

ARIC Manuscript Proposal # 1116

PC Reviewed: 11/22/05

Status: _____

Priority: _____

SC Reviewed: _____

Status: _____

Priority: _____

1.a. Full Title: Association of Uncoupling Protein 2 with Diabetes and possible effect modification of obesity: The ARIC Study

b. Abbreviated Title (Length 26 characters): UCP2, Diabetes, and Obesity

2. Writing Group:

Writing group members: Suzette J. Bielinski, Aaron R. Folsom, James S. Pankow, Eric Boerwinkle, Molly S. Bray, others to be added

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

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3. Timeline:

Starting Analyses: December 1, 2005
First Draft: March 1, 2006
Submission for Publication: June 1, 2005

4. Rationale:

Type 2 diabetes mellitus (T2DM) is characterized by impaired insulin secretion, peripheral insulin resistance, and increased hepatic glucose production. In 2000, the prevalence of T2DM was 15.5% in Native Americans, 13% in African Americans, 10.2% in Hispanics, and 7.8% in non-Hispanic whites¹. Diabetes is a major health burden in the United States with direct and indirect costs of diabetes totaling \$132 billion in 2002². Complications of T2DM include cardiovascular disease, stroke, blindness, kidney failure, neuropathy, and lower-extremity amputations.

T2DM is a heterogeneous disease with a complex etiology including a strong genetic component. A positive family history of T2DM is a major risk factor for this disease with 70-90% concordance observed between identical twins. The Framingham Offspring Study reported a 3.4 times higher risk of diabetes with one affected parent and 6.1 times greater risk if both parents were affected³. Other risk factors include obesity, physical inactivity, race/ethnicity, history of gestational diabetes, hypertension, low HDL cholesterol levels, high triglyceride levels, and history of vascular disease.

Genes that contribute to genetic susceptibility to T2DM function in numerous biochemical pathways. Of interest in this study is Uncoupling Protein 2 (UCP-2). UCP-2 expression has been observed in pancreatic islet cells and functions as a negative regulator of insulin secretion⁴. In addition, UCP is thought to regulate fatty acid metabolism.

Several studies have shown an association between variants of the UCP-2 gene and T2DM and obesity, although inconsistent results have been reported⁵⁻⁸. Yu et. al. reported a higher incidence of diabetes in those with the VV vs. AV or AA genotype of the Ala55Val polymorphism in 3,684 individuals participating in the Coronary Artery Risk Development in Young Adults (CARDIA) Study⁵. These researchers also reported that the VV genotype was associated with the incidence of impaired fasting glucose (IFG) but only in those without abdominal obesity⁵. Bulotta et. al. investigating a polymorphism in the promoter region of the UCP-2 gene, reported an increased risk of diabetes in people with the -866G/G genotype vs. G/A and A/A subjects in sample of 746 T2DM patients and 327 healthy Caucasians from Italy⁹. Therefore, we propose to investigate the relationship between variants of UCP-2 and T2DM and impaired fasting glucose using the Atherosclerosis Risk in Communities Study population.

5. Main Hypothesis/Study Questions:

1. To estimate the frequency of UCP-2 variants in a population sample of blacks and whites.
2. To describe the association of UCP-2 variants and incident diabetes in obese and non-obese individuals.
3. To describe the association of UCP-2 variants and impaired fasting glucose in obese and non-obese individuals without diabetes.

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

Design: Cohort Study

Outcome: Incident Diabetes, Impaired Fasting Glucose

Exposure: Variants of UCP-2 gene

Covariates include, but are not limited to, traditional risk factors including age, sex, race, lipid levels, hypertension, obesity, smoking status, and physical activity.

Analysis Plan

1. Hardy Weinberg equilibrium among genotypes will be calculated using the chi-square test on race-specific datasets.
2. An additive genetic model will be assumed unless indicated otherwise by the results. Therefore, genotypes will be coded as 0 (0 copies of candidate allele), 1 (1 copy), or 2 (2 copies). If appropriate given the results, a dominant model combining homozygotes and heterozygotes will be used.
3. Cox regression will be used to test the null hypothesis that the hazard rate of diabetes is the same across UCP genotypes. Furthermore, we will assess the impact of obesity on the association between UCP genotype and incident diabetes and IFG.

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 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?

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? 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 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.csc.unc.edu/ARIC/search.php>

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)?

There are no manuscript proposals investigating UCP-2.

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.csc.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

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