

ARIC Manuscript Proposal #1192

PC Reviewed: 10/27/06
SC Reviewed: 10/27/06

Status: A
Status: A

Priority: 2
Priority: 2

1.a. Full Title: Complement Factor H Y402H Genetic Polymorphism and Vascular Disease: the ARIC Study

b. Abbreviated Title (Length 26 characters): CFH and Vascular Disease

2. Writing Group: Writing group members: Kelly Volcik
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. KV [please confirm with your initials electronically or in writing]

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3. Timeline: Genotyping of the CFH Y402H polymorphism (rs1061170) is complete for the entire ARIC cohort.
Statistical Analyses: Nov 06 – Jan 07
Manuscript Preparation: Jan – Feb 07
Manuscript Revision: March 07
Manuscript Submission: April 07

4. Rationale:

Both human and animal studies have shown complement and complement regulatory proteins to play a role in the pathogenesis of atherosclerosis, particularly with regards to

vascular diseases.¹⁻³ Complement factor H (CFH) is a plasma protein that is essential in the regulation of the alternative complement pathway and has been suggested to take part in complement inhibition in atherogenesis.⁴ Recently, multiple studies have shown an association between the CFH Y402H (rs1061170) polymorphism and age-related macular degeneration, a disease sharing many pathological and epidemiological similarities with atherosclerosis and arteriolosclerosis.⁵⁻⁹ Subsequently, studies have begun to evaluate the association of the CFH Y402H polymorphism with CRP levels and risk of incident coronary heart disease, stroke and venous thromboembolism, with inconsistent results.^{4,10,11} Zee et al. found no association of the CFH Y402H polymorphism with risk of incident CHD, stroke or venous thromboembolism, nor with levels of CRP, in a nested case-control study with a population of 685 US Caucasian males.¹⁰ Goverdhan et al. also found no association between the CFH Y402H polymorphism and CHD in a case-control study of 730 British subjects.¹¹ Kardys et al. found the CFH Y402H polymorphism to be associated with an increased risk of myocardial infarction, but not to be associated with established cardiovascular risk factors or CRP levels, in a prospective cohort of 5,520 men and women from the Netherlands.⁴

Seeing that only a few under-powered studies, only one of which was prospective in design, have investigated the association of the CFH Y402H polymorphism with CHD, we propose to evaluate this polymorphism in the large bi-ethnic ARIC population and to extend our analyses to investigate multiple vascular diseases.

5. Main Hypothesis/Study Questions:

1. Estimate the frequency distribution of the CFH Y402H polymorphism (rs1061170) in a population-based sample of whites and African-Americans.
2. In a race-specific manner, utilize Cox regression to evaluate the ability of CFH Y402H genotype to independently predict incident CHD. Analyses will be carried out taking into account age, gender, field center, BMI, HDL and total cholesterol, smoking, diabetes and hypertension status.
3. In a race-specific manner, utilize Cox regression to evaluate the ability of CFH Y402H genotype to independently predict incident ischemic stroke. Analyses will be carried out taking into account age, gender, field center, smoking, diabetes and hypertension status.
4. In a race-specific manner, utilize logistic regression to evaluate the ability of CFH Y402H genotype to independently predict PAD case status. Analyses will be carried out taking into account age, gender, field center, BMI, HDL and total cholesterol, smoking, diabetes and hypertension status.
5. In a race-specific manner, utilize logistic regression to evaluate the ability of CFH Y402H genotype to independently predict kidney disease status. Analyses will be carried out taking into account age, gender, field center, diabetes and hypertension status.
6. In a race-specific manner, utilize linear regression to evaluate the effect of CFH Y402H genotype on multiple ultrasound scanning measurements, including popliteal artery and carotid artery measures. Analyses will be carried out taking into account age, gender, field center, BMI, LDL and total cholesterol, smoking, diabetes and hypertension status.

6. Data (variables, time window, source, inclusions/exclusions):

The usual DNA restriction, ethnic group and missing data exclusion criteria will be used. The following variables will be utilized for identification of each of the above endpoints: CHD (IN_03SP), ischemic stroke (IN03ISC), and PAD (pad02). We will look at kidney disease in two ways: 1) only doctor-diagnosed kidney disease (LABB1A), and 2) doctor-diagnosed kidney disease and/or doctor-diagnosed other kidney ailment (LABB1A and/or LABB1B). The multiple ultrasound scanning measurements utilized in our analyses will include the following: weighted mean of the DA45 variables (SUM45_2), average far wall width of the common

carotid anterior angle (LANAAV45, RANAAV45), average far wall width of the common carotid optimum angle (LOPAAV45, ROPAAV45), minimum lumen diameter common carotid optimum angle (LOPAMN34, ROPAMN34), average far wall width popliteal (LPPAAV45, RPPAAV45), minimum lumen diameter popliteal (LPPAMN34, RPPAMN34)

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

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 ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ☒ Yes ___ No

9. The lead author of this MS 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. ☒ 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)?

None

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

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

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