Genomics of a detailed profile of soluble lipids

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Introduction

Previous genomic studies have principally focused on a handful of major lipid fractions, such as total cholesterol, triglycerides and high-density lipoprotein (HDL) cholesterol concentrations.

We aimed to widen the scope for discovery by considering several hundred lipid species.

Methods

We studied 5,551 control participants from the Pakistan Risk of Myocardial Infarction Study. We measured 444 lipid species using direct infusion high-resolution mass spectrometry.

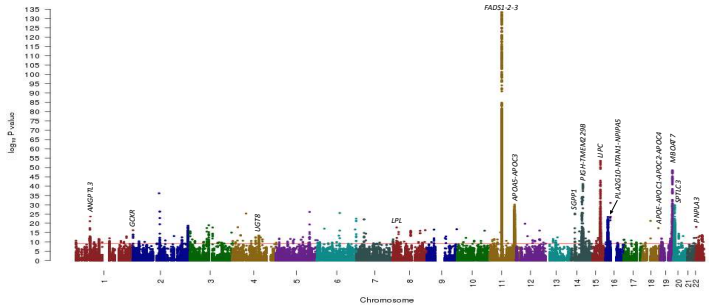
We conducted univariate genome-wide analyses to analyse the association of each lipid with 7.2 million genotyped and imputed single nucleotide polymorphisms.

We conducted conditional analyses to determine the number of independent associations within each locus. We used functional annotation to link the variants associated with each lipid to the most probable causal genes.

Results

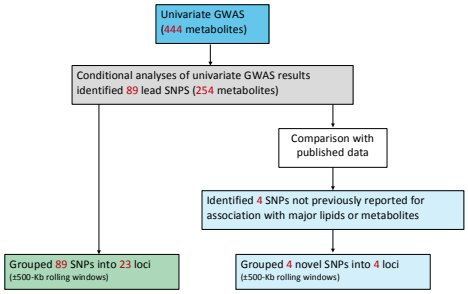
In univariate analyses we found 1,982 variants robustly associated with 301 lipids at genome-wide significance (**Figure 1**).

Figure 1. Global Manhattan plot of combined GWAS results for 301 lipids with significant associations



After conditional analyses and further QC, we identified genome-wide significant associations at 23 independent metabolic loci (**Figure 2**).

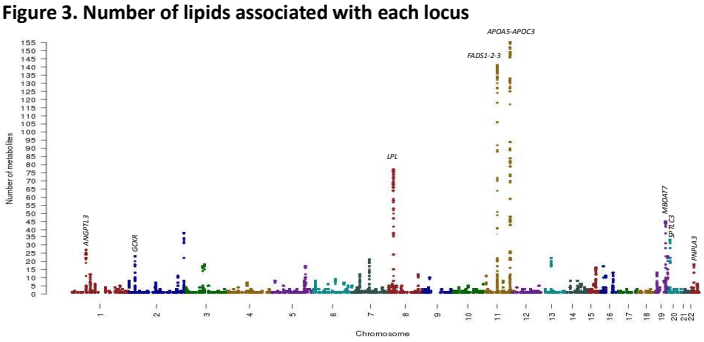
Figure 2. Flow chart of process to identify independent loci and loci not previously reported for association with major lipids or metabolites



The *FADS1-2-3*, *APOA5-APOC3* and *LPL* loci were each associated with over 80 lipids (**Figure 3**).

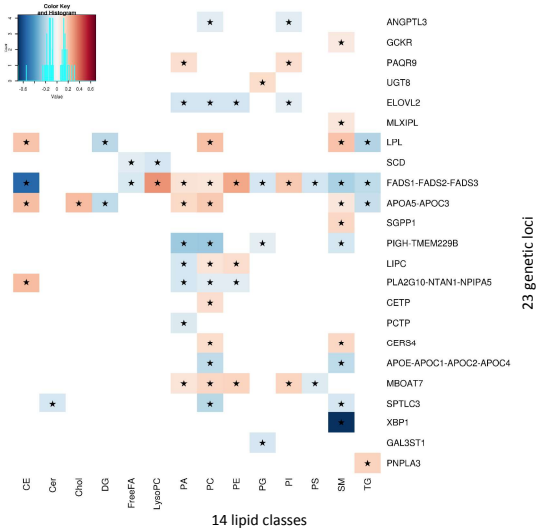
Results (continued)

Figure 3. Number of lipids associated with each locus



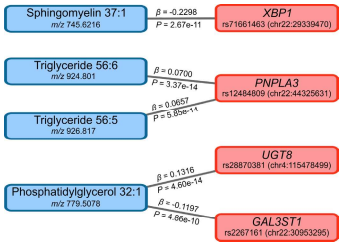
Several loci had associations across many lipid classes (e.g. *FADS1-2-3* and *APOA5-APOC3*), while other loci were specific to a single lipid class (e.g. *GCKR*, *UGT8*, *MLXIPL*, *CETP*, and *PNPLA3*) (**Figure 4**).

Figure 4. Heat map of effect sizes for associations between loci and lipid classes



We found four loci that had not been reported in previous GWAS for association with major lipids or metabolites (**Figure 5**).

Figure 5. Associations of four novel loci with specific lipid species



Conclusions

Using a new lipidomics platform, we identified several novel loci for lipids.

To extend the current discoveries, we will combine results with those from 50,000 participants in INTERVAL measured with the same assay.

To enhance mechanistic understanding, we will overlay these detailed lipid data on participants who have been ultra fine-mapped for established loci for coronary disease and for major lipid fractions.

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