Reconstruction and analysis of the blood pressure regulation protein interactome based on genome-wide association study (GWAS) and functional data

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ABSTRACT

Background: Genome-wide association studies (GWAS) have been valuable since late 2000s for the identification of disease-related single nucleotide polymorphisms (SNPs) in the human genome. For multi-factorial diseases, the associated genome variants may be analyzed collectively in the context of biomolecular networks, as the related pathophysiology results from dysfunction in the connectivity and activity of interacting multiprotein pathways. The protein-protein interaction (PPI) network provides a good representation of the molecular physiology as proteins are the catalysts and regulators of most cellular functions. The objective of this study was (a) to collect all SNPs having been associated with blood pressure (BP) regulation in a standardized meta-database along with other biological data connecting SNPs with genes and proteins, (b) analyze the GWAS-proteins within the human PPI network to identify BP-related pathways, (c) predict new BP-associated genes/proteins, and (d) develop systematic workflows for BP-associated protein and pathway prioritization.

Methods: The BP-GWAS meta-database was implemented in Microsoft SQL Server[1]. The BP GWAS-protein network was reconstructed from the human PPI meta-database PICKLE (www.pickle.gr), and extended with the shortest paths connecting all GWAS-proteins into one component, considering the shortest-path intermediates as BP-related. The proposed gene/protein prioritization method was based on three criteria: (i) the ranking of GWAS-genes based on a set of GWAS-data properties, (ii) the protein position in the extended BP PPI network and (iii) the protein position with respect to the prioritized in (i) GWAS-protein set. Prioritized proteins were ranked by the number of satisfied criteria.

Results: The 6687 collected BP-SNPs are linked to 1170 proteins, of which 1065 have known interactions in human. We predicted BP-association for 1443 additional proteins. From the 2058 proteins in the extended BP PPI network, 335 were prioritized as belonging to the most BP-significant based on any of the applied criteria. Estrogen receptor 1 (ESR1) was the only protein satisfying all three criteria whereas 126 proteins satisfied two. Pathway analysis of the extended BP-associated network revealed numerous bioprocesses, which are indeed functionally supported as BP-associated.

Conclusions: The implemented workflow could be used for other multifactorial diseases.

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KEYWORDS: Blood pressure regulation, GWAS meta-database, Protein–protein interaction network analysis, Gene/protein prioritization, Pathway enrichment analysis

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