Variants of the insulin receptor substrate-1 (IRS-1) and fatty acid binding protein-2 (FABP2) genes and the risk of type 2 diabetes mellitus, obesity, and hyperinsulinemia in African Americans: The Atherosclerosis Risk in Communities (ARIC) Study

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Few studies have addressed the genetic basis of type 2 diabetes mellitus in African Americans despite their high risk. We conducted a community-based case-control study of African American men and women in the ARIC Study. The allele frequencies of the Gly972Arg variant of the IRS-1 gene and the Ala54Thr variant of the FABP2 gene were compared in 1,050 normal controls to 3 case groups: 1) 263 diabetics (self-report of physician diagnosis, use of diabetic medication, or fasting glucose greater than or less than 7.8 mM), 2) 260 obese (body mass index (BMI) in top decile, greater than 38.3 kg/m^2), and 3) 258 hyperinsulinemics (fasting insulin in top decile, greater than 26U/ml). Detection of variants was performed by polymerase chain reaction and restriction fragment length polymorphism analysis. Allele frequencies of Gly972Arg IRS-1 and Ala54Thr FABP2 were 0.07 and 0.22 respectively; there were no differences in allele or genotype frequencies between case and control groups for either gene variant. In weighted linear regression of all cases and controls, the presence of the IRS-1 gene variant was associated with a 0.85 kg/m^2 higher BMI ($p=0.04$). However, BMI did not modify the effect of Gly972Arg IRS-1 on diabetes risk ($p=0.98$). Cardiovascular traits such as fasting insulin, fasting glucose, BMI, systolic blood pressure, HDL and LDL cholesterol, and triglycerides were also examined in the control group stratified by genotype. Of these, the only significant association was between the FABP2 gene variant and fasting glucose: Ala54 homozygotes and heterozygotes has a mean (SD) fasting glucose of 5.4 (0.6) mM vs. 5.6 (0.7) mM in Thr54 homozygotes ($p=0.01$). These results suggest that in African Americans, the IRS-1 and FABP2 gene variants do not markedly increase the risk of diabetes, obesity, and hyperinsulinemia, but may lead to small increases in BMI and fasting glucose.

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