Impact of Promoter and 9p21 Single Nucleotide Polymorphisms on Peripheral Blood Cell Expression of Genes Responsive to Levels of Obstructive Coronary Disease

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Authors: James A. Wingrove, Heng Tao, Susan E. Daniels, Steven Rosenberg, CardioDx, Inc. Palo Alto, CA; William E. Kraus , Duke Univ, Durham, NC; Robert S. Schwartz, Minneapolis Heart Institute and Foundation, Minneapolis, MN; Szilard Voros, Piedmont Heart Institute, Atlanta, GA; Eric J. Topol, Scripps Translational Science Institute, La Jolla, CA; for the PREDICT Investigators

Abstract:
Background: We have identified a set of genes whose expression levels in circulating peripheral blood cells distinguish patients with coronary artery disease (CAD). To understand the influence of genetics on the expression levels of theses genes, we have investigated the impact of *cis*- and *trans*- SNPs on the levels of gene expression.

Methods: DNA was isolated from 464 subjects (155 cases) undergoing coronary angiography participating in PREDICT, a multi-center trial, designed to compare peripheral blood gene expression with the extent of CAD. Cases had ≥50% stenosis in >1 major coronary artery; controls had <25% luminal stenosis in any major coronary artery as determined by quantitative coronary angiography. To evaluate the influence of promoter genotype on gene expression, we used TaqMan assays to genotype SNPs in the promoter regions of 12 genes. In addition to evaluating these *cis* effects, we also tested the impact of rs10757278, a SNP located at the 9p21 locus which has been correlated with coronary artery disease.

Results: Of the 12 genes evaluated, 7 showed a significant interaction ($p<0.05$) between SNP genotype and RT-PCR measured expression levels. The strongest interaction was seen with rs7559566, a SNP in the IL18RAP promoter ($p\ 2.5x10^{-47}$); this SNP also showed a significant interaction with disease status ($p=0.017$). *In silico* evaluation showed that 5 (42%) of the SNPs investigated resided within a putative transcription factor binding site, suggesting a possible mode of action. Evaluation of rs10757278, located at the 9p21 locus, showed a significant effect ($p<0.05$) on the expression levels of 2 genes: SLAMF7 and KLRC4. Interestingly, both of these genes are expressed predominantly in

natural killer cells.

Conclusion: We have identified *cis*- and *trans*- SNPs that affect the expression levels of a set of genes responsive to obstructive coronary disease. Further work will be required to elucidate the mechanisms by which these SNPs are influencing gene expression.