ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #257

1. Title:
Relation Between Factor VII Polymorphism and Factor VII Activation by Postprandial Hyperlipidemia

2. Writing Group:
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3. Timeline:
DNA (or buffet-coat) samples from 504 ARIC subjects who participated in the postprandial Lipemia study will be needed for determining factor VII gene polymorphism by PCR. These samples are stored in the Central Lipid Laboratory. Once the samples are available, factor VII polymorphism tests will be completed in 2-3 months.

Factor VIIa, VIIc, and VIIag measurements of basal and 3 1/2 hour postprandial samples are being performed and will be completed shortly.

Lipid measurements of these samples have been completed.

4. Rationale:
It was recently reported that an MspI polymorphism of the factor VII gene is strongly associated with plasma factor VIIc levels (1). This MspI polymorphism is caused by a single nucleotide change, a guanine to adenine substitution which leads to the replacement of arginine at position 353 amino acid residue of factor VII molecule (Arg-353) with glutamine (Gln-353). In this sample of 284 men from the UK, the frequency of the allele coding for factor VII Gln-353 was 0.1. Carriers for the Gln-353 allele had factor VIIc approximately 20% lower than the sample mean (1). A subsequent study of 84 European whites, 10% Afro-Caribbeans and 126 Gujarate Indians residing in London revealed a higher VII Gln-353 allele frequency in Gujarates Indians (0.25) than in Afro-Caribbeans (0.08) or whites (0.09). Individuals heterozygous for the Gln-353 allele had factor VIIc levels below that of individuals lacking the allele in all three ethnic groups. This association was not statistically significant in the European whtie or Afro-Caribbean groups because of the small sample size.

Factor VII gene polymorphism and its relation to factor VII levels or activity have not been investigated in US population. In this study, we propose to estimate the frequency of VII Arg-353 and Gln-353 alleles among whites and African-Americans in a sample of the ARIC population. We will determine the relationship between VII alleles and factor VIIag, VIIa, and VIIc. We will also determine the influence of triglyceride levels, particularly the postprandial levels on the association of VII alleles with VII levels.

We propose to examine 504 ARIC subjects participating in the PPL study. VII Arg-Gln polymorphism will be determined by PCR using primers reported by the London group (1). DNA of most samples has been extracted by Wolfgang Patsch and will be used in this study. For samples that require DNA extraction, we will request buffet coat samples and will extract DNA in the hemostasis laboratory. Factor VIIag, VIIc, and VIIa in these samples are being measured. Lipid profiles and other factors have been determined.

Data will be analyzed under the direction of Woody Chambless at the Coordinating Center.

5. Major Hypothesis:

Factor VII levels are influenced by factor VII gene polymorphism. Factor VII: Arg-353 allele has a higher factor VII levels than factor VII: Gln-353 allele. We further postulate that the factor VII level in individuals carrying Arg/Arg gene is more susceptible to triglyceride activation.

6. Data analysis:
All the laboratory data will be transmitted to the Coordinating Center. Data will be analyzed at the CC with input from all investigators. In the analyzing of data, special attention will be paid to the case-control nature of the selection.

REFERENCES

1. Green, F, Kellher, C, Wilkes, H, Temple, A, Meade, T, and Humphries. A common genetic polymorphism associated with lower coagulation factor VII levels in healthy individuals. Arterioscl. and Thromb. 11: 540-6, 1991.

2. Lane, A, Cruickshank, JK, Mitchell, J, Henderson, A, Humphries, S, and Green, F. Genetic and environmental determinants of factor VII coagulant activity in ethnic groups at different risk of coronary heart disease. Atheroscl. 94: 43-50, 1992.