

ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #536

1. a. Full title: The β 3-Adrenergic Receptor Trp64Arg Polymorphism and Risk of Incident CHD.
b. Abbreviated title: β 3-AR and CHD

2. Writing group:

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3. Timeline: Data collection is complete; analysis and manuscript preparation remain.

4. Rational:

The β 3-Adrenergic Receptor, [β 3-AR] is a G-coupled receptor expressed in white and brown adipose tissue, and likely plays a significant role in controlling energy expenditure through regulation of lipolysis and thermogenesis in these tissues. A tryptophan to arginine [Trp64Arg] polymorphism has been identified in the protein's first intracellular loop. This mutation has been implicated by multiple studies in the etiology of obesity, insulin resistance and diabetes. The possible clinical significance of this β 3-AR polymorphism and the known relationship of obesity insulin resistance and diabetes with CHD, prompts us to investigate the relationship between this gene mutation and atherosclerosis and CHD in the ARIC study.

5. Main issues/Hypotheses to be addressed:

- (a) Ability of the β 3-AR polymorphism to predict incident CHD case status, both individually and after considering the predictive ability of other risk factors, particularly BMI, insulin and glucose.
- (b) Ability of the β 3-AR polymorphism to predict carotid artery disease case status, both individually and after considering the predictive ability of other risk factors, particularly BMI, insulin and glucose.

6. Data:

The case-cohort study sample will be used for these analyses. The primary dependent variable is incident CHD case status. However, the results from incident CHD status will be compared to those obtained from the analysis of carotid artery wall thickness. Independent variables include, but are not limited to the β 3-AR polymorphism and the vector of traditional risk factors, such as age, BMI, plasma lipids, insulin, glucose, hypertension status, etc.