

## ARIC MANUSCRIPT PROPOSAL FORM

Manuscript # 436

**1. a. Title:** Relation between platelet glycoprotein IIIa (PL<sup>A2</sup>) polymorphism and a risk of incident coronary heart disease

**b. Abbreviated title:** GPIIIa and CHD

### 2. Writing Group:

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### 3. Timeline:

DNA samples from the incident coronary heart disease cases (CHD) and a cohort random sample will be needed for determining platelet alloantigen genotypes by ASA technique. Once the samples are available, around 250 polymorphism tests can be completed per month.

### 4. Rationale:

The blood platelet plays an important role in hemostasis, thrombosis and atherosclerosis (1). In stimulated platelets, major platelet membrane glycoprotein (GP) IIb-IIIa complex mediates platelet aggregation by serving as the receptor for fibrinogen and von Willebrand factor (2). Formation of a platelet aggregation is the final event in myocardial ischemic events such as myocardial infarction unstable angina.

Both the genes and the encoded glycoprotein products for GP IIb and GP IIIa have been found to be polymorphic. GP IIIa represents one of the most polymorphic molecules on the platelet surface. Amino acid substitutions in platelet membrane glycoproteins result in alloantigens. To date, three different alloantigenic systems have been localized to the GP IIIa, including PL<sup>A</sup> and Pen. A leucine to proline dimorphism at amino acid position 33 of GP IIIa is responsible for PL<sup>A</sup> (3). DNA analysis data demonstrates significant racial heterogeneity of the platelet alloantigen system including PL<sup>A1/A2</sup> (4). Preliminary data of Bray et. al suggested that GPIIIa polymorphism may represent the first inherited platelet thrombogenic risk factor for coronary thrombotic events (5). However, the

sample size was small and the design was not prospective. Hence, the association of PL<sup>A2</sup> and CHD remains uncertain.

To examine the potential relationship between GPIIIa polymorphism and artery disease, we propose to determine the platelet alloantigen PL<sup>A1/A2</sup> genotypes (GPIIIa Leu33 vs Pro33) in incident CHD cases and cohort random controls (2 groups). The ARIC population study is well suited for this investigation and important new information will be generated to enhance our understanding of hemostatic risk factors.

Platelet antigen genotypes will be determined from genomic DNA after PCR amplification and agarose gel electrophoresis using sequence-specific primers to discriminate between alleles, according to published procedure (ASA technique) (6).

### **5. Major Hypothesis:**

We postulate that individuals carrying PL<sup>A2</sup> allele (GP IIIa Pro33) are at a higher risk of developing coronary thrombotic events. Platelet GPIIIa polymorphism and its relation to CHD has not been studied in the US population. The ARIC study provides an excellent opportunity to test this hypothesis.

### **6. Data analysis:**

All the laboratory data will be transmitted to the Coordinating Center for statistical analysis.

### **7. References:**

1. K.K. Wu: Platelet activation mechanisms and markers in arterial thrombosis. *J Int Med* 239: 17-34, 1996.
2. P.J. Newman: Platelet GPIIb-IIIa: Molecular variations and alloantigens. *Thr Haem* 66(1): 111-118, 1991.
3. P.J. Newman, N. Valentin: Human Platelet Alloantigens: Recent findings, new perspectives. *Thr Haem* 74(1): 234-239, 1995.
4. H.O. Kim, Y. Jin, T.S. Kickler, K. Blakemore, O.H. Kwon, P.F. Bray: Gene frequencies of the five major human platelet antigens in African Americans, White and Korean populations. *Transfusion* 35(10): 863-867, 1995.
5. E.J. Weiss, P.J. Goldschmidt-Clermont, S.P. Schulman, T.S. Kickler, P.F. Bray: The platelet glycoprotein IIIa polymorphism PL<sup>A2</sup>: An inherited risk factor for coronary thrombotic events. Abstract S-1807, The American Society of Hematology, 37<sup>th</sup> Annual Meeting, Seattle, Washington, December 2-5, 1995.

6. B. Skogen, D.B. Bellissimo, M.J. Hessner, S. Santoso, R.H. Aster, P.J. Newman, J.G. McFarland: Rapid determination of platelet alloantigen genotypes by polymerase chain reaction using allele-specific primers. *Transfusion* 34:955-960, 1994.