1.a. Full Title: Transcription factor 7-like 2 gene (TCF7L2), adipokines and other inflammation markers: The Atherosclerosis Risk in Communities (ARIC) Study

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

2. Writing Group:
   Writing group members: Taryn Hall, James S. Pankow, Mark Pereira, Christie Ballantyne, Linda Kao, Eric Boerwinkle, David Couper, Kari North

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

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3. Timeline:
   Starting Analyses: July 1, 2007
   First Draft: September, 2007
   Submission for Publication: November, 2007

4. Rationale:
Studies have found an association between polymorphisms of the transcription factor 7-like 2 gene and type 2 diabetes in several populations\(^1\)\(^-\)\(^2\). 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\(^2\). TCF7L2 is part of the wnt signaling cascade, but little is known about its role in diabetes pathogenesis or inflammation. It has been previously hypothesized that chronic, low-grade inflammation is a part of the process causing diabetes\(^3\). One study (Helgason, 2007) found that the T-allele of rs7903146 is associated with increased levels of leptin in men but not in women. Associations between the allele and measures of adiposity have generally been weak or inconsistent, suggesting that other pathways may be involved.

Five TCF7L2 SNPs have been measured in the ARIC cohort, including rs7903146.

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

1. To test the hypothesis that “at risk” allele of TCF7L2 (T-allele of rs7903146) is associated with adverse levels of adipokines (adiponectin, leptin), inflammation markers or acute phase reactants (IL-6, CRP, orosomucoid, sialic acid, fibrinogen, white cell count, sICAM-1, complement C3), and other markers of disordered metabolism (free fatty acids, ALT, GGT).

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

Design: Cross-sectional study, restricted to the cohort random sample (n=600) of the “Inflammatory Precursors of Type 2 Diabetes” ancillary study. All of these subjects were non-diabetic at the baseline exam.

Outcome: visit 1 levels of adiponectin, leptin, IL-6, CRP, orosomucoid, sialic acid, fibrinogen, white cell count, sICAM-1, complement C3, free fatty acids, ALT, and GGT.

Exposure: T allele of TCF7L2 polymorphism rs7903146. Secondary analyses will include the other TCF7L2 polymorphisms (rs12255372, rs7901695, rs11196205, rs7895340), which are in linkage disequilibrium with rs7903146, at least in whites.

Covariates include, but are not limited to, risk factors for diabetes including age, race, sex, lipid levels, glucose level, hypertension, physical activity, and (in some analyses) measures of adiposity (BMI and waist).

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. Linear regression will be used to test the null hypothesis that there is no difference in the level of each inflammation-related analyte between at-risk and non-risk TCF7L2 genotypes.

4. Analyses will apply weights that are inversely proportional to the sampling fractions in the cohort random sample.

5. Some analyses will be stratified by sex, as levels of leptin and other adipokines differ between males and females.

6. If strong associations are found between TCF7L2 genotypes and inflammation markers, additional case-cohort analyses will be performed to evaluate whether associations between genotypes and incident diabetes are attenuated after adjustment for these markers as covariates.

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) will look at incident and prevalent diabetes, HbA1c, fasting insulin, and glucose responses to the oral glucose tolerance test but not the adipokines and inflammation markers specified in this proposal.
11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  X Yes  _ No

11b. If yes, is the proposal
   ___X__ A. primarily the result of an ancillary study (list number* 1995.09 )
   ___ 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

