1. Title:
Lewis Genotype and Incident CHD

2. Writing Group:
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3. Timeline:
Start Analyses: 01/99
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4. Rationale:
A prospective study in middle-aged Danish men has shown that the Lewis blood group phenotype Ld (a-,b-) is a significant predictor of CHD events (1). A similar cross-sectional finding was recently reported from the FHS Study for white Americans, including women (2). Mechanisms for this association are not established. The relationship of Lewis genotypes to CHD, other manifestations of atherosclerosis, or risk factors for CHD and atherosclerosis has not been examined at the moment.

The Lewis negative phenotype is fairly common. Both in the Danish study and in the FHS study its prevalence approached 10%. In African Americans it is even more common. If it doubles the risk of CHD and even more than doubles the risk of dying from a CHD event, as was suggested by the Danish study, its public health significance is considerable.

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The major Lewis antigens Le\(^a\) and Le\(^b\) are fucosylated glycosphingolipids synthesized by exocrine epithelial cells and then passively adsorbed onto erythrocytes in the peripheral circulation giving these blood cells their Lewis phenotype. Physiologically, they participate in different biological processes such as embryogenesis, tissue differentiation, tumor metastasis, inflammation and bacterial adhesion. Therefore, they may play a role also in the pathogenesis of CHD events. In studies mentioned above, the Lewis phenotype has been determined immunologically from red cells using monoclonal a and b antibodies. The human Lewis (1,3/1,4)-fucosyltransferase (FUT 3) gene, located on the short arm of chromosome 19 (19p13.3), has been cloned by Kukowska-Latallo et al (3), which has enabled more exact allelic characterization and genotyping of Lewis-negative individuals. Subsequent research has revealed that the genetic background of Lewis negative phenotype is heterogeneous. Furthermore, Lewis phenotype can change as a result of malignant and other severe diseases or pregnancy. There are, however, two dominating alleles among Caucasians: one with mutations at nucleotides 59 (T to G, Leu\(^{20}\) to Arg) and 1067 (T to A, Ile\(^{356}\) to Lys), and the other with
mutations at nucleotides 202 (T to C, Trp\textsuperscript{68} to Arg) and 314 (C to T, Thr\textsuperscript{105} to Met). When these alleles appear together the individual becomes phenotypically Le(a-b-) on the red cells. In a Swedish study (4) this allelic distribution explained 12 of the 15 Lewis negative phenotypes (i.e. 1 le\textsuperscript{59/1067} le\textsuperscript{59/1067}, 7 le\textsuperscript{59/1067} le\textsuperscript{202/314}, 4 le\textsuperscript{202/314} le\textsuperscript{202/314}). A recent study aimed to determine the relative contributions of T202C and C314T mutations to the Lewis negative phenotype (5), found that the T202C mutation decreased the enzyme activity to less than 1% of the wild type FUT 3 allele, whereas the isolated C314T mutation did not lead to a decrease in the enzyme activity. It was concluded that the T202C mutation leading to Trp\textsuperscript{68} to Arg substitution, is responsible for the appearance of the Lewis negative phenotype in individuals homozygous for both the T202C and C314T mutations. In a Japanese population (6), the mutations at nucleotides 202 and 314 are uncommon, but a mutation at nucleotide 508 (G to A, Gly\textsuperscript{170} to Ser) is common.

The genotyping will take place at the laboratory of Dr. Brent Weston, Department of Pediatrics, UNC, which is one of the pioneering laboratories in this field. The laboratory will be blinded to phenotype during the genotyping work.

5. Study Questions/Aims/Hypotheses:
We hypothesize that genetic mutations causing Lewis negative phenotype and inactivating the FUT 3 enzyme lead to dysfunctional inflammatory reactions and, hence, increased risk of incident CHD. Therefore, we propose to examine the associations of Lewis genotypes and incident CHD, contrasted to the cohort-representative sample. If an association is found, we will further examine, whether it is independent of apo E genotype, E-selectin genotype, plasma concentrations of soluble adhesion molecules, plasma lipid levels, and systemic markers of inflammation.

6. Data Requirements:
The Lewis genotype data will be transferred from Dr. Weston's laboratory to Dr. Pankow's office for inventory of completeness and for analysis of the blinded duplicate samples. The data and corresponding data management information will then be transferred to the ARIC coordinating center. The endpoint and covariate data required for analysis and publication are available.

7. Manuscripts with Overlap:
None to our knowledge

8. Agency Responsible for Analysis:
The analyses will be conducted at the ARIC Coordinating Center

9. References:
6) Liu Y, Koda Y, Soejima M, Uchida N, Kimura H. PCR analysis of Lewis negative gene mutations and the