ARIC Manuscript Proposal # 357f

1.a. Full Title: Positional cloning of a type 2 diabetes susceptibility gene on chromosome 1q21-q24

b. Abbreviated Title (Length 26 characters): Diabetes gene on 1q21-24

2. Writing Group (list individual with lead responsibility first):

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3. Timeline: Genotyping can begin immediately and will continue until the pathogenic SNP is identified. Although difficult to predict the timeline, it is hoped that this process will take no more than 1-2 years.

4. Rationale: Through genome-wide linkage analysis in the Amish Family Diabetes Study, we have identified a region on chromosome 1q21-24 that is likely to harbor a type 2 diabetes susceptibility gene (Hsueh, et al. Diabetes, in press). This same region has been shown to be linked to type 2 diabetes in Pima Indians, African Americans, Chinese, and Caucasians from France, United Kingdom and Utah. Dr. Shuldiner and his colleagues have begun the positional cloning of this putative type 2 diabetes susceptibility gene using linkage disequilibrium (LD) mapping. The Amish are a relatively young founder population and thus offer superb advantages during the early stages of LD mapping. However, once the region is localized, additional more outbred populations will be essential to the ultimate identification of the gene and its pathogenic SNP. The population-based ARIC study participants would be ideal for this effort since shared segments (haplotype blocks) are likely to be much smaller than in the Amish. Furthermore, cross-comparisons between the Amish, ARIC Caucasians, and ARIC African Americans will provide the greatest chances for success of this ambitious project.

5. Main Hypothesis/Study Questions: A region of chromosome 1q21-q24 identified repeatedly through genome wide approaches harbors a type 2 diabetes susceptibility gene that (1) can be identified through LD mapping, and (2) accounts for a significant proportion of the genetic burden in diverse populations, including Caucasians and African Americans.

6. Data (variables, time window, source, inclusions/exclusions): Genotype data will be collected in participants included in Brancati’s ancillary study genetics of obesity, insulin
resistance and type 2 diabetes in a biracial cohort (this study includes: (a) all African Americans with DNA (and consent) and defined diabetes status at baseline of the study, (b) all white prevalent and incident diabetic cases, and (c) a random sample of white non-diabetic controls.

High throughput SNP genotyping of Amish samples in the region of chromosome 1q21-q24 has identified a relatively well localized region that is likely to harbor a putative type 2 diabetes susceptibility gene. Our overall research plan includes two phases. In phase 1, we will genotype SNPs at approximately 5-10 kilobase density across this region (now approximately 1 megabase) in (1) ARIC African Americans with type 2 diabetes (n=250) and African Americans without type 2 diabetes (n=250), and (2) ARIC Caucasians with type 2 diabetes (n=250) and Caucasians without type 2 diabetes (n=250). Association of SNPs with diabetes will be performed within each population using both allelic and genotypic tests by chi square analysis. In phase 2, all SNPs in close proximity to the significantly associated SNPs in phase 1 will be determined by DNA sequence analysis of non-ARIC samples and through database mining. Once identified, these SNPs will be genotyped in the same ARIC cases and controls. The SNP or SNP haplotypes most significantly associated with T2DM will be designated the putative pathogenic SNP, which will then be pursued by further replication in other samples and through functional studies.

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”? _____ 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://bios.unc.edu/units/csc/aric/study/studymem.html](http://bios.unc.edu/units/csc/aric/study/studymem.html)

____X____ Yes _____ No