

## ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #466

1. a. Full Title: Relation of Coagulation Factor XIII Polymorphism (Val34Leu) and Risk of Incident Coronary Heart Disease.

b. Abbreviated Title: F XIII Polymorphism and CHD

2. Writing Group:

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3. Timeline:

F XIII Val34Leu polymorphism will be analyzed on DNA samples from the incident CHD cases and a cohort random sample, using PCR amplification of exon 2. Once the method is setup and DNA samples available, approximately 6 months will be needed for the analysis to be completed.

4. Rationale:

Coagulation Factor XIII is essential for normal hemostasis. It plays an important role in the final stages of blood coagulation and the regulation of fibrinolysis. It is responsible for the formation of bonds between fibrin chains during blood clotting. These crosslinks modify and stabilize the clot structure and reduce its sensitivity to degradation by proteases. F XIII also plays a role in wound healing and tissue repair processes. F XIII also cross-links several other proteins such as alpha-2-antiplasmin fibronectin and collagen. Although the human F XIII gene (subunit a) is one of the most polymorphic gene loci so far discovered (1, 2), very little is currently known about the residues involved in substrate binding and catalysis. Therefore, an analysis of mutations causing amino acid substitutions may provide insight into structure-function relationship of the various domains within the F XIII protein. Recently, new F XIII polymorphism has been described with the substitution at Val34Leu (3). This change may be important for the activation of the protein, since the change is only three residues away from the activation peptide cleavage site. The true effect of this mutation on the enzyme function needs to be

analyzed. We think that the ARIC population is an excellent opportunity for such an analysis. We propose to study the F XIII Val34Leu polymorphism in the ARIC incident CHD cases and random cohort samples. We postulate that this mutation leads to producing a clot of high mechanical strength with an increased resistance to degradation by plasmin, with increasing thrombotic risk.

#### 5. Main Hypothesis:

We postulate that individuals carrying Val34Leu mutation on the F XIII molecule are at higher risk of developing coronary thrombotic events. The relationship of F XIII polymorphism and thrombotic disorders has not been studied.

#### 6. Data (variables, time window, source, inclusions/exclusions):

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

#### References:

Mikkola, H., Syrjala, M., Rasi, V., Vahtera, E., Hamalainen, E., Peltonen, L., Palotie, A., (1994). Deficiency in the A subunit of coagulation factor XIII: two novel point mutations demonstrate different effects on transcript levels. *Blood*, 84;517-525.

Anwar, R. Stewart, A.D., Miloszewski, K.J.A., Losowski, M.S. (1995). Molecular basis of inherited factor XIII deficiency: identification of multiple mutations provides insights into protein function. *Br J Haematol*, 91;728-735.

Suzuki, K., Henke, J., Iwata, M., Henke, L., Tsuji, H., Fukunaga, T., Ishimoto, G., Szekelyi, M., Ito, S. (1996). Novel polymorphisms and haplotypes in the human coagulation factor XIII A-subunit gene. *Hum Genet*, 98;393-395.