Network-based Identification and Prioritization of Key Regulators of Coronary Artery Disease Loci

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Objective: Recent genome-wide association studies (GWAS) of coronary artery disease (CAD) have revealed 58 genome-wide significant and 148 suggestive genetic loci. However, the molecular mechanisms through which they contribute to CAD and the clinical implications of these findings remain largely unknown. We aim to retrieve gene subnetworks of the 206 CAD loci and identify and prioritize candidate regulators to better understand the biological mechanisms underlying the genetic associations.

Approach and Results: We devised a new integrative genomics approach that incorporated i) candidate genes from the top CAD loci, ii) the complete genetic association results from the CARDIoGRAM-C4D CAD GWAS, iii) tissue-specific gene regulatory networks that depict the potential relationship and interactions between genes, and iv) tissue-specific gene expression patterns between CAD patients and controls. The networks and top ranked regulators according to these data-driven criteria were further queried against literature, experimental evidence, and drug information to evaluate their disease relevance and potential as drug targets. Our analysis uncovered several potential novel regulators of CAD such as *LUM* and *STAT3*, which possess properties suitable as drug targets. We also revealed molecular relations and potential mechanisms through which the top CAD loci operate. Furthermore, we found that extracellular matrix genes coordinate multiple CAD-relevant biological processes such as complement and coagulation cascades and lipid metabolism through tissue-specific interactions in the CAD networks.

Conclusion: Our data-driven integrative genomics framework unraveled tissue-specific relations among the candidate genes of the CAD GWAS loci and prioritized novel network regulatory genes orchestrating biological processes relevant to CAD.

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