A genome-wide perspective of genetic variation in human metabolism.

Abstract:
Serum metabolite concentrations provide a direct readout of biological processes in the human body, and they are associated with disorders such as cardiovascular and metabolic diseases. We present a genome-wide association study (GWAS) of 163 metabolic traits measured in human blood from 1,809 participants from the KORA population, with replication in 422 participants of the TwinsUK cohort. For eight out of nine replicated loci (FADS1, ELOVL2, ACADS, ACADM, ACADL, SPTLC3, ETFDH and SLC16A9), the genetic variant is located in or near genes encoding enzymes or solute carriers whose functions match the associating metabolic traits. In our study, the use of metabolite concentration ratios as proxies for enzymatic reaction rates reduced the variance and yielded robust statistical associations with P values ranging from 3 x 10(-24) to 6.5 x 10(-179). These loci explained 5.6%-36.3% of the observed variance in metabolite concentrations. For several loci, associations with clinically relevant parameters have been reported previously.