1.a. Full Title: Association of Paraoxanase 1 Polymorphism with Retinopathy and Age-related Maculopathy.

b. Abbreviated Title (Length 26 characters): PON1 and Retinal Disease

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

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3. Timeline:
   The intent of this analysis is to investigate the association of paraoxanase 1 (PON1) and retinal diseases in the ARIC study, as part of a proposed series of analyses using Ancillary Study#1995.07 genetic data. Initial analyses and writing will take place between June and Oct 2005, and final writing and manuscript submission between Oct 2005 and Jan 2006.

4. Rationale:

   Paraoxonase 1 (PON1) is a serum enzyme closely associated with high density lipoprotein (HDL) (1). PON1 metabolizes toxic oxidized lipids associated with both low density lipoprotein (LDL) and HDL. Serum PON1 activity in a given population can vary by 40-fold with most of this variation explained by a glutamine to arginine interchange at position 192 (Gln192Arg). PON1 has been linked with both macrovascular disease, such as coronary heart disease and stroke in patients with (2-4) and without diabetes (5), and carotid artery atherosclerosis in individuals with elevated HDLs (6), as well as microvascular diseases, such as nephropathy in individuals with diabetes (7). Because both diabetic retinopathy and age-related maculopathy (ARM) may be influenced by lipid metabolism, PON1 gene has been suggested to play a role in their development

Retinopathy
There have been few studies that have investigated a possible association between PON1 and diabetic retinopathy (8-11). In one case control study of 280 patients with type 2 diabetes in Japan, Gln192Arg polymorphism of PON1 was associated with the prevalent retinopathy (OR 3.13, 95% CI 1.42-6.89, p = 0.0046, Gln/Gln vs. Gln/Arg and Arg/Arg). This polymorphism was also associated with nephropathy (OR = 3.01, 95% CI = 1.30-6.98, p = 0.0103) and was not
explained by age of diagnosis of diabetes, family history of diabetes, BMI, duration of diabetes, HbA1c levels and hypertension status. However, this association was not seen in three other studies in both type 1 and type 2 diabetes (9-11)

**Age-related Maculopathy**

Two studies have examined the association of PON1 with age-related maculopathy (ARM) (12,13). In one study on 72 Japanese patients with exudative ARM and 140 age-and sex-matched control subjects, the distribution of PON1 polymorphism was significantly different between the cases and controls (p=0.04). A high frequency of the Arg/Arg genotype was observed cases compared with control subjects (52.8% vs 35.0%; p=.013). Another study in Causcasian individuals found no association (13).

The proposal will examine the association of PON1 with retinopathy (in people with and without diabetes) and ARM. We hypothesize that these genes may play a role in their pathogenesis, either through their effects on lipid levels or through independent pathways.

5. **Main Hypothesis/Study Questions:**

   (1) To describe the association of PON1 polymorphism with retinopathy in people with and without diabetes, and to determine if the associations are independent of lipid and other factors.
   - Hypothesis: Polymorphism of PON1 is related to retinopathy, particularly in people with diabetes, independent of other factors.
   
   (2) To describe the association of PON1 polymorphism with ARM.
   - Hypothesis: Polymorphism of PON1 is related to ARM

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

   (1) Retinal microvascular variables: retinopathy, focal arteriolar narrowing, arterio-venous nicking, arteriolar and venular diameters, AV ratio.
   
   (3) ARM variables. Any ARM, early ARM, late ARM and specific ARM lesions (drusen, pigmentary changes).
   
   (2) Genotypes for PON1
   
   (3) Covariates: age, sex, race, diabetes and hypertension status, fasting glucose, HBA1C (visit 2), blood pressure (visit 1, 2, and 3), cigarette smoking, alcohol consumption, body mass index, waist hip ratio.
   
   (4) Exclusion criteria: From ARIC visit 3, exclude persons with no retinal photographs or ungradeable photographs and no genetic data.

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)?

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

Yes ___ No

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number*) 1995.07

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