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## Gene-wide Variation in Plasminogen Activator Inhibitor-1 (PAI-1) and MI in Women <60 Years Old

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**Background:** Plasma levels of the fibrinolytic inhibitor PAI-1 are associated with an increased risk of coronary disease and are regulated in part by factors related to smoking, overweight, and insulin resistance. We previously observed that the 4G allele of the PAI-1 promoter 4G/5G polymorphism, which has been linked to greater PAI-1 levels, was associated with a decreased risk of MI in women < 45 years old. In an expanded study of women < 60 years old, we assessed whether additional common genetic variants in PAI-1, common gene-wide haplotypes, or interactions between these genetic factors and traditional cardiovascular risk factors (smoking, obesity, and diabetes) might also be associated with risk of MI in women under the age of 60.

**Methods:** Single nucleotide polymorphism (SNP) discovery data from SeattleSNPs (<http://pga.mbt.washington.edu>) were used to identify six tagSNPs representative of common (>10%) genetic variation across the entire PAI-1 gene. These tagSNPs were genotyped in 671 women < 60 years old from a population-based case-control study of MI in western Washington. Gene-wide haplotypes were estimated from tagSNPs using PHASE. Additive genetic effects and interactions were analyzed using multivariate logistic regression.

**Results:** The six tagSNPs formed six PAI-1 gene haplotypes, each with frequency >5%. In general, neither tagSNPs nor gene-wide haplotypes were associated with risk of MI. The 4G/5G polymorphism was not associated with risk of MI, either individually or in combination with other SNPs. The haplotype uniquely tagged by the 10381T allele in intron 7 was associated with decreased risk of MI in non-obese women (OR 0.5, 95% CI 0.2-0.9) and an increased risk in obese women (OR 2.3, 95% CI 1.0 - 5.4; interaction p-value 0.002), relative to the haplotype containing the common allele at all six variant sites.

**Conclusion:** In this application of gene-wide variation data from the PAI-1 gene, we identified a common haplotype that, in combination with obesity, may be associated with MI in women < 60 years old. Additional studies are needed to confirm these findings, to determine generalizability to other populations, and to clarify the obesity-related contribution of genetic variation in PAI-1.