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Genetics meets metabolomics: Inborn variations in human metabolism

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Many complex diseases such as diabetes and cardiovascular disorders are associated with disruptions in metabolic processes. To better understand the role of genetic predispositions in the pathogenesis of these diseases, we systematically investigate the effect of genetic variation on human metabolism. Today, chip-based genotyping and high-throughput metabolomics allow for genome-wide association studies (GWAS) with a broad range of metabolites and thereby pave the way for unraveling the genetic basis of human metabolic individuality. In recent GWAS with metabolomics data, we identified more than 50 genetic loci where common genetic variants associate with metabolite abundances in various biofluids.

In addition to metabolic features with known chemical identity, we recently performed a GWAS using quantifications of 220 so-called "*unknown metabolites*" from untargeted metabolomics approaches. Thereby, we found seven new loci that are linked to metabolic individuality. In general, the identification of these "*unknown metabolites*" is still a demanding task, limiting their usability as functional markers of metabolic processes. To predict the identity of unknowns, we developed a systems biology method that combines our results from the genome-wide association analysis with Gaussian graphical modeling (GGM). Overlaying the inferred genetic associations, the GGM-based metabolic networks and knowledge-based pathway information, we derived testable hypotheses on the biochemical identities of 106 unknown metabolites. As a proof of principle, we experimentally confirmed nine concrete predictions. Our approach is generic in nature and can be directly transferred to metabolomics data from different experimental platforms.

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