1.a. Full Title:
Beta(2)-adrenergic receptor (ADRB2) genetic polymorphism (does not modify) modifies the effect of physical activity on hypertension

b. Abbreviated Title (Length 26 characters):
ADRB2 & physical activity & HTN

2. Writing Group:
Writing group members: Eric Boerwinkle, Kelly Evenson, Aaron Folsom (welcome suggestions of other members)

First author: Corinne Aragaki
Address: Human Genetics Center
UT School of Public Health
University of Texas Health Science Center at Houston,
1200 Herman Pressler Drive, Suite RAS-E511
Houston, Texas 77030

Phone: 713-500-9915   Fax: 713-500-0900
E-mail: Corinne.C.Aragaki@uth.tmc.edu

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author): Eric Boerwinkle
Address: Human Genetics Center
UT School of Public Health
University of Texas Health Science Center at Houston,
1200 Herman Pressler Drive, Suite RAS-E447
Houston, Texas 77030

Phone: 713-500-9800   Fax: 713-500-0900
E-mail: Eric.Boerwinkle@uth.tmc.edu

3. Timeline:
Begin analysis: September 2005
First draft: December 2005

4. Rationale:
Coronary heart disease (CVD) is the leading cause of death in the US (60% of overall mortality). An estimated 34% of all Americans, or 70 million, have CVD with an estimated 927,000 deaths per year at an estimated cost of $393 billion for 2005 (American Heart Association 2005). Identified risk factors for CVD include hypertension, physical inactivity, family history, and obesity.

Hypertension is a major risk factor for coronary heart disease and death. An estimated 30.1% of all Americans have hypertension (NCHS, 1999-2002). Primary prevention and management of hypertension include major lifestyle modifications: weight reduction, physical activity, and diet (JNC VII). Physical activity has been demonstrated to reduce hypertension risk. However, not all physically active adults are normotensive, which indicates that there potential genetic factors that alter the effect of physical activity on hypertension.

Beta(2)-adrenergic receptor (ADRB2) is a G protein-coupled receptor expressed in cardiac tissue. Polymorphisms in ADRB2 have been shown to be associated with heart failure, hypertension, and obesity, but the results are inconsistent. We focus on two non-synonymous single nucleotide polymorphisms (SNPs) in ADRB2: an A to G substitution at position 46 that leads to an arginine to glycine change at amino acid 16 and a C to G substitution at position 79 that leads to an glutamine to glutamic acid change at amino acid 27. Both of these polymorphisms have been shown to alter agonist-induced down-regulation and have been associated with hypertension. While there are no current studies about the interaction between ADRB2 and physical activity on hypertension, there have been a few small studies in obese women which have shown that physiologic response to physical activity can differ dependent on ADRB2 genotype.[1-4]

The Atherosclerosis in Communities (ARIC) cohort study was conducted to find the causes of cardiovascular disease. This paper examines single nucleotide polymorphisms (SNPs) in the ADRB2 and their interaction with exercise on hypertension in the ARIC cohort.

5. Main Hypothesis/Study Questions:
   Does ADRB2 genotype modify the effects of physical activity on hypertension?
   1. Is the effect of physical activity on baseline systolic and diastolic blood pressures different for subjects of differing ADRB2 genotypes?
   2. Is the effect of physical activity on change in systolic and diastolic blood pressures from baseline to visit 4 differ for subjects of differing ADRB2 genotypes?
      a. Change will be measured as incident hypertension as well as blood pressure change on those who are normotensive.

6. Data (variables, time window, source, inclusions/exclusions):
   Inclusion: ARIC cohort
   Outcome(s) of interest: baseline systolic and diastolic blood pressure and change in systolic and diastolic blood pressure during ARIC study (difference between baseline and Visit 4 systolic and diastolic blood pressure).
   Exposure of interest: physical activity as measured by work physical activity index and sports physical activity index.
SNP modifier of interest: ADRB2 Gly27Glu and Gly16Arg polymorphisms

Potential confounding factors: age, race, gender, center, education, anti-hypertensive medication use, BMI and WHR, energy intake, smoking status, and alcohol consumption measured at baseline and at Visit 4.

7.a. Will the data be used for non-CVD analysis in this manuscript?  
   _X___ Yes  
   ____ 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?  
   _X__ 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)?

   #422: Physical activity and incidence of hypertension in men and women (published in Pereira et al. 1999):  Pre-visit 4 and without ADRB2 SNP

   #1070: β2-adrenergic receptor, α-adducin, and G-protein β3 subunit polymorphisms and retinal microvascular signs (lead author: Tien Wong):  differing endpoints and no interaction proposed with physical activity

   #459: The relationship between physical activity to incident hypertension: The ARIC study (withdrawn, lead author: Kelly Evenson):  Pre-visit 4 and without ADRB2 SNP
#814: ADRB2, asthma, and obesity (lead author: Molly Bray): differing endpoints and no interaction proposed with physical activity

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
   _X_ A. primarily the result of an ancillary study (list number* __8__)
   ___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________)

8: Gene-environment interaction in CVD
*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


