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Identification of a human serum metabolome causal network using large scale data integration reveals pathways from the genome to risk factors and disease end points

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Background: Analyses of individual metabolites does not provide information about likely targets of intervention because of co-linearity among the metabolites. One approach to directly incorporate relationships among the metabolome is to consider networks.

Method: Powerful and advanced analytic strategies are required to identify pathways from genome and environmental exposures to disease endpoints using comprehensive data from different biological granularities. To address the emerging challenge of relating information among different biological granularities, a granularity directed acyclic graph (GDAG) algorithm has been introduced, validated and applied to create strong instrumental variables from the genome granularity (Mendelian principle) to identify robust causal/Bayesian networks over traits. Analyzing biological causal networks provides important insights into the hierarchical regulation of physiology and metabolism.

Results: For the application, information from 1,034,945 genetic variants distributed across the genome was extracted and then employed by the GDAG algorithm to identify a metabolomics causal network among 122 serum metabolites. Five modules, largely corresponding to functional categories (e.g. amino acids), were identified over the network and module boundaries were determined using directionality and causal effect sizes. Based on causal network parameters, individual metabolites were identified as hypothesized targets for intervention and prediction.

Conclusion: Given the metabolomics causal network, metabolites with direct effect on risk factors (e.g. triglyceride) were identified which improved the understanding of the role of metabolites in quantitative risk factor phenotypes. Finally, pathways from the genome to risk factors via metabolites were determined to reveal underlying biological networks. Future steps will connect these results to cardiovascular disease end points.

Biography

Azam Yazdani has completed her PhD in Statistical Causal Inference from Cambridge University, England, and Friedrich Schiller Jena University, Germany. She introduced the granularity directed acyclic graph (GADG) algorithm which is recognized at the 2015 Atlantic Causal Inference Conference and won "The Thomas R. Ten Have Award". The GDAG algorithm integrates different biological levels of granularity in large scales to identify causal networks. She has carried out first-rate studies on robust statistical structures. Her research work aims to tackle the problems of finding principals which govern the mechanism of disease to provide a better understanding of the disease mechanisms applying her expertise on data integration in large scales and generating causal relationships.

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