1. Full title: alpha-Adducin Gly460Trp polymorphism as a predictor of cardiovascular-related morbidity and mortality
   Abbreviated title: alpha-Adducin and cardiovascular disease

2. Writing group:
   First: Molly Bray
   Lead: Eric Boerwinkle
   Address: Human Genetics Center
   UT Houston Health Science Center
   PO Box 20334
   Houston, TX 77225
   Phone: (713) 500-9816; Fax: (713) 500-0900
   Email: eboerwin@gsbs.gs.uth.tmc.edu

   Other authors: Peter Doris, Alanna Morrison and Aaron Folsom

3. Timeline:
   Measurement of the alpha-adducin Gly460Trp polymorphism is currently underway and is expected to be complete by December 1998. A draft manuscript is projected to be distributed for internal circulation by April, 1999.

4. Rationale:
   Elevated blood pressure or hypertension is a well-established risk factor for cardiovascular disease. Though studies of families, adoptees, and twins estimate that approximately 30-40% of the inter-individual variation in blood pressure levels can be explained by genetic factors (Perusse, 1991; Rice, 1990), blood pressure levels and hypertension status are also influenced by age, sex, body mass, nutrition, exercise and stress. Animal models of hypertension have served as useful tools in elucidating genes and physiologic processes that underlie blood pressure regulation and hypertension etiology. One such model is the Milan hypertensive strain of rats (MHS). Bianchi et al. (1994) have determined that approximately 50% of the differences in blood pressure observed between MHS rats and their normotensive counterparts can be accounted for by a variant in the alpha-adducin gene. This variant has been demonstrated to enhance Na-K pump activity and produce an increase in renal tubular sodium reabsorption (Bianchi, 1994). Subsequently, several researchers have reported that a non-synonymous mutation in exon 10 of the human alpha-adducin gene (Gly460Trp) may also be associated with essential hypertension, as well as salt-sensitivity and low plasma renin activity in subjects from Europe and Japan (Casari, 1995; Cusi, 1997; Ishikawa, 1998; Manunta, 1998). Nevertheless, this locus was not associated with hypertension or blood pressure in two other Japanese studies or in a Scottish sample (Ishikawa, 1998; Kato, 1998; Kamitani, 1998). To date, no studies have investigated the contribution of the Gly 460Trp variant to incident CHD or to carotid arterial wall thickening. Therefore, the purpose of this investigation will be to determine the ability of the Gly 460Trp genotype to predict incident cardiovascular-related disease.

5. Main Issues/Hypotheses to be addressed:
   a. Influence of the Gly460Trp polymorphism on blood pressure levels and hypertension status.
   b. Influence of the Gly460Trp polymorphism on incident CHD and carotid artery wall thickness case status.
   Analyses will be done univariately and after controlling for a vector of traditional cardiovascular disease risk factors (excluding blood pressure levels
and hypertension status).

c. Influence of the Gly460Trp polymorphism on incident CHD and carotid artery wall thickness case status, after controlling for the influence of blood pressure levels and hypertension status.

d. For all analyses, race- and gender-specific effects will be explored. Comparison of the results obtained in b and c above will indicate whether the effects of this adducin polymorphism on CHD (if any) are mediated through its effects on blood pressure levels and hypertension status or through alternative pathways.

6. Data:
The Gly460Trp variant is being measured in the entire simultaneous batch, which includes the cohort random sample, incident CHD cases, ultrasound cases and controls, subjects measured by MRI, subjects measured for PAD, and an African American sample. Proportional hazard regression analyses will be conducted in the incident CHD cases, ultrasound cases and controls, and the cohort random sample. Relationships between Gly460Trp genotype and cardiovascular disease risk factors will be conducted in the cohort random sample, the PAD cases, the ultrasound cases, and the supplementary African-American cases and controls, with additional stratification of this sample as recommended by Dr. Chambless.