ARIC Manuscript Proposal # 1235

PC Reviewed: __3_/_13/07	**Status: _A___**	**Priority: _2__**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Transcription factor 7-like 2 (TCF7L2) and incident cardiovascular disease: The Atherosclerosis Risk in Communities (ARIC) Study

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

2. Writing Group:

Writing group members: Suzette J. Bielinski, James S. Pankow, Aaron Folsom, Kari E. North

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: March 1, 2007
First Draft: June, 2007
Submission for Publication: August, 2007

4. Rationale:

Diabetes is a major risk factor for cardiovascular disease (CVD) increasing the risk of stroke, angina, MI, and coronary heart disease[1]. Transcription factor 7-like 2 (TNF7L2) polymorphisms have been associated with diabetes in numerous studies[2-4]. The T-allele of rs7903146 is a common variant in the population and is hypothesized to be either the risk variant or the closest correlate[5]. Little is known about the normal role of TNF7L2 other than it functions in the wnt signaling cascade and appears to be ubiquitously expressed. Further investigation is needed to determine how variants may impact the normal role of the transcription factor and predispose to diabetes. To date, there are no studies published investigating the role of genetic variants of this gene and cardiovascular disease.

Five TCF7L2 SNPs have been measured in the ARIC cohort, including rs7903146. We propose to study the relationship of these SNPs and incident CVD in the ARIC cohort. Furthermore, we plan to investigate whether CVD risk differs in diabetics and non-diabetics with and without the putative TCF7L2 genotype.

5. Main Hypothesis/Study Questions:

1. To describe the association of the TCF7L2 polymorphisms and incident CVD (CHD, stroke, PAD).
2. To investigate the interaction of diabetes, TCF7L2 variants, and incident CVD. (i.e. Is there a risk of CVD associated with TCF7L2 variants? Does this risk vary by diabetes status? Does the risk of CVD differ in diabetics with the putative TCF7L2 genotype compared to diabetics without the TCF7L2 genotype?)

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

Design: Prospective cohort study
Outcome: Incident CVD, heart failure
Exposure: TCF7L2 polymorphisms genotyped in the whole ARIC cohort (rs12255372, rs7901695, rs11196205, rs7903146, rs7895340)
Effect Modifier or Pathway Variable: Diabetes
Covariates include, but are not limited to, traditional risk factors including age, sex, race, lipid levels, blood pressure medication use, smoking status and amount, 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 CVD is the same across TNF7L2 genotypes. Furthermore, we will assess the impact of diabetes on the association between TNF7L2 genotypes and incident CVD. We will

assess the risk of CVD in diabetics by genotype. Finally, individual CVD, namely CHD, stroke, and PAD, will also be examined.

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)?

Manuscript #1141 Transcription factor 7-like 2 (TCF7L2) gene and type 2 diabetes

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.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

1. Association AH. *Heart Disease and Stroke Statistics--2006 Update*. Dallas, Texas: American Heart Association; 2006.
2. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, Helgason A, Stefansson H, Emilsson V, Helgadottir A, Styrkarsdottir U, Magnusson KP, Walters GB, Palsdottir E, Jonsdottir T, Gudmundsdottir T, Gylfason A, Saemundsdottir J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen C, Gudnason V, Sigurdsson G, Thorsteinsdottir U, Gulcher JR, Kong A, Stefansson K. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. *Nat Genet*. 2006;38:320-323.
3. Humphries SE, Gable D, Cooper JA, Ireland H, Stephens JW, Hurel SJ, Li KW, Palmen J, Miller MA, Cappuccio FP, Elkeles R, Godsland I, Miller GJ, Talmud PJ. Common variants in the TCF7L2 gene and predisposition to type 2 diabetes in UK European Whites, Indian Asians and Afro-Caribbean men and women. *J Mol Med*. 2006;84:1-10.
4. Marzi C, Huth C, Kolz M, Grallert H, Meisinger C, Wichmann HE, Rathmann W, Herder C, Illig T. Variants of the Transcription Factor 7-Like 2 Gene (TCF7L2) are Strongly Associated with Type 2 Diabetes but not with the Metabolic Syndrome in the MONICA/KORA Surveys. *Horm Metab Res*. 2007;39:46-52.
5. Helgason A, Palsson S, Thorleifsson G, Grant SF, Emilsson V, Gunnarsdottir S, Adeyemo A, Chen Y, Chen G, Reynisdottir I, Benediktsson R, Hinney A, Hansen T, Andersen G, Borch-Johnsen K, Jorgensen T, Schafer H, Faruque M, Doumatey A, Zhou J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen C, Sigurdsson G, Hebebrand J, Pedersen O, Thorsteinsdottir U, Gulcher JR, Kong A, Rotimi C, Stefansson K. Refining the impact of TCF7L2 gene variants on type 2 diabetes and adaptive evolution. *Nat Genet*. 2007.