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ARIC Manuscript Proposal
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1. Title: Diabetes Genes in African Americans I: Case-Control Studies

2. Writing Group: Brancati (lead), Boerwinkle, Sharrett, Szklo, Kao, Lei, Shuldiner, Watson

3. Timeline: Depends on technical aspects of DNA processing and analysis (1-2 yrs.)

4. Rationale: Previous studies have identified mutations in a variety of candidate genes, which appear to be associated with obesity, insulin resistance, and/or non-insulin-dependent diabetes mellitus. Such candidate genes include those coding for the beta-3 adrenergic receptor, the insulin promoter, fatty acid binding protein 2, the glucagons receptor, glucose transporter 2, and mitochondrial tRNA. Previous studies of these genes have been limited by highly selected populations, small sample sizes, lack of data concerning known behavioral risk factors for obesity and NIDDM such as diet and physical activity, and few data on African Americans, a group high at risk for NIDDM and its complications. The identification of genotypes that confer risk for obesity, insulin resistance, and NIDDM in larger populations would represent an important advance in our understanding of the pathophysiology of these conditions. These genotypes would also have immediate applications as a prognostic markers in observational and interventional studies of persons at risk for NIDDM.

5. Main Hypothesis: Mutations in the aforementioned genes are associated with the presence of obesity, hyperinsulinemia, and NIDDM in African Americans.

6. Design: Case-control studies stratified by race, with three distinct case groups and a single comparison group.

Case #1:	Diabetes mellitus (ARIC definition, including undiagnosed cases)
Case #2:	Severe obesity (Top decile of body-mass index)
Case #3:	Hyperinsulinemia, without diabetes (Top decile in non-diabetes)
Control:	Random sample of all non-cases

7. Data: Case-control status: Diabetes, body-mass index; fasting glucose and insulin
Exposure status: Diabetes susceptibility genotypes to be determined from DNA extracted from existing frozen buffy coat
Covariates: Age, race, gender, education, physical activity indices, dietary energy intake, parental history of diabetes, smoking

8. Sample Size: 270 in each of the three case groups and 1,080 in the one control group, comprising a total of 1,803 distinct individuals. [See attachment for power calculations; note that case definitions partially overlap]

Frequency of Selected Diabetes Susceptibility Alleles by Ethnic Group with Corresponding Power to Detect Modest and Strong Associations with Diabetes, Hyperinsulinemia, and/or Obesity in a Sample of 1,803 African Americans ARIC Participants

Gene	**Mutation**	**Ethnicity/ Allele Freq**	**Prevalence**		**Power to detect**	
			Homo-zygotes	**Hetero-Zygotes**	**OR = 1.5**	**OR = 3.0**
Beta 3 adrenergic receptor	Trp64Arg	Afr Am = .120	.010	.210	.80	Greater than .99
Insulin promoter	8 bp insert	Afr Am = .009	.000	.017	Less than .20	.80
Glucagon receptor	Gly40Ser	Afr Am = ?	?	?	?	?
		White = .003	.000	.006	.60	.90
Fatty acid binding protein 2	Ala54Thr	Afr Am = ?	?	?	?	?
		Pima = .290	.090	.420	.80	Greater than = .99
Glucagon transporter	Thr110Ile	Afr Am = .400	.160	.480	.80	Greater than = .99
Mitochondrial tRNA	np3243 A-G	Afr Am = na	Na	?	?	?
		Japan = na	Na	.010	Less than .20	.60

Notes:

1. Where the prevalence of the genotype in African Americans is unknown, power is calculated using prevalence data in other ethnic groups, as indicated.
2. Homozygotes and heterozygotes are pooled for final power calculation.
3. Where alleles have been found only in diabetic individuals, population allele frequency was back calculated using race-specific diabetes prevalences from ARIC: 17.4% in African Americans vs. 7.1% in whites.