Genome-wide study of the human lipidome and links to cardiovascular disease risk

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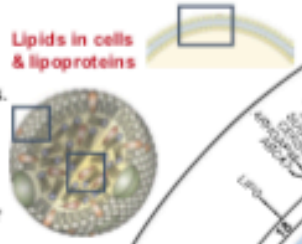
Background

- Dysregulation of lipid metabolism is as an important – and modifiable – risk factor for the initiation and progression of cardiovascular disease (CVD).
- Although lipid metabolism is established as crucial to numerous biological processes, the genetic factors that influence inter-individual variation are still not well understood.
- To address this issue, we apply an integrative approach to link genetic variants with altered lipid metabolism and CVD.
- We utilised our updated targeted lipidomics platform, which provides data on 596 lipid species across 33 lipid classes and subclasses.



Aim

To identify genetic variants influencing lipid metabolism and examine lines to cardiovascular disease risk in a large population cohort.

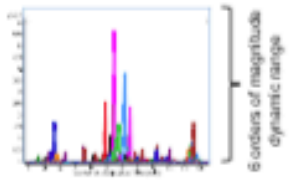
Methods

Plasma samples from Busselton Health Study (BHS n=4492)

Full method @ Huynh *et al.* 2019 *Cell Chemical Biology*

Liquid chromatography tandem mass spectrometry

MS: Agilent 6490 QqQ mass spectrometer
LC: Agilent 1290 UHPLC
MRM: 597 scheduled MRM transitions
Run-time: 15 minutes



Statistical analysis

- Genome-wide association analysis of 596 lipid species and 33 lipid classes using linear-mixed models (GEMMA), correcting for age, sex, their interactions, 10 genomic principal components and an empirical genetic related matrix.
- Genetic correlation assessed with linkage disequilibrium score regression against a meta-analysis of coronary artery disease in the UK Biobank and CARDIoGRAMplusC4D.
- Phenotypic associations with incident cardiovascular disease assessed using Cox Proportional Hazards regression, adjusting for age and sex.
- Coronary artery disease polygenic risk score (metaGRS) from Inouye *et al.* 2018 *Journal of the American College of Cardiology*. Associations of polygenic risk assessed using linear regression, adjusting for age, sex, their interactions and 10 genomic principal components.
- False discovery rate multiple testing correction (Benjamini-Hochberg) applied to phenotypic associations and genetic correlations. Genome-wide significance was set at 5e-08.

Results

Figure 1 – Circular Manhattan Plot of Genome-wide association study of the human lipidome – Results from linear mixed model of 13 million genetic variants against 596 lipid species (n=4992). Over 70,000 genome-wide significant (p<5e-08) associations were identified, with 543 lipid species having at least one significant association. Inner plot highlights lipid species significantly associated with loci; classes colour coded according to legend (centre). Outer plot indicates $-\log_{10}$ transformed p-values (scale truncated at 1e-40). Outer labels indicate the nearest gene for a subset of genome-wide significant loci.

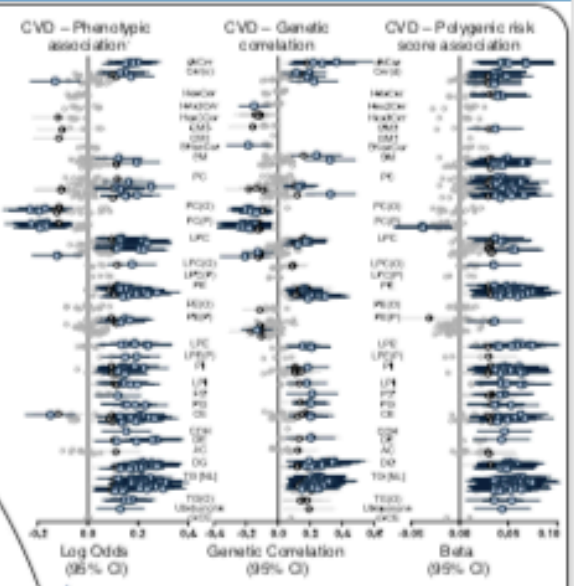


Figure 2 – Associations of lipid species with 1) CVD outcomes in the BHS, 2) genetic correlations with CVD, 3) polygenic risk score for CAD – All analysis was performed with adjustment for age and sex. Grey open circles show non-significant species, closed grey circles show species with nominal significance (p<0.05), blue circles show species significance after correction for multiple comparisons (Benjamini-Hochberg). Error bars show 95% confidence intervals. Left Panel – Associations between lipid species and incident CVD outcomes in BHS. Middle Panel – Genetic correlations between lipid species and CVD in over 500,000 individuals. Right Panel – Associations between lipid species and polygenic risk for CAD in over 480,000 individuals.

Conclusions

- Using our expanded lipidomics platform, we have performed the most detailed genomic analysis of lipids to date, revealing over 70,000 genome-wide significant associations and almost 300 lipid-associated loci.
- Genetic correlations suggest shared genetic pathways (pleiotropy) between many lipid species and CVD.
- Integration of lipidomics and genetics allows the utilization of external resources – estimation of associations in very large cohorts/populations.
- Our results present a detailed snap shot of the genetic regulation of lipid species.

Lipid class acronyms

dhCer, dihydroceramide; Cer(d), ceramide; HexCer, hexacylceramide; Hex2Cer, dihexacylceramide; Hex3Cer, trihexacylceramide; GM3, GM3 ganglioside; GM3, GM3 ganglioside; SM, sphingomyelin; PC, phosphatidylcholine; PC(O), alkylphosphatidylcholine; PC(P), alkenylphosphatidylcholine; LPC, lysophosphatidylcholine; LPC(O), lysoalkylphosphatidylcholine; LPC(P), lysoalkenylphosphatidylcholine; PE, phosphatidylethanolamine; PE(O), alkylphosphatidylethanolamine; PE(P), alkenylphosphatidylethanolamine; LPE, Lysophosphatidylethanolamine; LPE(P), lysoalkenylphosphatidylethanolamine; PI, phosphatidylinositol; LPI, lysophosphatidylinositol; PS, phosphatidylserine; PG, phosphatidylglycerol; CE, cholesteryl ester; COH, cholesterol; DE, dehydrocholesteryl ester; AC, acylcarnitine; DG, diacylglycerol; TG, triacylglycerol; TG(O), alkyl-diacylglycerol; OxCE, oxidised lipids.

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