ARIC Manuscript Proposal # 1141

PC Reviewed: 03/_21_/05	**Status: _____**	**Priority: ____**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Transcription factor 7-like 2 (TCF7L2) gene and type 2 diabetes

b. Abbreviated Title (Length 26 characters): TCF7L2 and diabetes

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

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3. Timeline: The DG10S478 microsatellite will be typed by Dr. Boerwinkle's laboratory on the ARIC cohort. Approval of this manuscript by the ARIC publications Committee and transfer of the genotyping data to the Coordinating Center will then enable work on this manuscript. Once started, this work will lead to a manuscript within six months.

4. Background and Rationale: Following reports of linkage of type 2 diabetes to chromosome 10q, Grant et al. recently reported an association of the intronic variant DG10S478 of the transcription factor 7-like 2 (TCF7L2) gene with type 2 diabetes. [1] Heterozygous (38% of the population) and homozygous (7% of the population) carriers of at risk alleles had (prevalence) relative risks of 1.45 and 2.4 1, respectively (95% CI not given). A population attributable risk of 21% was estimated in Caucasian populations of Iceland, Denmark and the U.S. The association of type 2 diabetes with the at-risk variant was reportedly not modified by body mass; carriers of the at-risk variant appeared to have and earlier age of onset.

The availability of data on the DG10S478 variant of TCF7L2 on the ARIC cohort will enable analyses focused on endpoints and target organs ranging from retinal variables, to atherosclerotic burden and atherothrombotic events, to inflammatory markers and estimated glomerular function / CKD, among others. Here we propose to focus on markers of impaired glucose metabolism.

The purpose of this proposal is to assess the association between DG10S478 variant of the transcription factor 7-like 2 (TCF7L2) gene with several indicators of glucose metabolism impairment in African American and white participants of the ARIC cohort. Dependent variables will include fasting insulin, fasting glucose and prevalent diabetes at baseline, fasting and post-load measures of insulin and glucose (Visit 4), and incident diabetes.

ARIC's assessment of age of (diabetes) onset is incomplete and open to misclassification. If an association of DG10S478 with impaired glucose metabolism/incident diabetes is found we propose to examine two markers of cumulative burden/severity of impaired glucose metabolism, namely heart rate variability and average intima-media thickness. Note: retinal abnormalities / microvascular retinal disease are thought to be better indicators of target organ damage in this case; others in ARIC are better equipped to address such questions in separate manuscript proposals.

5. Main Study Questions:

a. Assess the association between the DG10S478 variant of transcription factor 7-like 2 (TCF7L2) gene with fasting insulin levels, the level of HbA1c, the response to a 75 gm glucose load, the prevalence of diabetes at baseline and the risk of diabetes incidence in African American and white members of the ARIC cohort.
b. Examine the putative modification of the above associations by body mass index and gender.
c. Estimate the population burden of TCF7L2-associated diabetes mellitus and the metabolic syndrome in the four main demographic groups represented in the ARIC cohort.

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

ARIC Visit 1

Fasting insulin, fasting glucose, type 2 diabetes, heart rate variability, demographic characteristics, anthropometric variables, blood pressure(s), fasting lipids.

ARIC Visit 2

Glycolsylated hemoglobin

ARIC Visit 4

Fasting and post-load insulin and glucose, anthropometric variables, heart rate variability, (average) intima-media thickness.

Prospective

Incident diabetes

Reference:

1. Grant SF, Thorleifsson G, Reynisdottir I, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet. 2006 Jan 15; [Letters, pp. 1-4; Epub ahead of print]

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __X__ 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? __X__ 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"? __X__ 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.cscc.unc.edu/ARIC/search.php

___**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)?
None

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. primiarly 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.