1. **Full Title**: Variants of transcription factor 7-like 2 (TCF7L2) gene, heart rate variability, and type-2 diabetes.

   **Abbreviated Title (Length 26 characters)**: TCF7L2, HRV and T2D.

2. **Writing Group**:
   Writing group members:
   Sunil Kumar Agarwal, Eric Whitsel, Duanping Liao, Kari North, Kelly Volcik, Ronald Prineas, James Pankow, David Couper, Gerardo Heiss

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

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4. **Timeline**: Approval of this manuscript by the ARIC Publications Committee will then enable work on this manuscript. Once started, this work will lead to a manuscript within nine months.

4. **Rationale**:
   Multiple epidemiological studies across various ethnic groups and nationalities have reported consistent associations between variations in the TCF7L2 gene with type 2 diabetes mellitus (T2D) [1-25]. A recent meta-analysis by Cauchi et al [26] that included 28 published studies with no heterogeneity in genotypic distribution and no evidence of publication bias found a pooled Mantel Haenszel allelic (TCF7L2 rs7903046) odds ratio (OR) of 1.46 [1.42-1.51] for T2D. A similar analysis by Florez et [27] with study characteristics as above found a similar magnitude of this association (OR = 1.44 [1.40-1.49]) in 29 published reports. Also, in the Diabetes Prevention Program, the variants of TCF7L2 were associated with progression from impaired glucose tolerance (IGT) to diabetes[4]
TLF7L2 and its association with T2D was first reported in 2003 by the deCODE scientists [28]. They reported suggestive evidence for linkage in regions of chromosomes 5q34-q35.2, 6q, 10q and 12q. In early 2006, Grant et al. then described a robust association between a common microsatellite in the TCF7L2 gene region (DG10S478) and T2D with an overall relative risk of 1.56 (p=7.8x10^{-15} after adjusting for multiple comparisons). The non-coding SNPs rs12255372 and rs7903146(10q-25) were found to be in strong linkage disequilibrium with DG10S478 (r^2=0.95 and 0.78, respectively [5]. A recent follow up publication by the deCODE group which included additional European and new African samples suggests that the haplotype tagged by the T allele at rs7903146 is the source of the association [29]. However, the above two studies have not been able to uncover clear functional variants [5, 29]. Hence, the molecular mechanism of this intronic variant’s effect on glycemic control remains less unknown. Recent studies have suggested that paracrine and autocrine hormonal signaling or processing defects present in individuals with TCF7L2 variants lead to a decrease in insulin secretion[30] [31]. Such defects could also affect the release of other hormones influencing autonomic balance.

Heart rate variability (HRV), a measure of autonomic balance, is decreased in persons with diabetes [32, 33]. In population-based, observational studies a sizable proportion of the diabetic population is taking hypoglycemic medication, making it difficult to separate effects of medications and underlying metabolic impairments on HRV [34]. Cardiac autonomic impairment appears to be present at early stages of diabetic metabolic impairment [37], although of small magnitude. Also, autonomic impairment has been associated with development of T2D[35] and lifestyle modification has been associated with improved autonomic function and decrease in incident diabetes[36]. However, the degree to which pre-diabetic metabolic impairments in insulin and glucose metabolism measurably affect cardiac autonomic function in populations remains to be determined. We therefore propose to examine HRV in categories of impaired glucose regulation identified by glucose and insulin response to a 75 gm glucose load at the Visit 4 examination of the ARIC cohort. This question will consider HRV in non-diabetic ARIC participants and those with isolated IGT according to TCF7L2 carrier status. We anticipate that the presence of risk variants of TCF7L2 and glycemic abnormalities is associated with lower measures of HRV than either the glycemic abnormalities or TCF7L2 risk variants alone. This effect modification on HRV could be mediated by the effect of gene variants through pathways other than those leading from T2D.

Family aggregation, twin and linkage studies have shown high heritability estimates for measures of HRV [37-39] and gene mapping has been attempted [40]. However, there is no further published research refining the linkage with chromosome 15 and 2 found in one of the above studies [40] or other genetic mechanisms that influence HRV.

5. Main Hypothesis/Study Questions:

(1) Genetic variants of the TCF7L2 gene are associated with lower HRV.
(2) The association:
   i) is not modified by gender or race
   ii) is modified by impaired fasting glucose, impaired glucose tolerance and T2D
(3) This association persists after adjustment for other factors such as age, hypertension and BMI (minimum adjustment set to be found)

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodological limitations or challenges if present).
Exclusions: Participants who did not consent to genotyping will be excluded (use of DNA data distributed by the Coordinating Center with confirmation by using the variable RES_DNA = “No use/storage DNA” in the file ICTDER02).

Study Design: This study will use baseline and visit 4 data to examine the TCF7L2-HRV association and to determine whether this association varies by race, gender, IFG, IGT or TD2.

Variables:

From Visit 1-4:
ARIC community; Heart rate, HRV measures from 10 sec ECG: RR, SDNN and RMSSD; CVD risk factors: BMI, diabetes, glucose, HbA1c. hypertension, blood pressure, smoking, heart disease, renal disease, and COPD; Medication use: beta blockers, and anti-arrhythmics.

ARIC visit 1 and 4:
HRV measures from 2 minutes and 6 minutes record (HR, SDNN, RMSSD, HF, LF)

[HF=high frequency power; HR=mean heart rate; LF=low frequency power; rMSSD=root mean square of successive differences in normal-to-normal RR intervals. Transformed values will be used for SDNN, rMSSD, HF, and LF and untransformed values for HR and RR]

ARIC visit 1: Demographics: age, race and gender and, five SNPs of TCF7L2

ARIC visit 4:
Impaired fasting glucose, Impaired glucose tolerance, fasting insulin.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ 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? __X__ 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)?

ARIC Ms proposal no. 1141 (Y. Yan, Lead). Lead author has been invited to participate in this proposed writing group.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use ancillary study data?  ____ Yes  ____ No

11.b. If yes, is the proposal

____  A. primarily the result of an ancillary study (list number* ____________)

*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:


