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Implicating genes, pleiotropy, and sexual dimorphism at blood lipid loci through multi-ancestry meta-analysis

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Abstract

Background: Genetic variants within nearly 1000 loci are known to contribute to modulation of blood lipid levels. However, the biological pathways underlying these associations are frequently unknown, limiting understanding of these findings and hindering downstream translational efforts such as drug target discovery.

Results: To expand our understanding of the underlying biological pathways and mechanisms controlling blood lipid levels, we leverage a large multi-ancestry meta-analysis ($N = 1{,}654{,}960$) of blood lipids to prioritize putative causal genes for 2286 lipid associations using six gene prediction approaches. Using phenome-wide association (PheWAS) scans, we identify relationships of genetically predicted lipid levels to other diseases and conditions. We confirm known pleiotropic associations with cardiovascular phenotypes and determine novel associations, notably with cholelithiasis risk. We perform sex-stratified GWAS meta-analysis of lipid levels and show that 3–5% of autosomal lipid-associated loci demonstrate sex-biased effects. Finally, we report 21 novel lipid loci identified on the X chromosome. Many of the sex-biased autosomal and X chromosome lipid loci show pleiotropic associations with sex hormones, emphasizing the role of hormone regulation in lipid metabolism.

Conclusions: Taken together, our findings provide insights into the biological mechanisms through which associated variants lead to altered lipid levels and potentially cardiovascular disease risk.

Keywords: Cholesterol, Lipids, Genetics, Genome-wide association study, GWAS

Background

Abnormal blood lipid levels are a major cause of cardiovascular disease [1], the leading cause of morbidity and mortality worldwide [2]. Conventional blood lipid measures, low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and nonHDL-C (TC – HDL-C), are commonly used in clinical practice to identify individuals at high risk for cardiovascular events. Several treatments for reducing LDL-C, including statins, ezetimibe, and PCSK9 inhibitors [3], also reduce the risk of developing cardiovascular disease.

Genome-wide association studies (GWAS) for blood lipids have identified nearly 1000 associated genetic loci to date [4–23], including our recent multi-ancestry GWAS meta-analysis in 1.65 M individuals [24]. The latter focused on the gains from the multi-ancestry meta-analysis relative to the single-ancestry results, in terms of number of loci, fine-mapping, and polygenic score (PGS) transferability. However, a challenge in the field is that the underlying gene and biological pathways is often unknown for GWAS loci. Within lipid GWAS, prior fine-mapping studies combined with functional follow-up have successfully identified causal genes with high confidence for only a handful of associated GWAS loci, including *SORT1* [25], *TM6SF2* [12], and *ANGPTL3* [26], among others. Highly sophisticated methods are emerging to prioritize causal genes in well-powered GWAS studies, such as the Data-driven Expression-Prioritized Integration for Complex Traits [27] (DEPICT) and the Polygenic Priority Score [28] (PoPS), that take into account genome-wide properties of associated loci and larger sets of associated loci are beneficial. These methods can be combined with algorithms that integrate expression data such as transcriptome-wide association studies (TWAS) and comprehensive experimental data sets such as mouse gene knockouts. Gene sets enriched for

causal genes will enhance our ability to unravel the biological pathways underlying these associations and there is growing interest in using a combination of gene prioritization methods to provide compelling evidence for putative causal genes [29].

In parallel, the linkage of electronic health records with genetic data in large-scale population studies and patient biobanks allows for the systematic exploration of pleiotropy of lipid-associated alleles. While blood lipid levels have a well-documented causal effect on cardiovascular disease based on genetic association studies validated by randomized controlled trials [30–32], genetic pleiotropic associations might exist for other conditions. Unraveling such pleiotropy may yield new biological insights by revealing previously unrecognized connections between blood lipids and both cardiovascular and non-cardiovascular diseases. Phenome-wide association scans (PheWAS) adopt an agnostic approach to test for pleiotropic associations between genetic factors and a wide range of phenotypes [33]. Such knowledge may allow for the identification of lipid levels as novel diagnostic biomarkers, the repurposing of drugs, and the prevention of adverse drug events [34].

Finally, given empirical sex differences in blood lipid distributions, sex-specific genetic associations may yield novel biological insights. Pre-menopausal females have lower levels of LDL-C than same-age males, and HDL-C levels are higher among females of all ages compared to males [35]. Lipid levels also show a greater estimated heritability in females compared with males [36], especially for LDL-C and TC (> 1.3-fold difference). Sexual dimorphism in lipid levels may be partly explained by X chromosome variants. Evidence from human X-linked abnormalities (like Turner or Klinefelter syndromes) suggests an important role of this chromosome in lipid metabolism [37]. This is further corroborated by the lipid and atherosclerosis profiles in the Four Core Genotypes mouse model [38], which comprises XX and XY gonadal males and XX and XY gonadal females. GWAS studies have traditionally understudied the X chromosome due to technical and analytical difficulties. A recent high coverage whole X chromosome sequencing study [39] prioritized *CHRDL1* as a candidate causal lipid gene, suggesting with larger sample sizes we may be able to discover additional variation on the X chromosome associated with lipid levels.

In this study, we first prioritize genes at GWAS lipid loci through multiple in silico gene prediction algorithms and experimental data sources using the latest Global Lipids Genetics Consortium multi-ancestry meta-analysis [24]. We then identify novel disease associations related to lipid levels through PheWAS in two large biobanks using PGSs. Finally, we perform sex-stratified meta-analysis to compare the associations between males and females to identify genetic loci with sex-specific associations and GWAS meta-analysis of the X chromosome, to better understand lipid level differences between the sexes. Together, our results highlight biological mechanisms through which lipid-associated variants lead to altered lipid levels.

Results

Identifying functional genes in lipid-associated loci

In a GWAS meta-analysis of blood lipid levels from 1.65 million individuals (Additional file 1: Table S1) at 91 million genotyped and imputed genetic variants, we observed a total of 2286 genome-wide significant index variants associated with lipid levels at 923