Department of Medicine

Phenotype And Genotype Effects on The Transcriptome In Cardiovascular Disease – *Tools to Identify Candidate Genes*

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Abstract
The overarching purpose of this thesis was to investigate the expression of human genes and how they relate to cardiovascular disease. This was pursued through five papers, each of which investigated different aspects of gene expression.

Paper I improved the technology for extracting gene expression information from microarrays. Its main purpose was to introduce the software package *GeneRegionScan*, which was developed for analysis of genomic regions with inaccurate annotation.

Paper II explored the genomic region surrounding the first identified single-nucleotide polymorphism (SNP) associated with cardiovascular disease. The purpose of the paper was to investigate transcript isoforms of the regional genes and their association to the risk-SNPs in the region. Eight new transcript isoforms were introduced, but no pattern of association with genotype was observed.

Paper III extended the methods of paper II, by expanding the search to 166 risk-SNPs known at the time. For each of these SNPs, it was hypothesized that one or more proximal genes had expression levels that were associated to the genotype of the SNP in question. It was reported that 47 of the SNPs had such genes, thus progressing from risk-SNPs towards risk-genes. In addition the paper introduced new concepts on distance between gene and risk SNP and on the tissue-specificity of associations.

Paper IV investigated the gene expression pattern of thoracic aortic aneurysm. It had previously been observed that patients with congenital bicuspid aortic valve (BAV) had increased severity and earlier onset age of aneurysm, when compared to patients with the normal tricuspid aortic valve (TAV). A fundamentally differing gene expression profile was observed between these two patient groups, and a possible immunological involvement in TAV patients was reported.

Paper V asked if the high-throughput methods of genomics and transcriptomics could be applied towards better prediction of future ischemic events in patients with established atherosclerosis. Risk-SNP profiles, gene expression profiles of circulating blood cells, and gene expression profiles of carotid plaque samples were utilized. Particularly gene expression profiles of carotid plaque provided improved prediction above that of the established risk markers of serum lipids, gender, age and smoking.

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