
Associations between genetic variation in tumor necrosis factor receptors 1 and 2 and insulin resistance: The Coronary Artery Risk Development in Young Adults (CARDIA) Study

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Background: Members of the tumor necrosis factor receptor superfamily, including receptors 1 and 2 (TNFRSF1A, TNFRSF1B), have been shown to influence the regulation of insulin signaling pathways and may be involved in the development of insulin resistance (IR). Identifying genetic risk factors for the development of IR may help identify individuals at increased risk of developing diabetes and CVD. Using longitudinal data from CARDIA, we examined the association between IR and common patterns of variation in the TNFRSF1A and TNFRSF1B genes in non-diabetic African Americans (AA, n=1,598) and European Americans (EA, n=1,952), aged 18-30 at baseline. **Methods:** IR was measured by the homeostasis model assessment (HOMA) ((fasting insulin X fasting glucose)/22.5) using data from five exams (baseline (1985-86) and years 7, 10, 15, and 20). SNPs with a minor allele frequency $\geq 5\%$ were identified by resequencing 24 AA and 23 EA individuals (<http://pga.gs.washington.edu>). From those identified, 11 tagSNPs for TNFRSF1A and 28 for TNFRSF1B were chosen using linkage disequilibrium-based criteria. Haplotypes were estimated using Phase (v. 2.1). Race- and sex-specific GEE linear models were used to examine the associations between tagSNPs/haplotypes and IR. Models were adjusted for age, center and percent African ancestry. **Results:** The T allele for TNFRSF1A 10186 was associated with increased HOMA scores and insulin levels in the AA population compared to CC homozygotes (Table 1). In women this association was statistically significant. No evidence for other associations was found for the AA population, and no associations between IR and TNFRSF1A were found in the EA population. Haplotype results were consistent with SNP analyses. No associations with IR were found for TNFRSF1B. **Conclusions:** These findings suggest that TNFRSF1A 10186, which alters the amino acid residue at position 75 from PRO to LEU, is associated with increased insulin levels in young, non-diabetic AA women.

Table 1: Results of GEE Analysis of TNFRSF1A 10186 (rs4149637; MAF: 0.081); African American Population		
	Percent Change for Carriers of T Allele* (95% CI)	
	Men [n=665]	Women [n=933]
HOMA Score	8.2 (-1.0, 18.2)	15.2 (6.8, 24.3)
Fasting Plasma Glucose	0.1 (-1.5, 1.7)	0.5 (-1.0, 1.9)
Fasting Plasma Insulin	8.1 (-0.1, 17.0)	14.6 (6.8, 23.0)
*as compared to CC homozygotes		