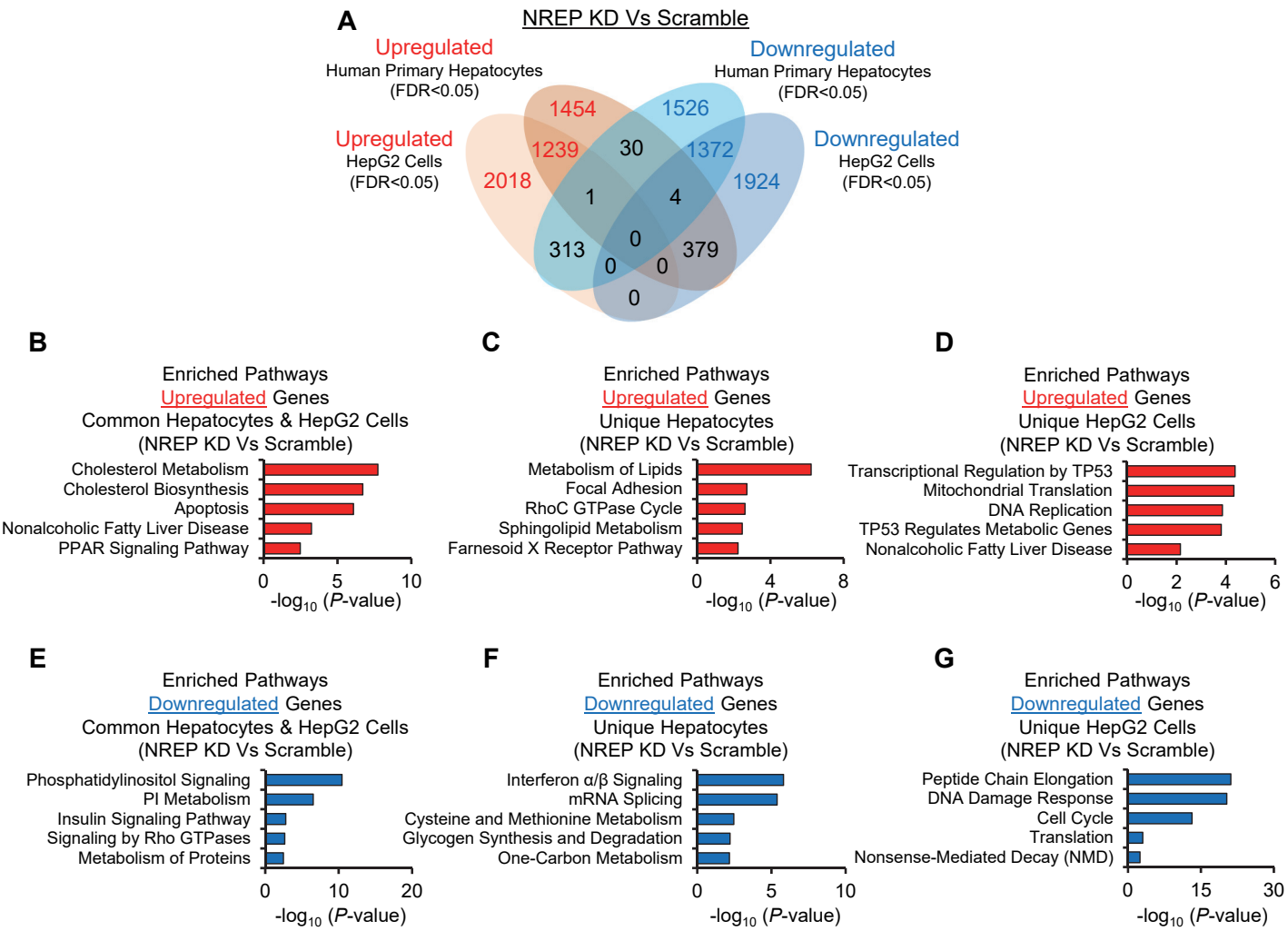
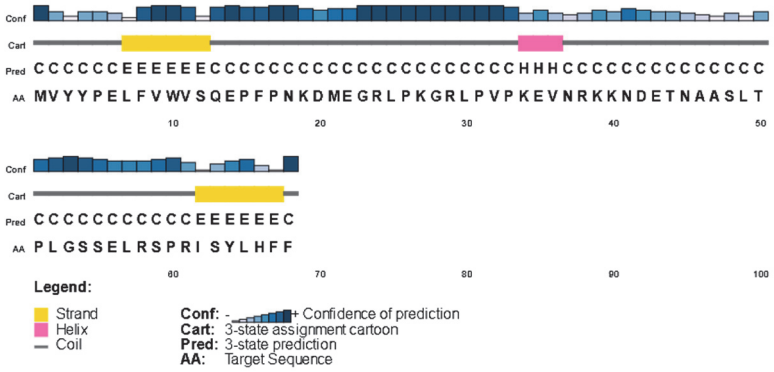


Supplementary Figure 1 (Related to Figure 1): Comparative transcriptomic impact of NREP silencing in HepG2 cells and primary human hepatocytes. (**A**) Venn diagram of intersected genes between NREP knock-down (KD) versus Scramble in primary human hepatocytes and HepG2 cells (GSE141078). (**B-D**) Pathway enrichment analyses on upregulated genes common between primary human hepatocytes and HepG2 (B); unique in primary human hepatocytes (C); or unique in HepG2 (D). (**E-G**) Pathway enrichment analyses on downregulated genes common between primary human hepatocytes and HepG2 (E); unique in primary human hepatocytes (F); or unique in HepG2 (G). Statistical analyses by Benjamini-Hochberg method (see Methods). All represented genes with FDR<0.05.

A



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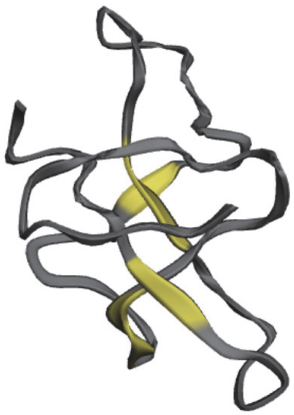
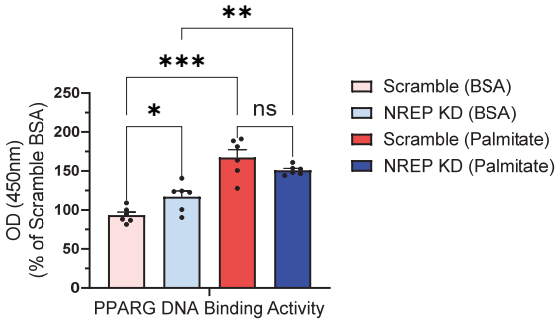


C

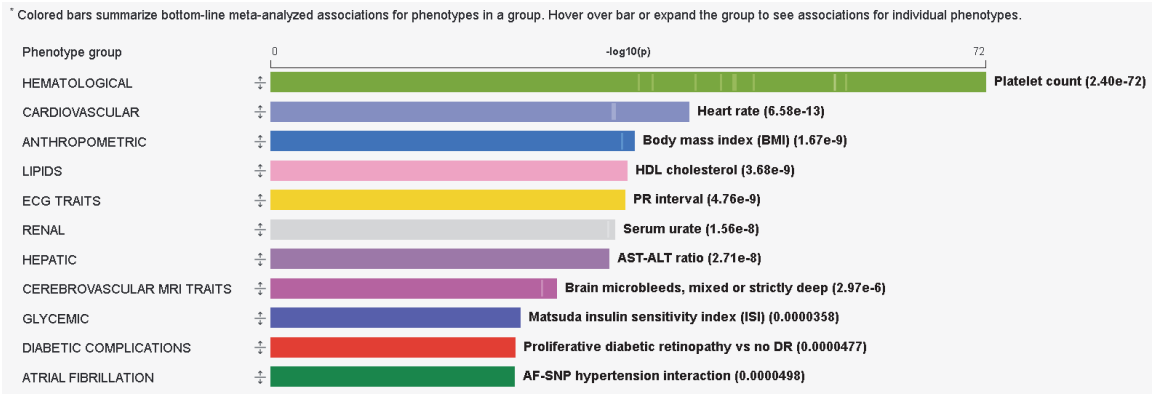
Molecular Function Predictions

GO term	Name	SVM Reliability
GO:0003676	nucleic acid binding	H
GO:0003677	DNA binding	H
GO:0003824	catalytic activity	H
GO:0003700	sequence-specific DNA binding transcription factor activity	H
GO:0001071	nucleic acid binding transcription factor activity	H
GO:0008092	cytoskeletal protein binding	H
GO:0016773	phosphotransferase activity, alcohol group as acceptor	H
GO:0003723	RNA binding	H
GO:0003779	actin binding	H
GO:0000166	nucleotide binding	H
GO:0030695	GTPase regulator activity	H
GO:0016740	transferase activity	H
GO:0005516	calmodulin binding	H
GO:0015631	tubulin binding	H

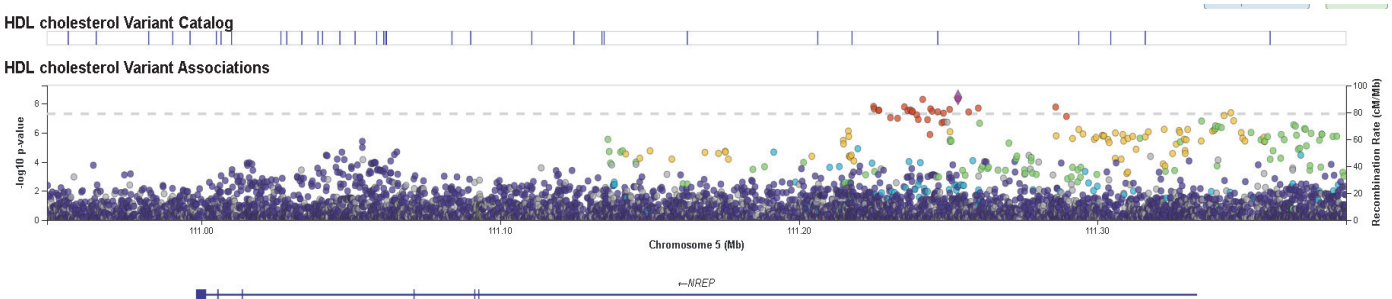
D



E



F

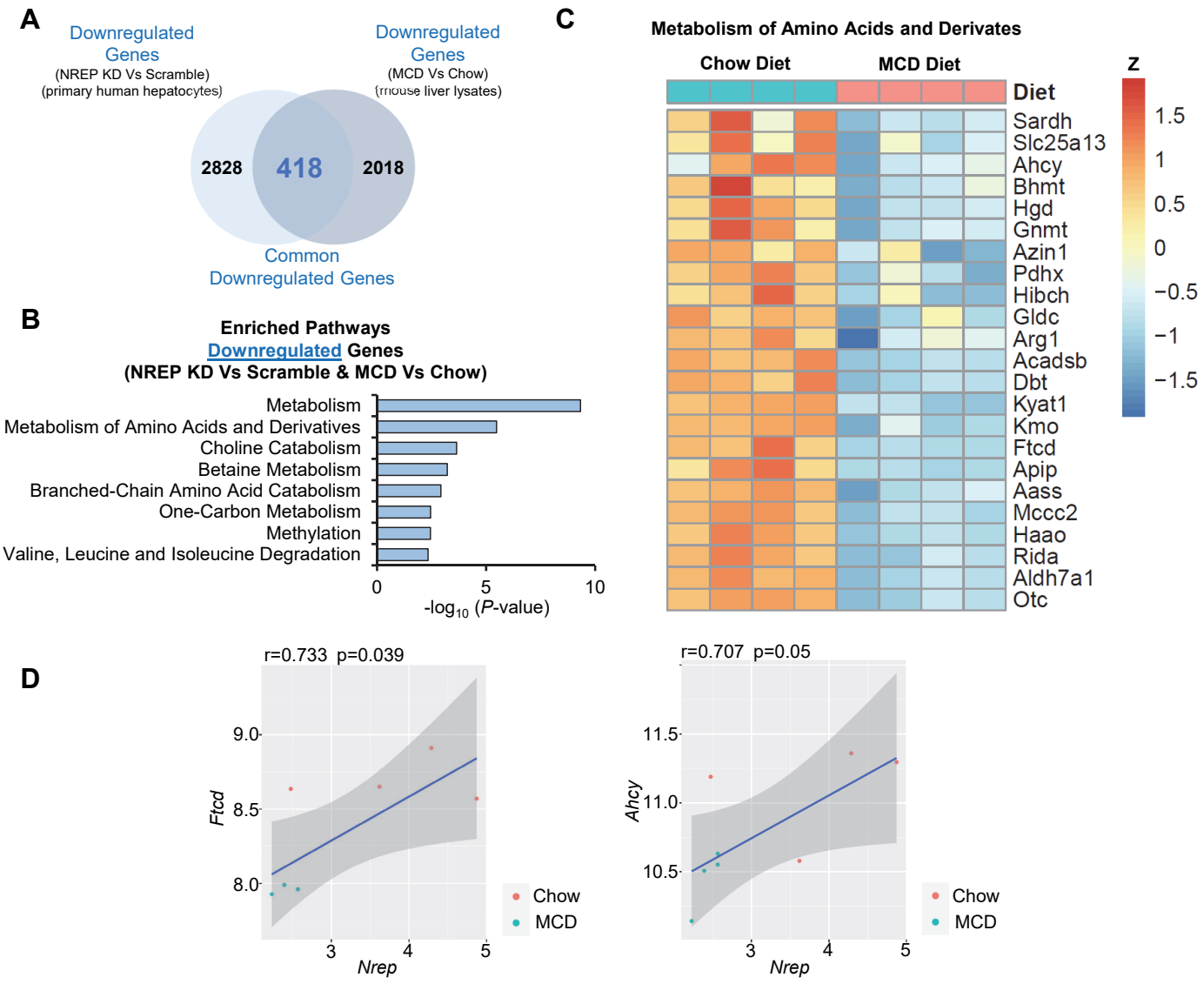


G

varId	alt	beta	chromosome	n	pValue	phenotype	reference	stdErr	zScore	reference
5:111253269:T:C	C	0.0076	5	1681390	3.69E-09	HDL	T	0.0012	5.898	T
5:111253225:C:A	A	0.0075	5	1681390	4.56E-09	HDL	C	0.0012	5.862	C
5:111241454:G:A	A	0.0074	5	1694140	5.08E-09	HDL	G	0.0012	5.845	A
5:111225001:C:A	A	0.0072	5	1668960	1.56E-08	HDL	C	0.0012	5.655	A
5:111235304:A:C	C	0.0072	5	1681390	1.66E-08	HDL	A	0.0012	5.645	A
5:111285955:C:G	G	-0.0072	5	1678500	1.71E-08	HDL	C	0.0012	-5.639	G
5:111260051:A:G	G	0.0073	5	1776130	2.02E-08	HDL	A	0.0012	5.61	A
5:111225171:C:T	T	0.0072	5	1668960	2.27E-08	HDL	C	0.0012	5.59	C
5:111244077:G:C	C	0.0071	5	1681390	2.29E-08	HDL	G	0.0012	5.589	G
5:111250451:T:A	A	0.0073	5	1775690	2.48E-08	HDL	T	0.0012	5.575	T

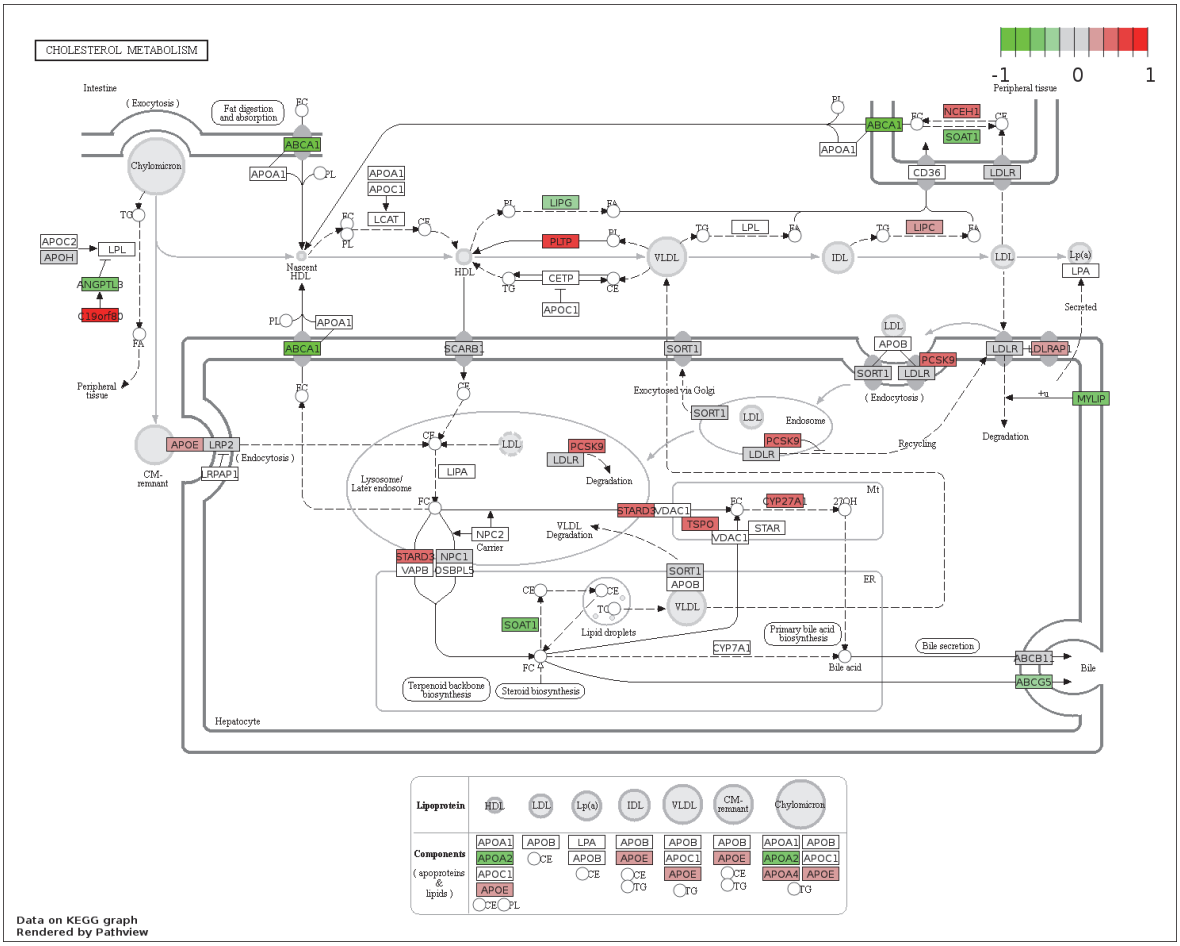
SUPPLEMENTARY FIGURE 2
(Related to Figure 1)

Supplementary Figure 2 (Related to Figure 1): *In silico* prediction of NREP protein structure and functions and GWAS meta-analyses phenotype associations with NREP loci. (**A**) NREP protein structure domains and features. (**B**) NREP 3D structure modeling. (**C**) Molecular function predictions for NREP based on its theoretical structure. In (A) and (B) the terms represent those predicted where support vector machine (SVM; a machine learning technique) training includes assigned GO terms across all evidence code types. SVM reliability is regarded as High (H) when sensitivity, specificity, and precision are jointly above a given threshold. Otherwise, reliability is indicated as Low (L). Terms with lower reliability are not shown. (**D**) PPARG transcription binding activity in nuclear extracts of HepG2 cells (n=6 biological replicates/group). (**E**) Summary of bottom-line associations with represented phenotypes. Associations are clumped by linkage disequilibrium (complete list in Supplementary Table 1). (**F**) LocusZoom interactive visualization of bottom-line *P*-values for variant associations with HDL cholesterol across NREP loci (complete list in Supplementary Table 2). (**G**) Top SNPs associations table with HDL cholesterol across NREP loci. Data retrieved from the Common Metabolic Disease Risk Knowledge Portal. Statistical analyses by One-way ANOVA with LSD test in D.



Supplementary Figure 3 (Related to Figure 2): NREP silencing in hepatocytes recapitulates the downregulation of one-carbon metabolism genes seen in the methionine/choline-deficient diet (MCD) model of NASH. (**A**) Venn diagram of intersected downregulated genes between NREP knock-down (KD) versus Scramble in primary human hepatocytes and liver lysates from methionine-choline deficient diet (MCD) versus Chow diet (n=4 biological replicates/group) (Tomohiko K & Kulkarni RN, unpublished). (**B**) Pathway enrichment analyses on intersected genes. (**C**) Heat-map representation selected genes associated with metabolism of amino acids and commonly downregulated in the MCD model and NREP KD primary human hepatocytes. (**D**) Pearson's correlations between NREP and represented one-carbon metabolism genes in Chow and MCD liver lysates. Statistical analyses by Benjamini-Hochberg method.

A



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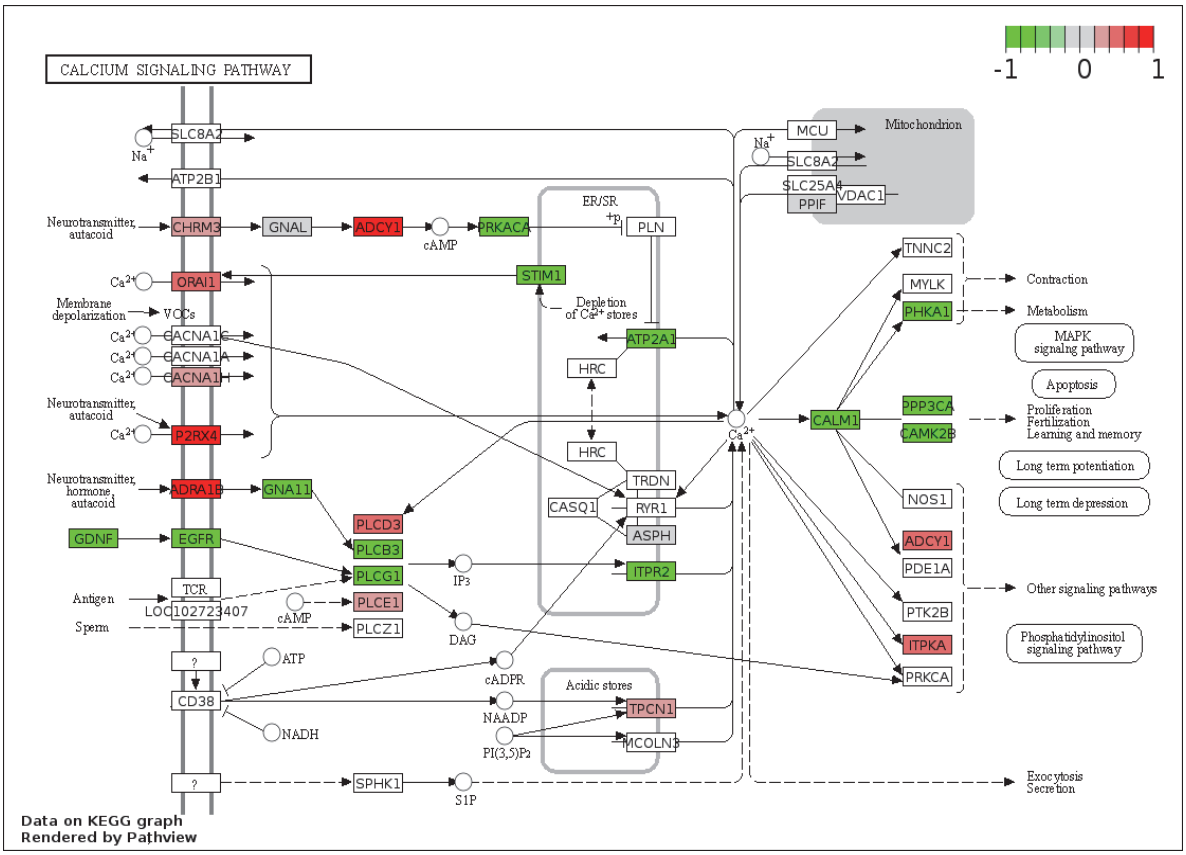

SUPPLEMENTARY FIGURE 4
(Related to Figure 3 and 4)

Supplementary Figure 4 (Relates to Figures 3 and 4): NREP downregulation impacts transcriptional regulation of cholesterol and calcium signaling pathways in primary human hepatocytes. (**A**) Cholesterol metabolism signaling pathway. (**B**) Calcium signaling pathway. RNA-sequencing of NREP KD compared to Scramble in primary human hepatocytes. Colors indicate upregulated (red) or downregulated (green) genes. Genes selected with FDR<0.05. Signaling pathways based on KEGG annotation and rendered by Pathview.