**ARIC Manuscript Proposal #2407**

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| **PC Reviewed: 8/12/14** | **Status: A** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: Genetic Determinants of Sporadic Thoracic Aortic Aneurysm and Dissection

**b. Abbreviated Title (Length 26 characters)**: Genetics of STAAD

**2. Writing Group**:

Writing group members:
Donchuan Guo
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Dianna Milewicz

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


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**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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**3. Timeline**: June 1, 2014 to May 31, 2015
*We anticipate publication of results within one year of approval of this proposal.*

**4. Rationale**:

*The goal of this study is to identify rare variants in genes that predispose patients to sporadic aortic aneurysms and dissections (STAAD). To identify rare variants, genes, or pathways that contribute to pathogenesis of STAAD, we have genotyped primarily rare variants on 800 patients of European descent with STAAD using the Illumina HumanExome BeadChip ("exome chip"). The same exome chip has been used to genotype approximately 13,000 individuals in the ARIC cohort. Therefore, we propose to perform a case-control association study using the data available in the ARIC cohort as controls which will be matched based on age, gender, ethnicity, and clinically relevant phenotypes.*

**5. Main Hypothesis/Study Questions**:

*The Main hypothesis of this project is that rare functional genomic variants predispose patients to STAAD. The goal of this project is to identify rare variants, genes, or pathways that contribute to pathogenesis of STAAD. Identification of genes and pathways will provide information necessary for defining the molecular mechanisms of genetic factors that contribute to the pathogenesis of STAAD.*

**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).**

*The major diseases affecting the ascending thoracic aorta are thoracic aortic aneurysms and aortic dissections which are associated with high mortality and morbidity. Approximately 80% of patients with TAAD do not have a genetic syndrome or family history of the diseases, termed STAAD. We recently conducted a three-stage single nucleotide polymorphism based genome-wide association study using three sets of samples from European American (EA) patients and identified one locus, 15q21.1*[1]*. To further investigate whether rare exome variants, genes, or pathways contribute to the pathogenesis of STAAD, we intend to perform a case-control association study using the exome chip.*

*We propose to select individuals from ARIC to serve as controls for the STAAD study. A member of Dr. Boerwinkle's team at UT Houston will match 1 STAAD case to 3 ARIC controls (2 hypertensive, 1 normotensive) using gender after exclusion on the following ARIC individuals: exome chip data not available, non-white, ictder03 DNA exclusion not equal to "Full Consent", participant had a MI or stroke before age 65, and subject had prevalent CHD or stroke.*

*The exome chip was created to comprehensively evaluate rare coding variants. The exome chip contains ~250,000 coding variants discovered through exome sequencing in approximately 12,000 individuals. In addition, the array includes many common genome-wide association study (GWAS) variants previously associated with cardiovascular disease. Collectively, the array represents nearly all non-synonymous coding and splice-*

*site variation with a minor allele frequency (MAF) > 0.001 in the European population. The exome chip has already been genotyped in both ARIC and STAAD. Rare variant calling methods and quality control analyses were performed independently in both the ARIC and STAAD studies in accordance with the CHARGE Exome Chip Best Practices Calling Protocol[2] and using the CHARGE analysis committee guidelines.*

*All analyses will be performed by Dr. Boerwinkle's statistician, thus individual genetic data for ARIC participants will not be shared outside the ARIC DNA laboratory. Analytical results will be shared for publication purposes. seqMeta (http://cran.r-project.org/web/packages/seqMeta/index.html) will be used for analyses which includes both single variant and gene-based tests (SKAT and T1) for variants with a MAF < 0.01. dbNSFP[3] was used for annotation of variants on the exome chip, and the resulting SNP info v5 file (http://www.chargeconsortium.com/main/exomechip) will be used to define the genes in the burden tests. Principal components will be calculated with EIGENSTRAT[4], and will be included in analyses to adjust for potential population admixture. All individuals included in this study are of European descent, thus race stratification is not necessary. Combined and stratified analyses (by dissection type A and B), will include the following covariates: age, gender, and PCs 1 and 2. Additionally, we will use results from an Ingenuity pathway analyses of the STAAD individuals (not published) to define the region of interest for the burden test.*

**REFERENCES:**


1. Lemaire, S.A., McDonald, M.L., Guo, D.C., Russell, L., Miller, C.C., 3rd, Johnson, R.J., Bekheirnia, M.R., Franco, L.M., Nguyen, M., Pyeritz, R.E., et al. (2011). Genome-wide association study identifies a susceptibility locus for thoracic aortic aneurysms and aortic dissections spanning FBN1 at 15q21.1. *Nature Genetics* 43, 996-1000.
2. Grove, M.L., Yu, B., Cochran, B.J., Haritunians, T., Bis, J.C., Taylor, K.D., Hansen, M., Borecki, I.B., Cupples, L.A., Fornage, M., et al. (2013). Best practices and joint calling of the HumanExome BeadChip: the CHARGE Consortium. *PLoS One* 8, e68095.
3. Liu, X., Jian, X., and Boerwinkle, E. (2013). dbNSFP v2.0: a database of human non-synonymous SNVs and their functional predictions and annotations. *Hum Mutat* 34, E2393-2402.
4. Price, A.L., Patterson, N.J., Plenge, R.M., Weinblatt, M.E., Shadick, N.A., and Reich, D. (2006). Principal components analysis corrects for stratification in genome-wide association studies. *Nature Genetics* 38, 904-909.


**7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __X__ 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? __X__ 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?**
**__X__ 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"?**
**__X__ 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.cscc.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)?**
*The most related ARIC manuscript proposal is titled "Genome wide association (GWAS) and candidate gene approach to identify relationship between SNP's and aortic and carotid diameter measurements in the ARIC Study" (MS#1598). The aforementioned study hypothesized that common genetic variants in seven candidate genes would "have an effect on aortic root diameter taken as quantitative trait" for susceptibility to thoracic aortic aneurysm and dissection. This proposal is significantly different as we are proposing to primarily use ARIC exome chip data as a matched control dataset for an independent STAAD case study.*

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No**

**11.b. If yes, is the proposal**
**____ A. primarily the result of an ancillary study (list number* _____)**
**__X__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* (2009.12)**

*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.