ARIC Manuscript Proposal # 1283

PC Reviewed: _8_/21_/07 **Status: __D__** **Priority: ___**
SC Reviewed: _________ **Status: _____** **Priority: ____**

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1.a. Full Title: Variants of the *TCF72L* gene and the risk of sudden cardiac death

b. Abbreviated Title (Length 26 characters): TCF72L and sudden death

2. Writing Group:
Writing group members: Anna Kucharska-Newton, Kari E. North, Suzette J Bielinski, Wayne D. Rosamond, Anna Kottgen, Gerardo Heiss, Eric Boerwinkle, ; others welcome

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

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3. Timeline: Analysis to begin immediately following approval of the proposal. A draft of the manuscript should be ready within nine months of study approval.

4. Rationale:

Sudden cardiac death constitutes up to 50% of all cardiac deaths[1], yet, despite this large burden of disease, to date no specific risk factors have been identified [2-4]. Strategies aimed at decreasing risk of sudden cardiac death are therefore also not specific and it is difficult to identify populations at risk.

Comment [AK1]: I am not terribly familiar with SCD, but I think prior MI, CAD, HF, cocaine use, and arrhythmias such as long QT and WPW are identified risk factors for SCD. I think there have also been studies on genes that increase SCD risk.

Comment [AMKN2]: Yes, all those factors are associated with SCD, but they are not specific to SCD, especially if we consider SCD as death within one hour from the onset of acute symptoms in persons without prior clinical manifestation of cardiovascular disease. Risk does change in the high risk groups such as you mentioned. The challenge is in identifying high risk individuals in low-risk populations.

Results of many studies suggest that Type 2 diabetes is associated more strongly with sudden cardiac death than with other cardiovascular outcomes. [5, 6] Type 2 diabetes is a complex disease in which insulin insufficiency, or insulin resistance is a clinical manifestation of multiple metabolic pathways involving both genetic and environmental factors. A large body of diabetes research to date has focused on the role of cardiovascular disease risk factors and obesity in the development of the disease. Recent discoveries of the association of multiple genetic mutations with diabetes however, underscore the need to examine the etiology of diabetes at both the environmental and genetic level [7].

Genetic variants found to be associated with diabetes are located on chromosome 10q in a region coding for transcription factor 4, a member of the canonical Wnt signaling pathway [8] involved in cell proliferation. Variants of this gene, *TCF7L2*, have been estimated to contribute up to 21% of the population attributable risk of diabetes in a number of different population groups [9, 10]. This large contribution to the overall risk of diabetes and the fact that the results have been replicated in different populations establish the role of this gene as a susceptibility variant for type 2 DM.

In this study we would like to examine the possible association of the rs7903146 *TCF7L2* gene variant with incident sudden cardiac death. To our knowledge, despite the strong association of diagnosed diabetes with sudden death, there are no studies of the association of diabetes-related genes with sudden death.

Comment [AK3]: Paper of KCNJ11 and SCD attached for reference.

Comment [AMKN4R3]: The paper you mentioned (thanks for sending it) deals with potassium channel coding genes. Most of the literature on the genetic basis of SCD is in that area – ion channels and their role in induction of arrhythmias. I have not found any reference to genes specifically associated with diabetes.

The effects of the *TCF7L2* gene variants on the risk of diabetes are relatively modest, suggesting that their presence does not constitute sufficient cause for the development of the disease. Those effects however, are strongly modified by cardiovascular disease risk factors, especially obesity and hypertension[11, 12] (Kari North, unpublished data from the ARIC study). Obesity is an important risk factor for the development of diabetes; it is therefore possible that manifest diabetes and also obesity can modify the association of the *TCF7L2* gene variants with sudden death. In this study we propose to examine the association of the *TCF7L2* rs7903146 gene variant with sudden cardiac death in the presence and absence of diabetes and, by extension, presence and absence of elevated blood glucose levels. We will further examine the above associations as a function of obesity.

Comment [AK5]: Could think about how to phrase this – the paragraph above states that TCF7L2 has a large contribution to the overall risk of diabetes, here is says effects on risk are modest.

Comment [AMKN6R5]: I am referring to the effect estimate, rather than population attributable risk.

[1] Zheng Z-J, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. *Circulation* 2001;104:2158-2163.

[2] Burke AP, Farb A, Pestaner J, *et al.* Traditional risk factors and the incidence of sudden coronary death with and without coronary thrombosis in Blacks. *Circulation* 2002;105:419-424.

[3] Thorgeirsson G, Thorgeirsson G, Sigvaldason H, Witteman J. Risk factors for out-of-hospital cardiac arrest: the Reykjavik study. *European Heart Journal* 2005;26:1499-1505.

[4] Kannel WB, Schatzkin A. Sudden death: lessons from subsets in population studies. *Journal of the American College of Cardiology* 1985;5:141B-149B.

[5] Jouven X, Lemaitre RN, Rea TD, Sotoodehnia N, Empana J-P, Siscovick DS. Diabetes, glucose level, and the risk of sudden cardiac death. *European Heart Journal* 2005;26:2142-2147.

[6] Balkau B, Jouven X, Ducimetiere P, Eschwege E. Diabetes as a risk factor for sudden death. *The Lancet* 1999;354:1968-1969.

[7] Gerich JE. The Genetic Basis of Type 2 Diabetes Mellitus: Impaired Insulin Secretion versus Impaired Insulin Sensitivity. *Endocr Rev* 1998;19(4):491-503.

[8] Clevers H. Wnt breakers in colon cancer. *Cancer Cell* 2004;5(1):5-6.

[9] Grant SFA, Thorleifsson G, Reynisdottir I, *et al.* Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. 2006;38(3):320-323.

[10] Zhang C, Qi L, Hunter DJ, *et al.* Variant of Transcription Factor 7-Like 2 (TCF7L2) Gene and the Risk of Type 2 Diabetes in Large Cohorts of U.S. Women and Men. *Diabetes* 2006;55(9):2645-2648.

[11] Duan QL, Dube M-P, Frasure-Smith N, *et al.* Additive Effects of Obesity and TCF7L2 Variants on Risk for Type 2 Diabetes Among Cardiac Patients. *Diabetes Care* 2007;30(6):1621-1623.

[12] Helgason A, Palsson S, Thorleifsson G, *et al.* Refining the impact of TCF7L2 gene variants on type 2 diabetes and adaptive evolution. 2007;39(2):218-225.

[13] Resnick HE, Howard BV. Diabetes and cardiovascular disease. *Annual Review of Medicine* 2002;53(1):245-267.

[14] Marshall MC, Jr. Diabetes in African Americans *Postgrad Med J* 2005;81(962):734-740.

Main Hypothesis/Study Questions:

1. The rs7903146 SNP of the *TCF7L2* gene is associated with risk of sudden cardiac death.
2. This association is modified, in race-specific analyses, by presence of diabetes or impaired fasting glucose.

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 methodologic limitations or challenges if present).

Study objectives:

The main objective of this study is to quantify the association of the rs7903146 *TCF7L2* gene variant with incident sudden cardiac death in African Americans and whites, and the possible effect modifying roles of gender, obesity and type 2 diabetes.

Methods of analysis:

1. **Study population:** All ARIC cohort members with non-missing data on the *TCF7L2* rs7903146 SNP.
2. **Outcome:** incident sudden cardiac death, defined as proposed by the Reynolds Project (MS#1086r) to be "death adjudicated by a physician panel to be a sudden, pulseless condition without known non-cardiac cause, or death certificate codes indicating death due to underlying heart disease that occurs outside the hospital or in the emergency department."
3. **Variables to be included in analysis:**
   -<u>Independent variables:</u> The rs7903146 SNP located within the *TCF7L2* gene will be examined. This SNP has been found to be the best candidate in the region for a functional effect and is most predictive across populations[12], including in the ARIC study (Kari North, unpublished data from the ARIC study).
   -<u>Baseline variables:</u> we will evaluate the following variables for inclusion into multivariate models:
   <u>a. Demographic variables:</u> age, gender, race/ARIC center. The burden of diabetes is higher among women than among men[13] and it is higher among African Americans than Caucasians[14]. Furthermore, the prevalence of the *TCF72L* genotype differs by race. We will therefore examine gender and race as covariates for inclusion into regression models of the association of the *TCF7L2* gene variants with incidence of sudden death as well as their potential role as effect modifiers of this association.
   <u>b. Covariates:</u> The following variables: smoking status, hypertension, HDL-cholesterol, LDL-cholesterol, triglycerides, use of anti-hypertensive medication will be evaluated for inclusion into the regression analysis.
   <u>c. Effect of BMI:</u> Since obesity is a strong factor predisposing towards development of diabetes and BMI has been shown to be a strong effect modifier in studies of the association of the *TCF7L2* gene with diabetes [11, 12], we will evaluate the role of measures of obesity (body mass index, in the association of the *TCF7L2* gene variants and sudden cardiac death.
   <u>d. Presence of diabetes or impaired fasting glucose:</u> we will evaluate the effect of existing diabetes or pre-diabetes on the found associations by stratifying our analysis by the presence of those conditions at baseline and during follow-up.
4. **Data Quality Analyses:** Tests of Hardy-Weinberg equilibrium will be performed for each SNP in the cohort using the control samples. Significant deviations from Hardy-Weinberg will be assessed using a chi-square test, by comparing the observed distribution of genotypes to the Hardy-Weinberg 'expected' distribution, with degrees of freedom equal to the number of alleles (n) – 1.

Comment [AK7]: Do you have an estimate of the number of people with the outcome? My guess is it might be difficult to get sufficient numbers for analyses by race, 3 genotypes, and stratified on the effect modifiers.

Comment [AMKN8R7]: There are currently 320 cases of incident sudden death in follow-up until 2001. This includes definite and possible cases according to the Reynolds project definition. The association of baseline diabetes with SCD does not appear to depend on the definite/possible classification.

Comment [AK9]: Rather than stratifying during f-u, could include as time-varying covariate in model.

Comment [AMKN10R9]: Diabetes may be included in the model as a time-varying covariate based on an incident diabetes variable that was derived by interpolation of information on diabetes status at visits subsequent to baseline visit1 and associated fasting glucose levels. We do not have such data for pre-diabetes. I think that stratification is still the best option, especially if we are interested in potential effect modification by diabetes and pre-diabetes.

5. **Analysis Strategy:** We will use the additive model of interaction to analyze the gene-disease association. For dominant or recessive genetic transmission models, a single indicator variable will be used. A variable taking on the values -1 for genotype XX, 0 for genotype X0, and 1 for genotype 00 will be used to test for additive genetic effects.
6. **Analytical method:** We will estimate the association of the *TCF72L* gene variants and incidence of sudden cardiac death in crude analysis and controlling for the selected variables. The time scale used in modeling will be age-at-risk. Estimation based on age-at-baseline will be conducted as a parsimonious sensitivity analysis. The hypothesized modifying effect of diabetes/IFG will be evaluated as an interaction term with the main exposure. Additional, plausible effect modification by gender and obesity will be performed as exploratory analysis.
   .

Comment [AK11]: Could specify using a Cox model.

Comment [AMKN12]: Cox model is one option that we considered, but given that exposure is since birth, age may be more appropriate than time-since-baseline, although, as stated in the next sentence, both models will be explored.

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? _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)?
MS# 1235 Bielinski S J et al., "Transcription factor 7-like 2 (*TCF7L2*) and incident cardiovascular disease. The Atherosclerosis Risk in Communities (ARIC) study"
The outcomes of interest in this proposal are incident cardiovascular disease, whereas the outcome of interest in our proposal is cardiovascular mortality, specifically sudden cardiac death.

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

11.b. If yes, is the proposal
_X__ A. primarily the result of an ancillary study (list number_2004.03)

___ 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.