ARIC Manuscript Proposal # 1650

PC Reviewed: 5/11/07	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Generalization of genome-wide association study findings for blood pressure to orthostatic hypotension traits in individuals of European and African ancestry.

b. Abbreviated Title (Length 26 characters): Generalization of blood pressure genetic findings to orthostatic hypotension

2. Writing Group: Nora Franceschini, Kathryn M Rose, Kari E North, Aravinda Chakravarti, Eric Boerwinkle, Gerardo Heiss, and other interested investigators.

Collaborators: Dr Artur Fedorowski and Dr Olle Melander, investigators of the Malmö Preventive project and other investigators of the ICBP consortium.

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

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3. Timeline: All genotyping is complete. Analyses to begin immediately

4. Rationale: Orthostatic hypotension (OH), a manifestation of autonomic dysfunction, was associated with incident hypertension [1], coronary heart disease [2], stroke [3] and increased mortality [4] among ARIC participants. For example, ARIC participants with OH at baseline had a 2-fold increase in risk of dying from cardiovascular disease (CVD) and a 2-fold increase in risk of dying of other causes, unrelated to cancer, including kidney disease [4].

Supine and standing blood pressure measurements were taken at ARIC Visit 1 during the carotid ultrasound examination and are available on ~ 13000 participants. The blood pressure response to a change in posture was normally distributed (a mean ~0 for SBP), with a substantial portion of individuals having either strong blood pressure increases or decreases [5].

Recently, several GWAS of blood pressure traits have been published, mostly in individuals of European ancestry [6 7, 8]. Ongoing analyses of the ICBP consortium have identified additional blood pressure genetic variants. We propose to study the association of published and unpublished (from ICBP) genome-wide variants of blood pressure traits with postural changes in blood pressure using both quantitative orthostasis blood pressure measures and the categorical outcome of OH.

5. Main Hypothesis/Study Questions: Investigate the association of genome-wide variants for blood pressure traits and postural changes in blood pressure or OH in individuals of European and African ancestry.

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).

Subjects: Individuals of European and African ancestry with supine and standing t blood pressure measures.

Exclusions: missing data on supine and standing blood pressure, age, sex and genetic variants.

Exposure: candidate genetic variants identified in GWAS of blood pressure traits

Outcome: OH will be defined as a decrease in systolic blood pressure of 20 mm Hg or more, or a decrease in diastolic blood pressure of 10 mm Hg or more per established guidelines [9]. We will also investigate the association of genetic variants with quantitative measures of orthostatic changes in SBP and DBP.

Study design: Cross-sectional analysis of prevalent OH and continuous postural changes in systolic and diastolic blood pressures.

Statistical analyses*:* We will use additive models (1 df) adjusted for sex, age, and center. Further analysis will adjust for sex, age, center, education, resting, seated SBP, smoking status, alcohol use, HDL and LDL cholesterol, physical activity, BMI, resting heart rate, and history of diabetes, CHD, and stroke.

Statistical significance: expected false discovery rate adjustment (1/ number of tests

performed) (~10^{-7})
Validation and Replication: We will pursue validation/replication of findings by genotyping selected variants in existing databases with measures of postural changes in blood pressure (eg, HyperGEN) and the Malmö Preventive project.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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)?

ARIC manuscript #361A, Rose K. Orthostatic hypotension and the incidence of coronary heart disease: The Atherosclerosis Risk in Communities Study.
ARIC manuscript # 768. Rose, K. Orthostatic Hypotension Predicts Mortality in Middle-Aged Adults.The Atherosclerosis Risk in Communities (ARIC) Study
ARIC manuscript #1415. Franceschini, N. Genome-wide Association Study of Orthostatic Hypotension in individuals of European Ancestry and in African descent– The ARIC 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* _ _2006.03_____)

___ 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/

12. 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.

References:

1. Rose KM, Holme I, Light KC, Sharrett AR, Tyroler HA, Heiss G. Association between the blood pressure response to a change in posture and the 6-year incidence of hypertension: prospective findings from the ARIC study. *J Hum Hypertens.* 2002;16(11):771-777.

2. Rose KM, Tyroler HA, Nardo CJ, Arnett DK, Light KC, Rosamond W, Sharrett AR, Szklo M. Orthostatic hypotension and the incidence of coronary heart disease: the Atherosclerosis Risk in Communities study. *Am J Hypertens.* 2000;13(6 Pt 1):571-578.

3. Eigenbrodt ML, Rose KM, Couper DJ, Arnett DK, Smith R, Jones D. Orthostatic hypotension as a risk factor for stroke: the atherosclerosis risk in communities (ARIC) study, 1987-1996. *Stroke.* 2000;31(10):2307-2313.

4. Rose KM, Eigenbrodt ML, Biga RL, Couper DJ, Light KC, Sharrett AR, Heiss G. Orthostatic hypotension predicts mortality in middle-aged adults: the Atherosclerosis Risk In Communities (ARIC) Study. *Circulation.* 2006;114(7):630-636.

5. Nardo CJ, Chambless LE, Light KC, Rosamond WD, Sharrett AR, Tell GS, Heiss G. Descriptive epidemiology of blood pressure response to change in body position. The ARIC study. *Hypertension.* 1999;33(5):1123-1129.

6. Newton-Cheh C, Johnson T, Gateva V, Tobin MD, Bochud M, Coin L, Najjar SS, Zhao JH, Heath SC, Eyheramendy S, Papadakis K, Voight BF, Scott LJ, Zhang F, Farrall M, Tanaka T, Wallace C, Chambers JC, Khaw KT, Nilsson P, van der Harst P, Polidoro S, Grobbee DE, Onland-Moret NC, Bots ML, Wain LV, Elliott KS, Teumer A, Luan J, Lucas G, Kuusisto J, Burton PR, Hadley D, McArdle WL, Brown M, Dominiczak A, Newhouse SJ, Samani NJ, Webster J, Zeggini E, Beckmann JS, Bergmann S, Lim N, Song K, Vollenweider P, Waeber G, Waterworth DM, Yuan X, Groop L, Orho-Melander M, Allione A, Di Gregorio A, Guarrera S, Panico S, Ricceri F, Romanazzi V, Sacerdote C, Vineis P, Barroso I, Sandhu MS, Luben RN, Crawford GJ, Jousilahti P, Perola M, Boehnke M, Bonnycastle LL, Collins FS, Jackson AU, Mohlke KL, Stringham HM, Valle TT, Willer CJ, Bergman RN, Morken MA, Doring A, Gieger C, Illig T, Meitinger T, Org E, Pfeufer A, Wichmann HE, Kathiresan S, Marrugat J, O'Donnell CJ, Schwartz SM, Siscovick DS, Subirana I, Freimer NB, Hartikainen AL, McCarthy MI, O'Reilly PF, Peltonen L, Pouta A, de Jong PE, Snieder H, van Gilst WH, Clarke R, Goel A, Hamsten A, Peden JF, Seedorf U, Syvanen AC, Tognoni G, Lakatta EG, Sanna S, Scheet P, Schlessinger D, Scuteri A, Dorr M, Ernst F, Felix SB, Homuth G, Lorbeer R, Reffelmann T, Rettig R, Volker U, Galan P, Gut IG, Hercberg S, Lathrop GM, Zelenika D, Deloukas P, Soranzo N, Williams FM, Zhai G, Salomaa V, Laakso M, Elosua R, Forouhi NG, Volzke H, Uiterwaal CS, van der Schouw YT, Numans ME, Matullo G, Navis G, Berglund G, Bingham SA, Kooner JS, Connell JM, Bandinelli S, Ferrucci L, Watkins H, Spector TD, Tuomilehto J, Altshuler D, Strachan DP, Laan M, Meneton P, Wareham NJ, Uda M, Jarvelin MR, Mooser V, Melander O, Loos RJ, Elliott P, Abecasis GR, Caulfield M, Munroe PB. Genome-wide association study identifies eight loci associated with blood pressure. *Nat Genet.* 2009.

7. Levy D, Ehret GB, Rice K, Verwoert GC, Launer LJ, Dehghan A, Glazer NL, Morrison AC, Johnson AD, Aspelund T, Aulchenko Y, Lumley T, Kottgen A, Vasan RS, Rivadeneira F,

Eiriksdottir G, Guo X, Arking DE, Mitchell GF, Mattace-Raso FU, Smith AV, Taylor K, Scharpf RB, Hwang SJ, Sijbrands EJ, Bis J, Harris TB, Ganesh SK, O'Donnell CJ, Hofman A, Rotter JI, Coresh J, Benjamin EJ, Uitterlinden AG, Heiss G, Fox CS, Witteman JC, Boerwinkle E, Wang TJ, Gudnason V, Larson MG, Chakravarti A, Psaty BM, van Duijn CM. Genome-wide association study of blood pressure and hypertension. *Nat Genet.* 2009.

8. Adeyemo A, Gerry N, Chen G, Herbert A, Doumatey A, Huang H, Zhou J, Lashley K, Chen Y, Christman M, Rotimi C. A genome-wide association study of hypertension and blood pressure in African Americans. *PLoS Genet.* 2009;5(7):e1000564.

9. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. *Neurology.* 1996;46(5):1470.