1. Full Title: Polymorphisms of matrix metalloproteinase (MMP) 3 and MMP9 and the Risk of Cardiovascular Disease

Abbreviated Title: MMP and CVD

2. Writing Group
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3. Timeline: Genotyping data is already available in Table 3 for MMP-3 and Table 4 for MMP-9. We project that analyses and manuscript preparation will take place over the next year.

4. Rationale:

Matrix metalloproteinases (MMPs) have proteolytic activity against a number of tissue elements that play an integral role in vascular integrity, including collagen, elastin and proteoglycans.[1] Increased activity of MMPs within arterial plaques may contribute to plaque instability and ultimately rupture. MMPs are released by macrophages within damaged vasculature and hence, are generally considered part of the inflammatory response.

Genetic variations in the promoter region of MMP-3 (5A/5A and 5A/6A) have been associated with increased risk of myocardial infarctions in several case-control studies compared to the 6A variant.[2-6] However, the 5A variant, which is associated with plaque instability due to greater proteolytic activity, is not the same variant that has been associated with increased stenosis on coronary angiography (6A).[4] Consistent with this observation, Gnasso et al. and Rundek et al. have independently shown that individuals with the 6A/6A genotype had larger common carotid diameters and intimal medial thickness.[7;8] Hence, the 5A polymorphism may lead to plaque instability and identify persons at risk of plaque rupture, whereas the 6A variant appears to be more strongly associated with plaque size. However, prior studies have generally been small and none were prospective. Furthermore,
most studies have not been able to evaluate the potential for gene/environment interactions. Only one study examined the potential for a gene x smoking interaction and found a synergistic effect of smoking and the presence of the 5A allele. [6] We propose to extend these findings to ARIC participants and examine, in a prospective fashion, the association between MMP-3 polymorphisms and the risk of cardiovascular events (including myocardial infarction and stroke) and measures of subclinical disease (IMT). In addition, we will explore interactions between genetic polymorphisms and traditional CVD risk factors (including smoking) and inflammation, as measured by C-reactive protein (CRP).

Serum levels and genetic polymorphisms of MMP-9 have also been associated with increased risk of cardiovascular events. A prospective study of 1127 patients with known cardiovascular disease demonstrated that person in the highest quartile of circulating MMP-9 had a approximately a 3-fold increase in risk of cardiovascular mortality after a mean of 4 years of follow-up. [9] Genetic variations in the promoter region of the MMP-9 gene have also been associated with increased risk of cardiovascular disease. [9-12]

5. Main hypothesis/study questions:

Do polymorphisms in the promoter region of MMP-3 and MMP-9 predict incident CHD or stroke events? To the extent the case-cohort design allows, CVD mortality, IMT thickness and all-cause mortality will be examined as well.

Do levels of inflammatory markers differ according to the type of MMP-3 or MMP-9 polymorphism? The inflammatory markers of interest are: whole cohort - fibrinogen, vWF; Table 3 - CRP IL-6, MMP-1, TIMP-1 and TNF-alpha; Table 4 - hsCRP, LpPLA2, ICAM-1

Are there gene x environment interactions with MMP-3 or MMP-9 polymorphisms and smoking? BMI? Lipids? Blood pressure?

Do these associations differ by race and/or sex?

To the extent possible, we will examine the combined effects the two polymorphisms on outcomes.

6. Data: The following variables will be needed for these analyses: age, sex, race, center, CVD events, IMT thickness, mortality events. Covariates of interest include age, race, sex, blood pressure, diabetes, history of coronary heart disease, body mass index, smoking status, lipid levels and levels of markers of inflammation (CRP, fibrinogen).

Analysis will use the Barlow Macro for analysis of case-cohort data following the design layout in Table 3 and Table 4. When each gene is analyzed separately the analysis will follow the usual setup for the table. However, in examining the two variables together, the overlap between the case and sub-cohort selection criteria will have to be considered and advice from the coordinating center on the extent to which an overlap analysis will yield valid results will be needed.

MMP-3 and MMP-9 polymorphisms will be used to predict CVD events and all-cause and CVD mortality, independent of potential confounders, including age, race, sex, blood pressure, lipids diabetes, history of CAD, BMI, smoking status and markers of inflammation (CRP, fibrinogen). Additional analyses, stratified by these covariates, will also be performed.
We will also determine the association between these polymorphisms and levels/categories of traditional CVD risk factors (lipids, blood pressure, etc.) and markers of inflammation as the latter are available in each case-cohort subgroup.

7. **Will the data be used for non-CVD analysis in this manuscript?** No; the outcomes of interest are CVD events and all-cause and CVD mortality.

8. **Will the DNA data be used in this manuscript?** Yes.

9. **Review of existing ARIC Study manuscript proposals:** No overlapping proposals were found. Related analyses were done using the public use data with fewer events. Ron Hogeveen will provide input about overlap with manuscripts which focus on levels of inflammatory markers (without genotype data) from Tables 3 & 4.
Reference List


