ARIC Manuscript Proposal # 986

PC Reviewed: 12/15/03	**Status: A**	**Priority: 2**
SC Reviewed: 12/16/03	**Status: A**	**Priority: 2**

1.a. Full Title: Association between two maturity-onset diabetes of the young (MODY) genes and type 2 diabetes (T2DM) susceptibility

b. Abbreviated Title (Length 26 characters): MODY genes and T2DM

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

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3. Timeline: Genotyping can begin immediately and will be completed by March 2004. A first draft of the manuscript will be circulated amongst co-authors by September 2004.

4. Rationale: Variations in several genes have been identified to be responsible in causing MODY, an autosomal dominant form of T2DM characterized by an early onset (# 25 years) and a primary defect in insulin secretion, including insulin promoter factor-a (IPF1, MODY4) and hepatocyte nuclear factor-4α (HNF4α, MODY1)(1). Recent evidences have shown that variations in IPF1 and HNF4α may also contribute to susceptibility to the more common form of T2DM. A common amino acid variant (InsCCG243) in the IPF1 gene was identified in a small number of French Caucasian families, where it appeared to segregate in a dominant-like fashion and was shown to be associated with a 50% reduction in the activity of IPF1(2). This insertion was also found to be about twice more prevalent in non-diabetic African-American controls than in African-Americans cases with the common form of T2DM (unpublished, direct communication with Dr. Steve Elbein who identified this insertion through sequencing of participants of the GENNID families from the American Diabetes Association. Since this insertion was not found in the Caucasian population from the GENNID study, we will first type about 100 Caucasian ARIC participants to determine the frequency of the insertion the general US Caucasian population. Given that the prevalence of the insertion allele is not high (approximately 10% in diabetic cases) and that the participants of GENNID tend to be younger, we believe the ARIC study offers a unique opportunity to study this “MODY” variant in middle-aged adults with the more common form of T2DM who were not recruited for the disease.

Although a few previous studies suggested that variations in HNF4a were not associated with the common form for T2DM(3;4), at the last American Society of Human Genetics Meeting, two groups independent groups reported evidence for association between T2DM and SNPs in and near HNF4a on chromosome 20q13.12 (an area that has been previously identified by several groups to harbor a T2DM susceptibility genet through linkage analyses). These four SNPs, in nearly perfect linkage disequilibrium (r2 > 0.95) are associated with T2DM in both the Ashkenazi and Finnish populations (rs4810424, rs1884613, rs1884614, and rs2144908). We propose to first type these 4 SNPs in a subgroup of about 100 individuals to determine if the same pattern of LD exist in the African-American and Caucasian populations of the ARIC Study. Through person communications with Dr. Mike Boehnke at the University of Michigan, we have learned that different SNPs (of the four listed above) were associated with T2DM in different populations, suggesting that the causative variant is traveling on a different longer haplotype in these two populations or that there is more than one common susceptibility allele in or near HNF4α. Therefore, we will genotype additional SNPs in and around HNF4α for haplotype-based analyses.

5. Main Hypothesis/Study Questions: Variations in IPF1 and HNF4α (MODY4 and MODY1, respectively) are associated with susceptibility to the more common form of T2DM. In addition, variations in IPF1 and HNF4$\alpha$are associated with the HOMA-beta cell index, a marker for beta cell function, among non-diabetic individuals.

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 (1:1 case-control ratio)

All analyses (cross-sectional or prospective) will assume the following steps:

1. Hardy-Weinberg equilibrium among genotypes will be checked by calculating expected frequencies of genotypes and using the chi-square goodness-of-fit test.
2. All analyses will first be stratified by ethnicity to test for interaction. If no interaction is detected, pooled analyses will be performed.
3. Genotype will be coded as 0 (zero copies of the candidate allele), 1 (one copy of the candidate allele), or 2(two copies of the candidate allele). An additive genetic model will be assumed unless indicated otherwise by results of the analysis or unless the allele frequency of a given candidate variant is low, in which case, a dominant model combining the risk of heterozygotes and homozygotes will be used. We will establish multiple associations using multiple linear regression models or multiple logistic regression models to fit better models that explain the separation of the genotype groups and to control for the effects of potential confounders.
4. A Bayesian-based method by Matthew et al. (PHASE v.1.2) will be used to estimate and assign individual specific probabilities of haplotypes (within a candidate gene) for each individual. The specifications for the proposed study will be for biallelic markers only.

5. Analysis of haplotypes will be performed in a similar manner as analysis of genotype except the independent variable will be haplotypes instead of genotypes. Each individual will be modeled using all of his/her possible haplotype combinations with weights according to the probability of each haplotype. An overall omnibus likelihood ratio test for all haplotypes having a null effect will be conducted.

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://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

____X__ Yes _____ No

Reference List

(1) Hattersley AT. Maturity-onset diabetes of the young: clinical heterogeneity explained by genetic heterogeneity (vol 15, pg 15, 1998). Diabetic Medicine 1998; 15(5):437.

(2) Hani EH, Stoffers DA, Chevre JC, Durand E, Stanojevic V, Dina C et al. Defective mutations in the insulin promoter factor-1 (IPF-1) gene in late-onset type 2 diabetes mellitus. Journal of Clinical Investigation 1999; 104(9):R41-R48.

(3) Urhammer SA, Rasmussen SK, Kaisaki PJ, Oda N, Yamagata K, Moller AM et al. Genetic variation in the hepatocyte nuclear factor-1 alpha gene in Danish Caucasians with late-onset NIDDM. Diabetologia 1997; 40(4):473-475.

(4) Moller AM, Urhammer SA, Dalgaard LT, Reneland R, Berglund L, Hansen T et al. Studies of the genetic variability of the coding region of the hepatocyte nuclear factor-4alpha in Caucasians with maturity onset NIDDM. Diabetologia 1997; 40(8):980-983.