ARIC Manuscript Proposal # 3200

PC Reviewed: 7/10/17 Status: _____ Priority: 2
SC Reviewed: _________ Status: _____ Priority: _____

1.a. Full Title: Methylome-Wide Association Study of Hyperlipidemia, Hypertension, and Diabetes Medications

   b. Abbreviated Title (Length 26 characters): Medications EWAS

2. Writing Group:
   Writing group members: Amanda A Seyerle, Steve Nguyen, James Pankow, Ellen Demerath. Additional interested investigators welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _AAS_____ [please confirm with your initials electronically or in writing]

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4. Rationale: In recent years, personalized medicine has been promoted as a tailored approach towards individual health which includes improving patient responses to drug therapies. The National Center for Health Statistics reports that nearly half of Americans uses at least one prescription drug and that the most common prescribed drugs are for hyperlipidemia and diabetes [1]. Additionally, there is variability in drug response.
Statins were associated with incident diabetes mellitus in post-menopausal women in the Women’s Health Initiative (WHI); the association was higher in Whites (Hazard Ratio [HR]=1.49), Hispanics (HR=1.57), and Asians (HR=1.78) than in Blacks (HR=1.18) [2, 3]. In the National Health and Nutrition Examination Survey (NHANES), Blacks had less hypertension control (Odds Ratio [OR] = 0.73) compared to Whites (OR=1.29) despite receiving more intensive drug therapy, such as polytherapy [4]. In the Treatment Options for Type II Diabetes in Adolescents and Youth (TODAY) study, metformin with rosiglitazone was more effective in girls compared to boys in achieving a glycated hemoglobin level of less than 8 percent, and treatment failure, defined as a persistently elevated glycated hemoglobin level of greater than 8 percent, was higher in non-Hispanic Blacks (52.8%) versus non-Hispanic Whites (36.6%) and Hispanics (45.0%) [5]. Thus an increased understanding of drug response in various groups is needed to further develop personalized medicine.

One area of focus in personalized medicine is investigating the contributions of genetics to differences in drug response. However the literature suggests that genetics explains a small proportion of the inter-individual variation in phenotypes, which could extend to drug response [6]. Still, some genetic variants have been observed to be associated with drug response such as in SLC01B1, which modifies the risk of myopathy among statin users, prompting the Clinical Pharmacogenetics Implementation Consortium (CPIC) to establish prescription recommendations for SLC01B1 genotypes [7]. In the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) trial, a variant in ALDH1A2 was associated with uncontrolled blood pressure in patients on combination therapy with a thiazide diuretic and beta-blocker [8]. Although drug response-related genetic variants have been identified, other potential sources of inter-individual variation in drug response need to be investigated. Multiple explanations and approaches have been suggested to explain the missing heritability including rare variants, variants with effects too small to detect, inadequate control for shared environmental factors, and more recently, the role of epigenetics [9].

Epigenetics, the study of changes in gene transcription and expression not involving changes to the base sequence, may be involved in drug absorption, distribution, and metabolism. Epigenetic modifications can be influenced by both genetic and environmental factors, suggesting a mechanism for the interaction of the genome with external environment and potential drug targets [10]. The most studied form of epigenetic modification, DNA methylation, involves the addition of a methyl group on the cytosine of cytosine-guanine dinucleotides (CpG). DNA methylation is essential for normal human development and gene function and is a key mechanism for environmental regulation of gene expression [11]. CpG methylation in gene promoters can affect gene expression by affecting the binding of transcription factors, thus influencing phenotypes. Epigenome-wide association studies (EWAS) have identified multiple CpG sites associated with phenotypes such as adiposity, blood pressure, and diabetes, which have genetic and environmental components [12-14]. Although EWAS are often cross sectional in nature, Mendelian randomization analysis using genotype data can be used to estimate causal effects [15].

DNA methylation changes may be influenced by hyperlipidemia, hypertension, and diabetes medications and mediate drug actions as suggested for statins in cultured cell studies [16]. However, the association of these medications with DNA methylation in
Recently, investigators in the Framingham Heart Study (FHS) carried out a medications EWAS and approached Atherosclerosis Risk in Communities (ARIC) study investigators for replication. This proposal will be a replication of the FHS medications EWAS to replicate their findings and identify medication-related DNA methylation. The identification and characterization of the medication-DNA methylation association via EWAS may yield more insight in drug response variability to further develop personalized medicine.

5. **Main Hypothesis/Study Questions**: This proposal is for a replication of a medications EWAS carried out by FHS investigators. This proposal will identify and characterize DNA methylation probes associated with medications used to treat hyperlipidemia, hypertension, and diabetes. We will additionally use existing genotype and phenotype data to infer causal effects using a Mendelian randomization approach.

6. **Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present)**

This proposal will be conducted in collaboration with studies with medication use data, DNA methylation data, and phenotype data through the Cohorts for Heart and Aging Research using Genomic Epidemiology (CHARGE) consortium.

This analysis will use a cross sectional study design using data from ARIC visits 1, 2, and 3. Demographic data was recorded at visit 1 while DNA methylation data was mainly measured at visit 2, or visit 3 for a subset of participants. Phenotype data will come from visits 2 and 3, the same visit as when DNA methylation was measured, as with medication use data. Participants with prevalent MI or stroke will be excluded from analyses.

To identify significant CpGs associated with medications, two linear regression models will be used:

\[ Y_i = B_0 + B_1 \text{Risk} + B_2 \text{Medications} + B_3 C_i \]

\(Y_i\) is CpG methylation, \(B_0\) is the intercept, Risk refers to CVD risk factors such as blood pressure for hypertension medications, lipid levels for hyperlipidemia medications, and fasting blood glucose for diabetes medications. Medications refer to medications use and \(C_i\) refers to covariates. The main parameter of interest in this proposal is \(B_2\). These models will be run separately for each CpG and for African American and European American participants. Model 1 will contain participant age, sex, educational attainment, income, physical activity, smoking status, alcohol use, CVD risk factors, medications use, white blood cell count, and technical covariates. Model 2 will additionally contain
BMI and imputed white blood cell type proportions estimated using the Houseman et al. method [17].

For CpGs significantly associated with medications use, genotype data will be used to estimate causal effects on the phenotype targeted by drug use, using a Mendelian randomization analysis [15].

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ Yes  ____ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used?  ____ Yes  ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?  ____ Yes  ____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  ____ Yes  ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscce.unc.edu/ARIC/search.php

 __X__ Yes  ______ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

This manuscript proposal is related to two manuscript proposals entitled “Pharmacoepigenomics: Human population studies of DNA methylation and satins treatment response” submitted by James Floyd and “Epigenetic Characterization of Statin Use and Diabetes Association in Multiethnic Populations” submitted by Amanda Seyerle. The main hypothesis of James Floyd’s and Amanda Seyerle’s proposal is that pre-existing methylation levels modify statin response while this proposal examines the effect of statins on methylation. All author groups are in contact with each other as the manuscripts move forward.
11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  ___ Yes  ___ No

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study (list number* __________)
___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

References


