Expression Quantitative Trait Loci Acting Across Multiple Tissues Are Enriched in Inherited Risk for Coronary Artery Disease

Abstract:

Background-Despite recent discoveries of new genetic risk factors, the majority of risk for coronary artery disease (CAD) remains elusive. As the most proximal sensor of DNA variation, RNA abundance can help identify subpopulations of genetic variants active in and across tissues mediating CAD risk through gene expression. Methods and Results-By generating new genomic data on DNA and RNA samples from the Stockholm Atherosclerosis Gene Expression (STAGE) study, 8156 cis-acting expression quantitative trait loci (eQTLs) for 6450 genes across 7 CAD-relevant tissues were detected. The inherited risk enrichments of tissue-defined sets of these eQTLs were assessed using 2 independent genome-wide association data sets. eQTLs acting across increasing numbers of tissues were found increasingly enriched for CAD risk and resided at regulatory hot spots. The risk enrichment of 42 eQTLs acting across 5 to 6 tissues was particularly high (< = 7.3-fold) and confirmed in the combined genome-wide association data from Coronary Artery Disease Genome Wide Replication And Meta-Analysis Consortium. Sixteen of the 42 eQTLs associated with 19 master regulatory genes and 29
downstream gene sets (n > 30) were further risk enriched comparable to that of the 153 genome-wide association risk single-nucleotide polymorphisms established for CAD (8.4-fold versus 10-fold). Three gene sets, governed by the master regulators FLYWCH1, PSORSIC3, and G3BP1, segregated the STAGE patients according to extent of CAD, and small interfering RNA targeting of these master regulators affected cholesterol-ester accumulation in foam cells of the THP1 monocytic cell line. Conclusions-eQTLs acting across multiple tissues are significant carriers of inherited risk for CAD. FLYWCH1, PSORSIC3, and G3BP1 are novel master regulatory genes in CAD that may be suitable targets.