thrive during and after the award period.

UAB SCHOOL OF PUBLIC HEALTH

May 18, 2016

Dear Review Committee Members:

I am writing to confirm our exceptionally strong institutional commitment to Dr. Stella Aslibekyan, who has served as a full-time, tenure-earning assistant professor in the Department of Epidemiology since October 1, 2013. As described in her Mentored Career Development Award (K01) proposal, our department will provide solid support for Dr. Aslibekyan to devote the proposed protected time for research and career development for the entire 4 years of the award period. Specifically, the institution will provide Dr. Aslibekyan the facilities and resources necessary for a structured research career development experience (independent of this Career Development Award). Without any reservations, the UAB Department of Epidemiology is committed to Dr. Aslibekyan's growth as a scientist and her transition to independent research.

Because Dr. Aslibekyan is a population researcher and not a clinical scientist, she will not have any clinical duties during the grant period. Furthermore, she will have limited teaching and administrative responsibilities to allow for at least 75% of her time to be protected for research and career development activities during the entire award period.

Dr. Aslibekyan will be provided with office space and support staff, and access to substantial computational power (including the high performance computing cluster, computing time, and staff) needed to accomplish her proposed research plan. The Department of Epidemiology collaborates closely with the Section on Statistical Genetics, which employs seven full-time programmers and several part-time and contract programmers. The Department of Epidemiology also has a full-time programmer with extensive experience in genomic and epigenomic analyses. All of these staff and resources will be available to Dr. Aslibekyan to help her with her scientific project. The aforementioned individuals are highly skilled and work almost exclusively on statistical genetics and epigenetics projects, so they represent an extremely useful resource.

UAB, through the submission of the application, certifies that all items outlined above will be provided and that we will abide by the applicable assurances and PHS policies.

We highly recommend Dr. Aslibekyan for this K01 award, and our institution will be delighted to support her development into an independent, cutting edge, big data investigator.

Sincerely,

Gerald McGwin, MS, PhD
Professor and Chair, Department of Epidemiology

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Protection of Human Subjects

a. Human subjects involvement, characteristics, and design: Completion of all three specific aims involves only archived specimens collected from GOLDN and HAPI Heart participants, and does not involve any new sample collection or contact with study participants. Included in the proposed research are data and specimens from 1048 GOLDN and 828 HAPI Heart participants that have whole genome sequence and phenotypic data. Participants were originally recruited from the Minnesota and Utah sites of the NHLBI Family Heart Study (GOLDN) and prior cardiovascular health studies in the Old Order Amish communities of Lancaster County, PA (HAPI Heart). The GOLDN Study has been approved by the University of Alabama at Birmingham Committee on the Use of Human Subjects, as well as collaborating institutions. HAPI Heart was approved by the Institutional Review Board of the University of Maryland, Baltimore, and other participating institutions and is monitored by an external Data Safety and Monitoring Board. Informed consent was obtained before participation. In the current study, the only new measurements (namely bisulfite sequencing) will be conducted on ~100 GOLDN participants with currently available RNASeq measurements. All other analyses involve existing data and aim to: 1) identify novel genetic predictors of postprandial lipoprotein subfraction changes using whole genome sequence data; 2) evaluate associations between postprandial changes in lipoprotein subfractions and small molecule lipids, and identify any shared genetic determinants between those phenotypes; 3) assess whether methylation (as measured by bisulfite sequencing) and transcription (RNASeq, existing data) patterns in the top genomic regions play a role in postprandial lipoprotein variation.
b. Sources of materials: No new data will be collected from human subjects over the course of the proposed study. DNA will be isolated and bisulfite sequencing will be performed from existing, currently stored whole blood samples. Each sample from GOLDN and HAPI Heart participants has a unique study identification number. Neither Dr. Aslibekyan nor HudsonAlpha Institute for Biotechnology, who will perform the aforementioned laboratory procedures, will be able to link these study identification numbers with any individually identifiable private information.
c. Potential risks: There are minimal risks to any of the participants in the proposed study because the specimens have already been collected and de-identified; Dr. Aslibekyan will not have access to any individually identifiable private information for the purposes of this study. Additionally, all data will be securely stored in a folder on the School of Public Health database server with restricted access and protected by passwords and data encryption. Therefore, the likelihood for unintentional disclosure of genetic or phenotypic data, which could result in distress or discrimination, is extremely low.

Inclusion of Women and Minorities

Inclusion and exclusion criteria for the GOLDN Study and HAPI Heart did not restrict or preferentially admit participants based on sex. In the current study, approximately half of all participants are female. All GOLDN participants were self-reported Caucasian, as that was the Family Heart Study recruitment base from which the study drew. The HAPI Heart study recruited only (Caucasian) Old Order Amish, a unique, closed founder population who are relatively genetically homogeneous, and have very large family sizes and well documented genealogies and, therefore, uniquely suited for genetic analysis. GOLDN's and HAPI Heart's focus on a Caucasian population was considered scientifically acceptable when originally funded because PROGENI—the parent program—had representation of African Americans and Chinese populations in the other funded projects.

PHS Inclusion Enrollment Report

This report format should NOT be used for collecting data from study participants.

OMB Number:0925-0001 and 0925-0002
Expiration Date: 10/31/2018

***Study Title:** Integrative -omics study of postprandial lipoprotein phenotypes

***Delayed Onset Study?** ❑ Yes ☑ No

If study is not delayed onset, the following selections are required:

Enrollment Type ❑ Planned ☑ Cumulative (Actual)

Using an Existing Dataset or Resource ☑ Yes ❑ No

Enrollment Location ☑ Domestic ❑ Foreign

Clinical Trial ❑ Yes ☑ No

NIH-Defined Phase III Clinical Trial ❑ Yes ☑ No

Comments: This study consists of participants from the following two studies: GOLDN: 1048 total, all Caucasian, 546 women and 502 men HAPI HEART: 838 total, all Caucasian, 382 women and 456 men

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/Alaska Native	0	0	0	0	0	0	0	0	0	**0**
Asian	0	0	0	0	0	0	0	0	0	**0**
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	**0**
Black or African American	0	0	0	0	0	0	0	0	0	**0**
White	928	958	0	0	0	0	0	0	0	**1886**
More than One Race	0	0	0	0	0	0	0	0	0	**0**
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	**0**
Total	**928**	**958**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1886**

Report 1 of 1

Funding Opportunity Number: PA-16-190. Received Date: 2016-06-09T16:27:00.000-04:00

Inclusion of Children

Participants 18 years or older were included in GOLDN, and 20 years or older in HAPI Heart. No participants under the age of 18 were allowed to participate in either arm of GOLDN. No participants under the age of 20 were allowed to participate in the HAPI Heart Study.

Resource Sharing Plan

As the proposed research makes use of the TOPMed data, all analyses involving WGS data will follow the data sharing procedures outlined by the program. Specifically, at the end of the 6-month embargo period since the receipt of the genomic data, during which I will conduct the proposed analyses and prepare the publications, I will deposit redacted and de-identified data through an NHLBI data repository such as dbGAP as per TOPMed policy. Additionally, we will share raw data generated by bisulfite sequencing (namely, quantitative DNA methylation levels in candidate genomic regions) as supplementary materials in publications resulting from the proposed research. While this constitutes my current plan, I will work closely with NHLBI program stuff to devise additional approaches ensuring that the needs of the Institute are met.

Authentication of Key Biological and/or Chemical Resources

All assays and chemistry that will used for analysis of samples for this study will make use of standardized and commercially available materials. No new biological or chemical resources are being created. DNA methylation analysis conducted by HudsonAlpha uses standardized chemistry and bisulfite sequencing procedures that are used consistently for all similar analysis, and methodologies have been published extensively in the literature.