Pleiotropy testing identifies genetic variants with pleiotropic evidence lipid traits

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INTRO

- We tested for bi-directional causal relationships between four lipid traits and used causal estimates to perform genome-wide pleiotropy testing to detect novel variants with potential pleiotropy evidence.

METHODS

1. *Data*
   - ~1.3M EUR[1] (AFR, EAS, SAS, HIS in process)
   - GWAS meta-analysis summary statistics
2. *Phenotypes*
   - HDL, LDL, log triglycerides (logTG), total cholesterol (TC)
3. *Tests*
   - Bi-directional Mendelian Randomization for causal effects using selected instruments (each lipid-lipid pair)
   - Pleiotropy T-test (genome-wide)
   - CPASSOC: multi-trait SNP-outcome meta-analysis (genome-wide)

Table 1: *Select lipid-lipid pair causal estimates*

Exposure	Outcome	Est (P)	n	Prop. pleio.
HDL	LDL	-0.01 (0.524)	1682	0.22
HDL	logTG	-0.61 (<0.001)	1682	0.35
LDL	HDL	-0.03 (<0.001)	1277	0.28
LDL	logTG	0.11 (<0.001)	1277	0.32
logTG	HDL	-0.78 (<0.001)	1425	0.32
logTG	LDL	0.23 (<0.001)	1425	0.28

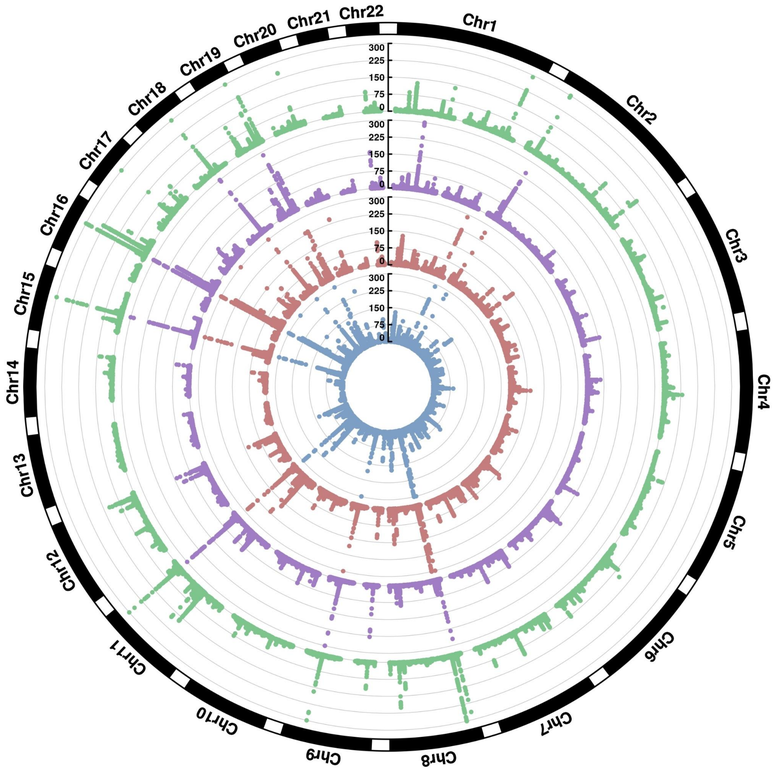
Table 2: *Novel loci identified by pleiotropy testing*

	Signals		
Lipid	GWAS	Novel	Novel loci
HDL	1675	105	53
LDL	1264	131	64
logTG	1417	192	66
TC	1568	336	132

DISCUSSION

- MR pleiotropy testing can identify novel SNP associations with lipids undetected by standard GWAS. These SNPs potentially have pleiotropic effects on respective exposure and outcome.

Figure 1: *HDL GWAS & Pleiotropy testing Manhattan Plot*



- HDL GWAS
- LDL → HDL Pleiotropy test
- logTG → HDL Pleiotropy test
- TC → HDL Pleiotropy test

Figure 2: *CPASSOC, Pleiotropy QQ-Plot*

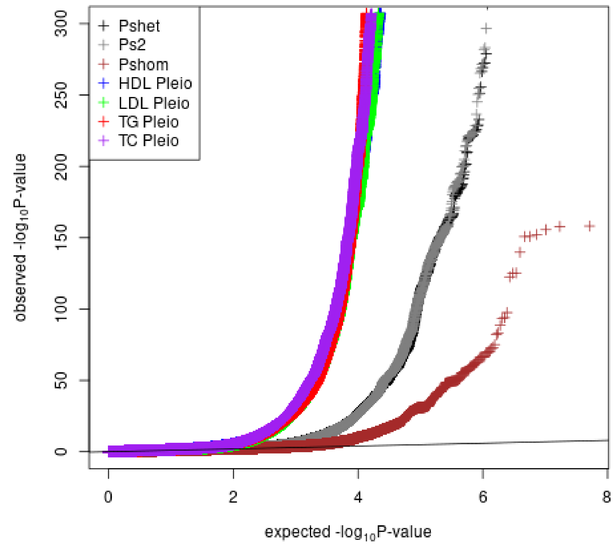
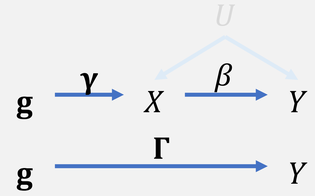


Table 3: *Genes in novel loci and their historically associated traits*

Lipid	Genes in novel loci	Top 3 most common gene-associated traits in GWAS Catalog (ref. counts)
HDL	44	Blood protein levels (602), BMI (12), coronary artery disease (11)
LDL	74	White blood cell count (19), **triglycerides** (17), **HDL** (16)
logTG	71	Platelet count (24), height (18), mean corpuscular hemoglobin (18)
TC	178	Serum metabolite levels (32), red cell distribution (21), **triglycerides** (19)

Genes in novel loci are a priori plausibly associated with HDL, LDL, logTG, or TC

Mendelian Randomization



$\mathbf{g}$ is an n-vector of genetic instruments; X is an exposure; Y is an outcome.

Assume $\boldsymbol{\Gamma} = \boldsymbol{\gamma}\beta$. If $\Gamma_i \neq \gamma_i\beta$, instrument i is pleiotropic. Pleiotropy is a violation of an MR assumption but is of scientific interest.

Pleiotropy t-test

Pleiotropy: A SNP is associated with multiple traits. (e.g) Let $\phi(\text{HDL}, \text{LDL})$ be the causal estimate of HDL on LDL. Pleiotropy $H_{0(\text{HDL},\text{LDL})t}$:

$$\Gamma_t - \gamma_t\phi(\text{HDL}, \text{LDL}) = 0$$

for $t = 1, \ldots, m$ GWAS SNPs. We test H_0 genome-wide using a t-test. If we reject H_{0t}, SNP t is potentially pleiotropic.

CPASSOC

Let $(\beta_1, \ldots, \beta_4)'$ be the true effects of one SNP on HDL, LDL, logTG, and TC, respectively. CPASSOC tests $\text{H}_0: \beta_1 = \beta_2 = \beta_3 = \beta_4 = 0$ and is more powerful than a single trait analysis.

Acronyms

MR: Mendelian Randomization
logTG: log triglycerides
TC: total cholesterol

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References

[1]: PMID 34887591 (Graham et al., 2021)