

ARIC Manuscript Proposal # 944

PC Reviewed: 07/01/03
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Status: A
Status: A

Priority: 2
Priority: 2

1.a. Full Title: Apolipoprotein E polymorphism and its relationship to Age-Related Maculopathy, Diabetic Retinopathy and Retinal Arteriolar Abnormalities.

b. Abbreviated Title (Length 26 characters): ApoE and Retina Diseases

2. Writing Group (list individual with lead responsibility first):

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3. Timeline:

The intent of this analysis is to investigate the cross-sectional association of the apolipoprotein E gene polymorphism to age-related maculopathy, diabetic retinopathy and maculopathy and retinal arteriolar abnormalities (generalized retinal arteriolar narrowing, focal arteriolar narrowing, and arterio-venous nicking) at Visit 3. Initial analyses and writing will take place between October and December 2003, final analysis between Jan 2004 and May 2004, and final writing and manuscript submission between June 2004 and October 2004.

4. Rationale:

Age-related Maculopathy (ARM)

ARM is a multifactorial disorder known to have a substantial genetic component. The relationship of apolipoprotein E gene (APOE) and ARM remains unclear. The epsilon4 allele (APOE-4) has previously been reported to have a protective effect on ARM risk, while the APOE-2 allele has been suggested to increase ARM risk.¹⁻³ In one multi-center case control study with 617 ARM cases and 1260 controls, the presence of APOE-4 allele was associated with a lower risk of ARM (age- and sex-adjusted odds ratio (OR) for APOE-4 carriers 0.54, 95% confidence interval (CI) 0.41-0.70, $p < 0.0001$), whereas APOE-2 allele was found to increase the risk of ARM in men, but not women (OR for men 1.54, 95% CI 0.97-2.45; OR for women 0.74, 95% CI 0.52-1.06, $p = 0.01$ for interaction of sex and APOE-2 carrier status).⁴ However, other studies have not found such associations.⁵ Additionally, whether APOE polymorphism interacts with other risk factors of ARM, such as cigarette smoking, is unknown.

Diabetic Retinopathy And Maculopathy

Diabetic retinopathy (DR), including maculopathy, is an important cause of visual impairment among people with diabetes. There are few studies that have examined the link between APOE polymorphism and DR or diabetic maculopathy, although it has been suggested that APOE polymorphism may influence risk of maculopathy via its effect on lipoprotein metabolism in diabetic patients.⁶⁻⁸ This is based on the fact that individuals with APOE-2 appear to have higher triglyceride levels while individuals with APOE-4 may have elevated plasma cholesterol levels.^{7,8} Additionally, several studies have shown that APOE polymorphism may be associated with a genetic predisposition for microangiopathy, specifically diabetic nephropathy.^{9,10}

However, few studies have examined a direct link with DR and maculopathy. A recent small study on 36 patients with DR and 22 healthy age-matched controls showed that the frequency of retinal hard exudates was higher in those APOE-4 ($p < 0.05$).¹¹

Retinal Arteriolar Disease

APOE polymorphism has been associated with increased risk of large vessel atherosclerosis and clinical cardiovascular disease.¹²⁻¹⁴ However, there are few data on whether APOE polymorphism may also influence the occurrence of small vessel disease. In a study of 88 hypertensives, patients who were carriers of APOE-4 had significantly higher prevalence of hypertensive retinopathy ($p < 0.05$) as well as left ventricular hypertrophy ($p < 0.001$), as compared to those who were not carriers of APOE-4.¹⁵ These results suggest that APOE-4 may be associated with a higher prevalence of retinal microvascular disease in patients with mild to moderate hypertension.

Strengths of ARIC data

There are few population-based studies that have APOE genotyping and large numbers of ARM and DR cases, as well as a precise photographic assessment of retinal arteriolar changes. Because of the large sample size, the ARIC study will offer a unique opportunity to test interaction between APOE genotype and race and other risk factors of ARM (e.g., cigarette smoking), DR (e.g., glucose control, duration of diabetes, blood pressure) and retinal microvascular disease (e.g., blood pressure).

5. Main Hypothesis/Study Questions:

1. Is the APOE-4 allele associated with a lower prevalence and the APOE-2 allele associated with a higher prevalence of ARM?
 - If so, are these associations different by race (blacks versus whites) and cigarette smoking status?
2. Is the APOE-4 allele associated with a higher prevalence of DR and diabetic maculopathy and hard exudates?
 - If so, are these associations different by race, fasting glucose levels and duration of diabetes?
3. Is the APOE-4 allele associated with a higher prevalence of retinal arteriolar changes (generalized arteriolar narrowing, focal arteriolar narrowing and arterio-venous nicking)?
 - If so, are these associations different by race, hypertension status, blood pressure levels and cigarette smoking status?

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

- (1) APOE alleles.
- (2) ARM variables. Any ARM, early ARM, late ARM and specific ARM lesions (drusen, pigmentary changes)
- (3) Diabetic retinopathy variables. Diabetic retinopathy presence and severity score. Macular edema and hard exudates.
- (4) Retinal arteriolar variables. Focal retinal microvascular changes (arteriovenous nicking, focal arteriolar narrowing, retinal hemorrhage, type of hemorrhage, microaneurysms and soft exudates. Generalized arteriolar narrowing quantified as retinal arteriole-to-venule ratio (AVR), central retinal arteriolar equivalent, central retinal venular equivalent.
- (5) Covariates: age, sex, race, center, prevalent CHD and MI, diabetes and hypertension status, blood pressure, hemostatic and inflammatory markers (von Willebrand factor, factor VIIIc, fibrinogen, WBC), cigarette smoking, alcohol consumption, body mass index (variables from ARIC visit 1-3, except for von Willebrand factor, factor VIIIc, WBC, fibrinogen available ARIC visit 1 only)
- (6) Exclusion criteria: From participants at ARIC visit 3 (n=12,887), exclude persons who whose race is not black/white, with no APOE information, ungradeable retinal photographs or missing retinal variables at visit 3.

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

b. If Yes, is the author aware that the file ICTDER01 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 ICTDER01 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? ☒ 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 ICTDER01 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ☒ 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://bios.unc.edu/units/csc/ARIC/stdy/studymem.html>
☒ 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)?

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