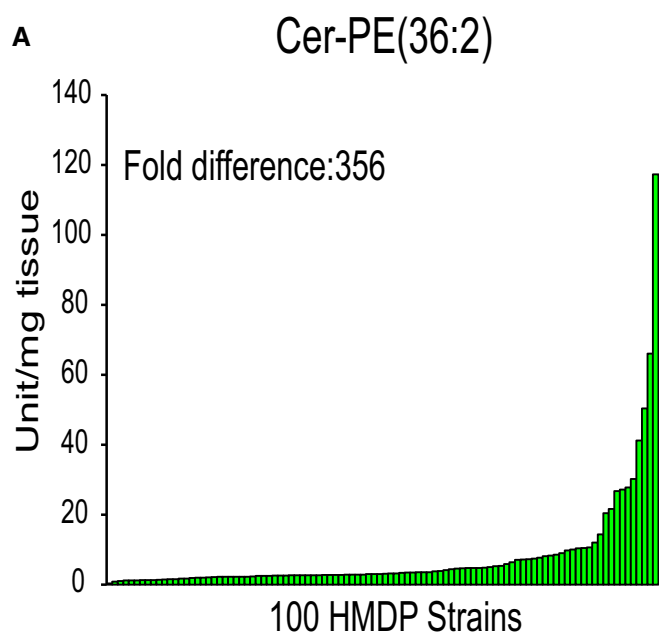


Expanded View Figures

**Figure EV1. Highly variable lipids within the HMDP.**

A, B Ceramide-phosphatidylethanolamine 36:2 (Cer-PE(36:2)) and phosphatidylinositol 38:4 (PI(38:4)) are examples of hepatic lipid species with a substantial variation among the mice strains across the HMDP. Cer-PE(36:2) showed measured levels in 100 out of 101 HMDP strains. PI (38:4) showed measured levels in 81 out of 101 HMDP strains.

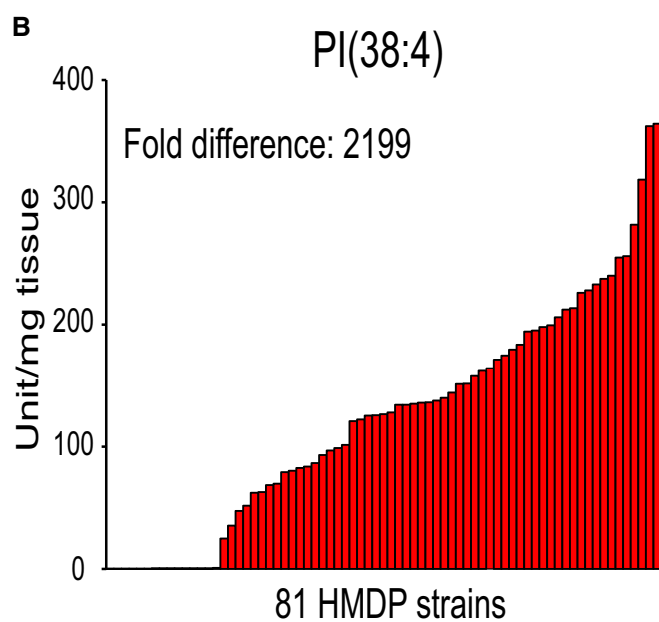


Figure EV2. WGCNA analysis and correlations with microbiota.

WGCNA was performed to dissect which lipids segregated into modules and correlated with microbiota abundances. Samples were first arranged by hierarchical clustering to detect outliers, where a height of 2,100 (red line) was used as a cutoff for inclusion (top left). Scale-free topology (top middle) and mean connectivity (top right) are also provided for analysis. Microbes were summarized at the levels of order (o), genus (g), or family (f). Heatmap showing the lipid modules (y-axis) and correlation with type of microbiome abundances (x-axis). * $P < 0.001$. P -values were calculated based on significance of regression (students test) and adjusted for multiple comparisons (FDR = 0.05).

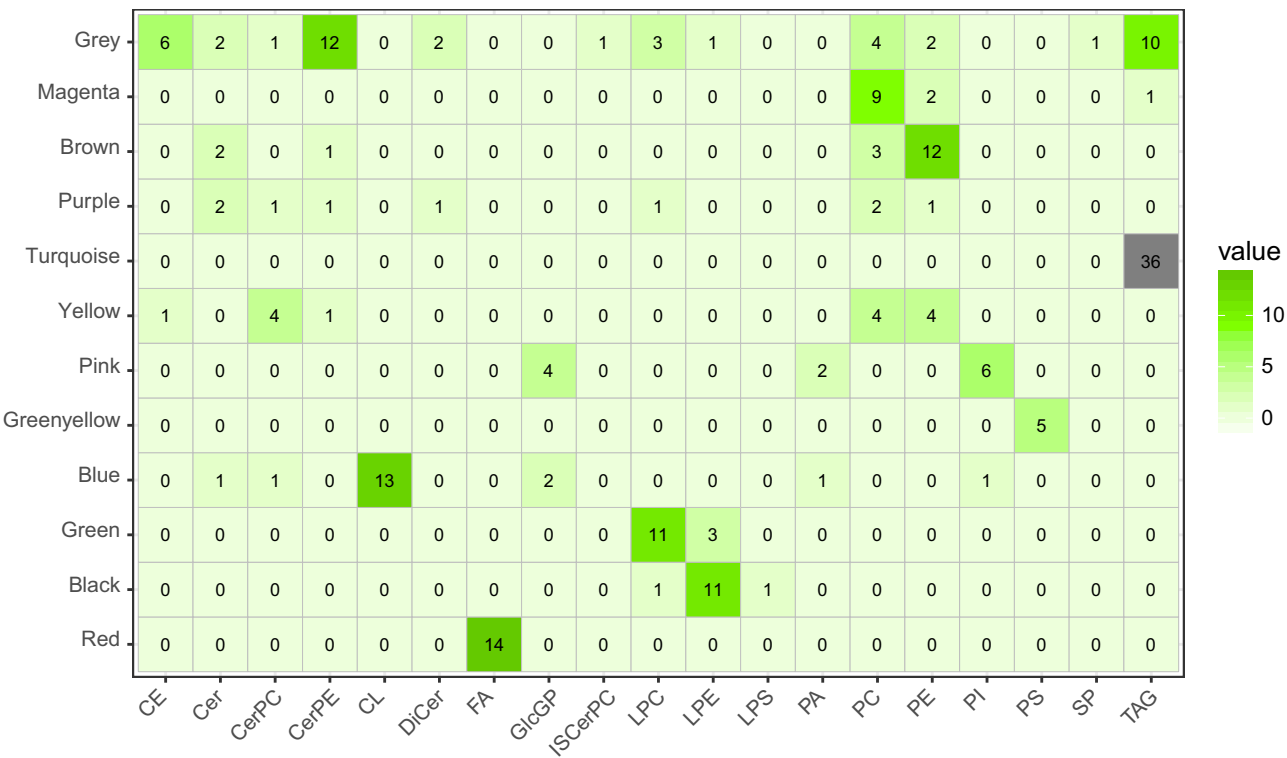


Figure EV3. Module membership by lipid class. Heatmap showing the number of lipids within a class per module.

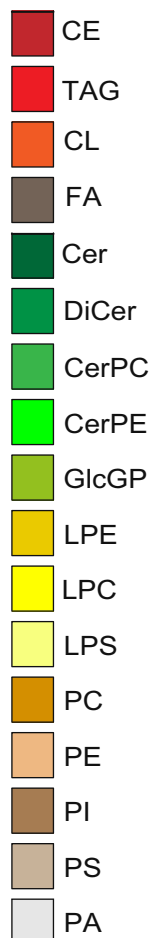
WGCNA was performed to dissect which lipids segregated into modules and correlated with traits (body fat %, body weight, HDL, LDL, liver total cholesterol, liver mitochondria, liver total phosphatidyl cholesterol, plasma free fatty acids, plasma glucose, plasma insulin, and plasma triacylglycerol). The darker the color, the more lipids per module, with the highest membership shown in gray. CE, cholesterol esters; Cer, ceramides; CerPC, ceramide phosphatidylcholines; Cer-PE, ceramide-phosphatidylethanolamines; CL, cardiolipins; DiCer, dihydroceramides; FA, free fatty acids; GlcGP, glycosylglycerophospholipids; ISCerPC, IS-ceramide phosphatidylcholines; LPC, lysophosphatidylcholines; LPE, lysophosphatidylethanolamines; LPS, lysophosphatidylserines; PA, phosphatidic acid; PC, phosphatidylcholines; PE, phosphatidylethanolamines; PI, phosphatidylinositols; PS, phosphatidylserines; SP, sphingolipids; TAG, triacylglycerols.

Figure EV4. Undirected network of interactions between hepatic lipids and indicated phenotypic traits in 101 strains of mice fed a HF/HS diet.

Nodes show either individual lipid species or phenotypic traits, where color indicators are given in the figure. Edges are connected between nodes with a significant correlation ($P < 0.01$), with the distance reflecting increasing significance of correlation. P -values were calculated based on significance of regression (Student's test) and adjusted for multiple comparisons ($FDR = 0.05$). CE, cholesterol esters; Cer, ceramides; CerPC, ceramide phosphatidylcholines; Cer-PE, ceramide-phosphatidylethanolamines; CL, cardiolipins; DiCer, dihydroceramides; FA, free fatty acids; GlcGP, glycosylglycerophospholipids; LPC, lysophosphatidylcholines; LPE, lysophosphatidylethanolamines; LPS, lysophosphatidylserines; PA, phosphatidic acid; PC, phosphatidylcholines; PE, phosphatidylethanolamines; PI, phosphatidylinositols; PS, phosphatidylserines; TAG, triacylglycerols.

Liver Lipid and Phenotypical Trait Network

Liver Lipid Class



Phenotypical Trait

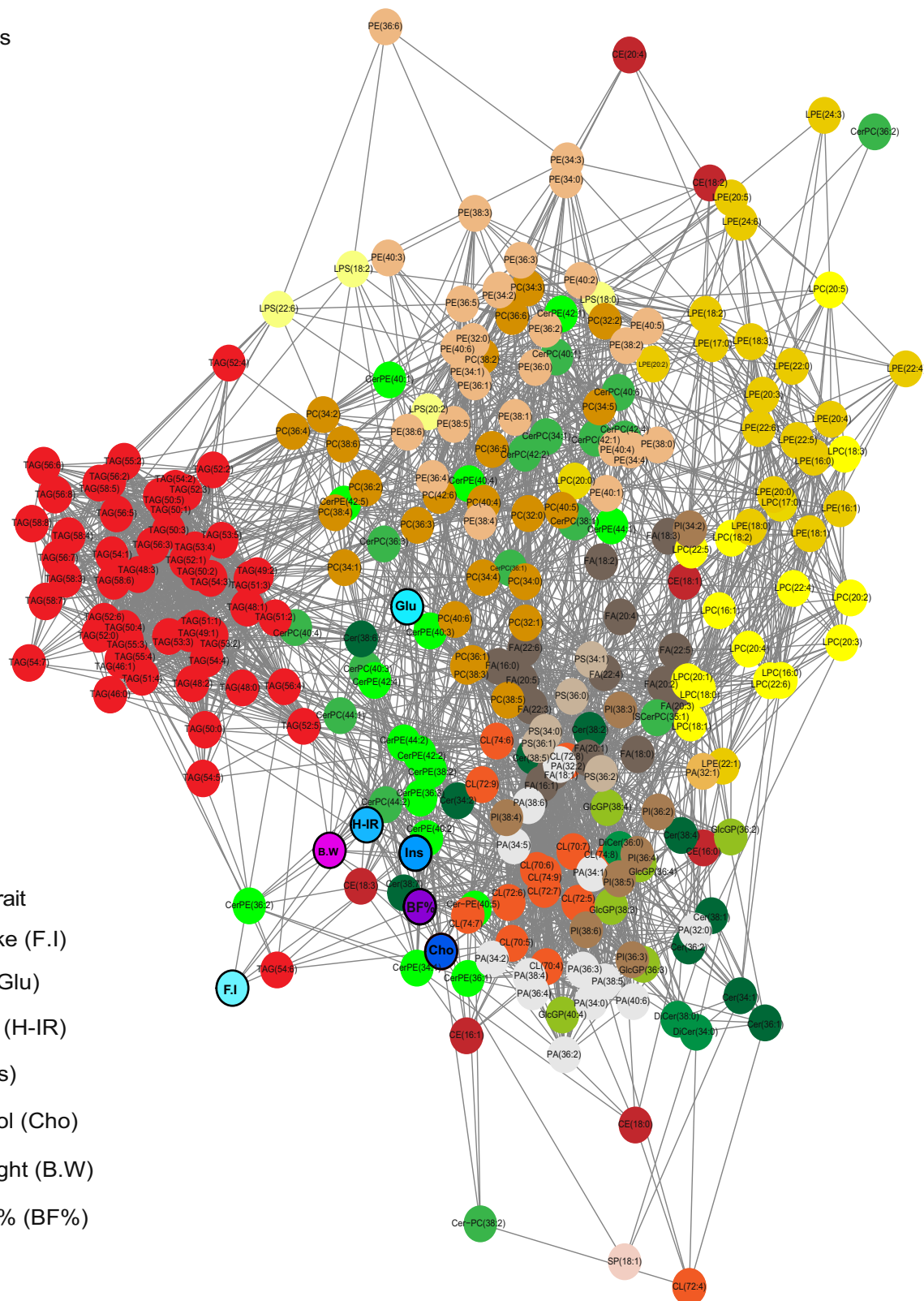
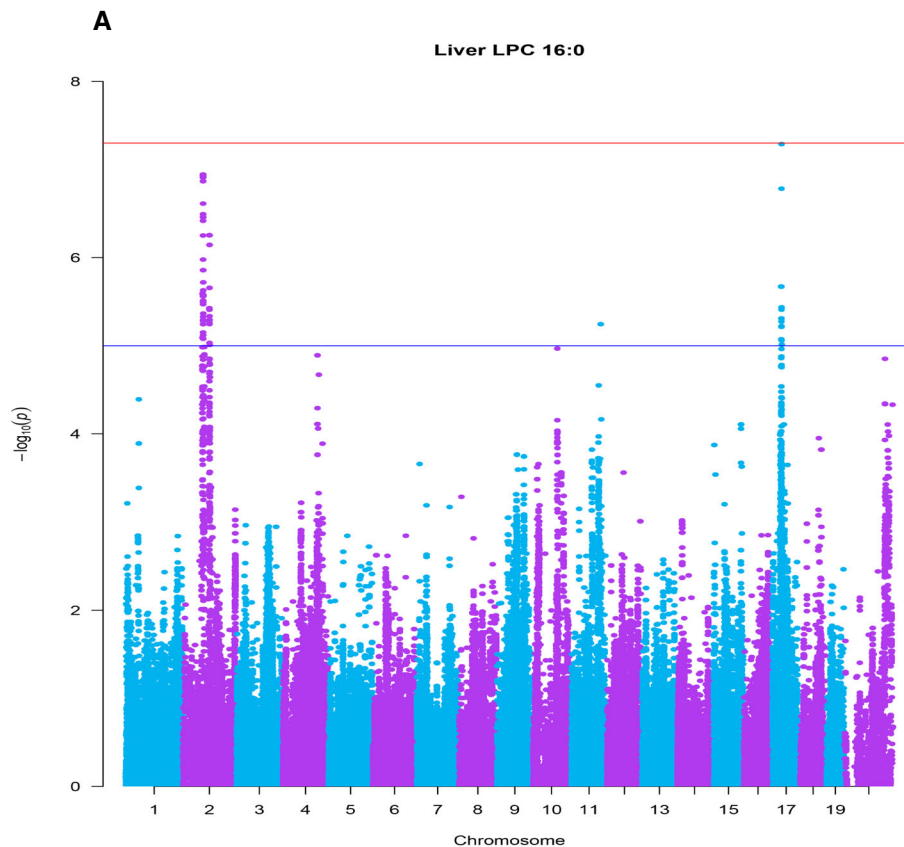


Figure EV4.

**Figure EV5. Mediation example.**

- A GWAS for levels of hepatic LPC (16:0), where the locus on Chr2 comapped to a cis-eQTL for Pex16. Red line shows Bonferroni-corrected threshold, and blue shows an FDR = 0.01 *P*-value of significance calculated based on FaST-LMM *P*-values.
- B The same GWAS as in (A), with the exception of adding expression levels of Pex16 as a covariate to the linear mixed model. The locus on Chr2 was significantly lower in its association *P*-value.

