ARIC Manuscript Proposal # 465 (Revised-Change in Lead Author)

PC Reviewed: 08/14/02   Status: __A__   Priority: _____
SC Reviewed: 08/15/02   Status: __A__   Priority: _____

1.a. Full Title: The variable number of tandem repeat polymorphism of platelet glycoprotein Iba and risk of coronary heart disease

  b. Abbreviated Title (Length 26 characters): Platelet GPIb Polymorphism

2.   Writing Group (list individual with lead responsibility first):

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   Writing group members:
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                              Chul Ahn

3.   Timeline:
        For the analysis of the GPIb genotype, DNA samples from random cohort sample and the incident CHD cases will be used. We expect to complete the analysis within 1 year; a report formatted as a draft manuscript will be presented to the Publication and the Steering Committee three months after the completion of the analysis.

4.   Rationale:
        Platelets play an essential role in the development of arterial thrombi, which can lead to myocardial infarction and stroke. In the development of the coronary thrombus, platelets can become activated initially by two means, by the exposure of thrombogenic substances in the artery wall following plaque rupture and by the high shear forces found in regions of arterial stenosis. One platelet receptor that participates in both of these processes is the glycoprotein Ib-IX-V complex, which is the first receptor to attach the platelets to the vessel wall by recognizing von Willebrand factor exposed at the site of vessel damage. The interaction of the complex with soluble von Willebrand factor in regions of high shear is also a sine qua non of shear-induced platelet aggregation. Thus polymorphisms of this receptor complex are likely to be determinants of thrombotic risk. Those variants that lower the threshold for thrombosis may represent risk factors for myocardial infarction or stroke.
We have characterized a polymorphism of GPIba (the ligand-binding subunit of the complex) that results in four alleles that produce polypeptides that differ in the number of

thirteen amino acid repeats present in a mucin-like region of the molecule. Because this polymorphism affects a region thought to act as a spacer between the plasma membrane and the ligand-binding region, the distance of the ligand-binding region from the plasma membrane will vary greatly between individual alleles. This change in structure may predispose platelets with longer polypeptides to shear-induced platelet activation. We propose to study the prevalence of the polymorphism in defined subset of large population for which a number of clinical and molecular parameters have been defined.

5.   Main Hypothesis/Study Questions:
    Because of the profound challenges in the GPIba structure induced by added repeats, we postulate that individuals with the longer variants of platelet GPIba are at the higher risk of developing coronary and cerebral thrombotic events. The ARIC study provides a great opportunity to test this hypothesis.

6.   Data (variables, time window, source, inclusions/exclusions):
    The clinical data necessary to correlate the GPIba genotype with risk of thrombosis already exists. We will use DNA samples from individuals belonging the random cohort and incident CHD events occurring between Visit 1 and December 31st 1998 to determine their GPIba genotype. These data will be analyzed locally by Dr Chul Ahn.

7.a. Will the data be used for non-CVD analysis in this manuscript?   _____ Yes   __x__ No

  b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used?   _____ Yes   _____ No
     (This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?   __x__ Yes   _____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"?   __x__ Yes   _____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.
     ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

     ____x__ Yes   _____ No