1.a. Full Title:
Factor H Variant FY402 and the prevalence of hypertension and proteinuria: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):
FY402Htnproteinuria

2. Writing Group:
Writing group members Marta Suárez, Kelly Volcik, Michael Braun, Josef Coresh Eric Boerwinkle.

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

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3. Timeline:
January 2008 Submission of Proposal
January-March 2008 Data Analysis
April 2008 Submit for publication
4. **Rationale:**

A major risk factor for the development of heart disease is hypertension (1). The effects of hypertension are assessed by evaluating end organ damage. End organ damage in hypertension is associated with cardiovascular structure alterations secondary to the sustained elevation in blood pressure to different organs including the heart (left ventricular hypertrophy), vasculature (e.g. carotid intimal-media thickness) and the kidney (elevated creatinine or presence of microalbuminuria). Microalbuminuria is one marker for end organ damage in hypertension. It has also been described as a predictor of cardiovascular disease (2, 3) in both the diabetic and non diabetic population. The Steno hypothesis by Deckert et al proposed that albumin leakage results from endothelial dysfunction and vasculature damage; meaning that microalbuminuria reflects damage to the glomeruli and cardiovascular disease reflects systemic vascular injury (4).

Expanding on the Steno hypothesis it has been suggested that individuals are born with different levels of vascular function and this renders them more or less susceptible to vascular injury (5). A potential candidate gene polymorphism that may play a role in susceptibility to hypertension and endothelial damage is the Complement Factor H FY402 SNP. Factor H is a plasma protein that participates in the regulation of the alternative complement pathway. Haines et al and Edwards et al both independently reported the association of the Factor H Y402 polymorphism to be highly associated with a higher risk of age related macular degeneration (RR 2.7 Edwards, 2.45 Haines) (6,7). The FY402H polymorphism has been studied in other disease process like ischemic heart disease (8). Since Factor H is a regulator of the alternative complement pathway it is hypothesized that this leads to inflammation and damage to host tissues. While the precise mechanism by which FH mutations drives the specific disease phenotypes remains unclear, each of these diseases is associated with excess complement deposition on endothelial surfaces. Thus is would appear that dysfunction in FH, in conjunction with pre-existing damage to endothelial surfaces, as commonly seen in both long standing HTN and ESRD, may act to accelerate pathogenic processes and thus increase both the severity and rate of progression of renal disease. The ARIC study provides a unique opportunity to study hypertension and the Steno hypothesis across 4 distinct evaluations spanning a period of approximately 12 years (from 1989 to 2003).

The main objective of the original study was to study the etiology of atherosclerosis and its clinical consequences (9). A major advantage of the ARIC cohort is the availability of this population for genetic analysis in conjunction with the prospective clinical information.

References:


5. Main Hypothesis/Study Questions:
We propose to investigate the Factor H FY402 variant in the bi-racial community based cohort of the ARIC study in order to accomplish the following objectives:

1. Determine the association between the Factor H FY402 polymorphism and the prevalence and nine year incidence of hypertension in Non-Hispanic white and African-American participants in the ARIC study.

2. Determine the association between the Factor H FY402 polymorphism and the visit 4 prevalence of microalbuminuria (>30 mg/g) in Non-Hispanic white and African American participants in the ARIC study. Microalbuminuria will be defined as 30-299 mg/g albumin to creatinine ratio.

3. Determine if there is an interaction between the Factor H FY402 polymorphism and hypertension on the visit 4 prevalence of microalbuminuria in Non-Hispanic white and African American participants in the ARIC study. Microalbuminuria will be defined as 30-299 mg/g albumin to creatinine ratio.

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 Factor H FY402 variant (rs1061170) has been measured on the entire ARIC cohort, and all data for these analyses are already available. Because of allele frequency differences between blacks and whites, all analyses will be done in a race-specific manner. Routine statistical analyses will be used throughout using Stata (10, College Station, TX). Because no good “time-to-event” estimate is available for incident hypertension, 9 year incident cases will be defined as new hypertensives (definition 5= BP≥140/90 ± medication) in visit 4 (compared to baseline). Modeling of incident hypertension will be done using logistic regression. Severity of hypertension will be evaluated by mean systolic pressures as a surrogate for poor blood pressure control. The only exclusion criteria are...
Albuminuria will be analyzed cross-sectionally at visit 4 when all individuals had levels measured. The albumin to creatinine ratio will be log transformed since it is heavily skewed and analyzed as the dependent variable using linear regression.

The analyses will be performed under the supervision of Dr Boerwinkle. Dr Josef Coresh will help guide the analysis and interpretation of the albumin/creatinine ratio data.

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? ___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)?
    MS#1192 – CHF and CHD/STROKE (Volcik)

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ___ Yes _X__ 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/

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.