ARIC Manuscript Proposal # 1073

1.a. Full Title: Association of β3-Adrenergic Receptor polymorphism with Retinopathy

b. Abbreviated Title (Length 26 characters): ADRB3 Gene and Retinopathy

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 the β3-adrenergic receptor (ADRB3) gene and diabetic retinopathy 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 May and July 2005, and final writing and manuscript submission between August 2005 and December 2005.

4. Rationale:

   Diabetic retinopathy is a sight-threatening complication of the retinal microvasculature. While important environmental factors have been clearly identified as influencing its development, increasing evidence suggests that diabetic retinopathy has a genetic component (1,2). A variety of studies have explored associations between candidate genes and frequency and severity of retinopathy (2). However, few groups have identified a strong association between a gene and the frequency or severity of retinopathy. Most published studies have been based on small patient samples, and case definitions of retinopathy were not based on standardised assessment or criteria.

   The β3-adrenergic receptor (ADRB3) gene, located on human chromosome 8p12-p11.2, is mainly expressed in adipose tissue and contributes to population variations in energy expenditure and body fat distribution (3). A missense mutation of the gene, resulting in replacement of tryptophan by arginine at codon 64 (Trp64Arg), has been described recently. A number of studies have shown this variant is associated with glucose intolerance, insulin resistance and diabetes (4-6), obesity (7-12), and hypertension (13). Associations, however, have not been inconsistent in other studies (14-17). The Trp64Arg variant has been genotyped in the entire ARIC cohort.

   Three studies have examined the association of the ADRB3 gene and diabetic retinopathy (18-20), with inconsistent results. Sakane and colleagues examined polymorphism of ADRB3 gene, and retinopathy in 215 Japanese Type 2 diabetes patients,
and found that the Trp64Arg allele was significantly more frequent in the patients with proliferative retinopathy (p = 0.002), but not non-proliferative retinopathy (P = 0.151), as compared to those without diabetic retinopathy (18). Participants with the Trp64Arg mutation had an earlier onset of diabetes, a longer duration of diabetes, and higher BMI, as compared with those without the mutation. In models that controlled for age, age at diagnosis, duration of diabetes, current BMI, systolic blood pressure, HbA1c, and serum lipids, the Arg/Arg or Arg/Trp genotype was significantly associated with proliferative retinopathy (OR 2.55, 95% CI 1.25-5.16), as compared with the Trp/Trp genotype. However, two other studies in Caucasian people have not been able to find an association with either proliferative or non-proliferative retinopathy (19,20).

We have previously described cardiovascular associations of retinopathy in people with and without diabetes the ARIC study (21-23). The current proposal will examine the association of the ADRB3 gene with retinopathy signs.

5. Main Hypothesis/Study Questions:

(1) To describe the association of retinopathy signs with Trp64Arg polymorphism of ADRB3 gene in people with and without diabetes.

- Hypothesis: Polymorphism of this gene is related to retinopathy signs and is independent of age, glycemia levels, BMI, waist hip ratio, blood pressure and other factors. Associations are likely stronger in people with diabetes than in those without diabetes

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

(1) Retinal variables: diabetic retinopathy severity, microaneurysms, retinal hemorrhages, focal arteriolar narrowing, arterio-venous nicking, arteriolar and venular diameters, AV ratio

(2) Genotype for ADRB3

(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 data on ADRB3.

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/cscc/ARIC/stdy/studymem.html

   __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)?

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*)   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
8. Kurabayashi, T, Carey, DG, Morrison, NA. The beta 3-adrenergic receptor gene Trp64Arg mutation is overrepresented in obese women: effects on weight BMI, abdominal fat, blood pressure, and reproductive history in an elderly Australian population Diabetes 1996; 45,1358-1363 [Abstract]