Large-scale gene-centric meta-analysis across 32 studies identifies multiple lipid loci.

Genome-wide association studies (GWASs) have identified many SNPs underlying variations in plasma-lipid levels. We explore whether additional loci associated with plasma-lipid phenotypes, such as high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglycerides (TGs), can be identified by a dense gene-centric approach. Our meta-analysis of 32 studies in 66,240 individuals of European ancestry was based on the custom ~50,000 SNP genotyping array (the ITMAT-Broad-CARe array) covering ~2,000 candidate genes. SNP-lipid associations were replicated either in a cohort comprising an additional 24,736 samples or within the Global Lipid Genetic Consortium. We identified four, six, ten, and four unreported SNPs in established lipid genes for HDL-C, LDL-C, TC, and TGs, respectively. We also identified several lipid-related SNPs in previously unreported genes: DGAT2, HCAR2, GPIHBP1, PPARG, and FTO for HDL-C; SOCS3, APOH, SPTY2D1, BRCA2, and VLDLR for LDL-C; SOCS3, UGT1A1, BRCA2, UBE3B, FCGR2A, CHUK, and INSIG2 for TC; and SERPINF2, C4B, GCK, GATA4, INSR, and LPAL2 for TGs. The proportion of explained phenotypic variance in the subset of studies providing individual-level data was 9.9% for HDL-C, 9.5% for LDL-C, 10.3% for TC, and 8.0% for TGs. This large meta-analysis of lipid phenotypes with the use of a dense gene-centric approach identified multiple SNPs not previously described in established lipid genes and several previously unknown loci. The explained phenotypic variance from this approach was comparable to that from a meta-analysis of GWAS data, suggesting that a focused genotyping approach can further increase the understanding of heritability of plasma lipids.
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