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Supplemental information

Human gain-of-function variants in HNF1A confer protection from diabetes but independently increase hepatic secretion of atherogenic lipoproteins

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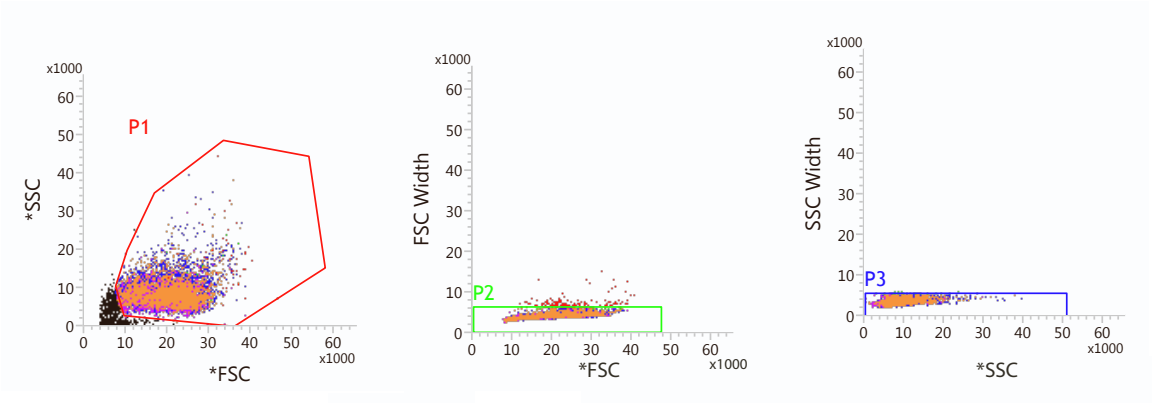
a



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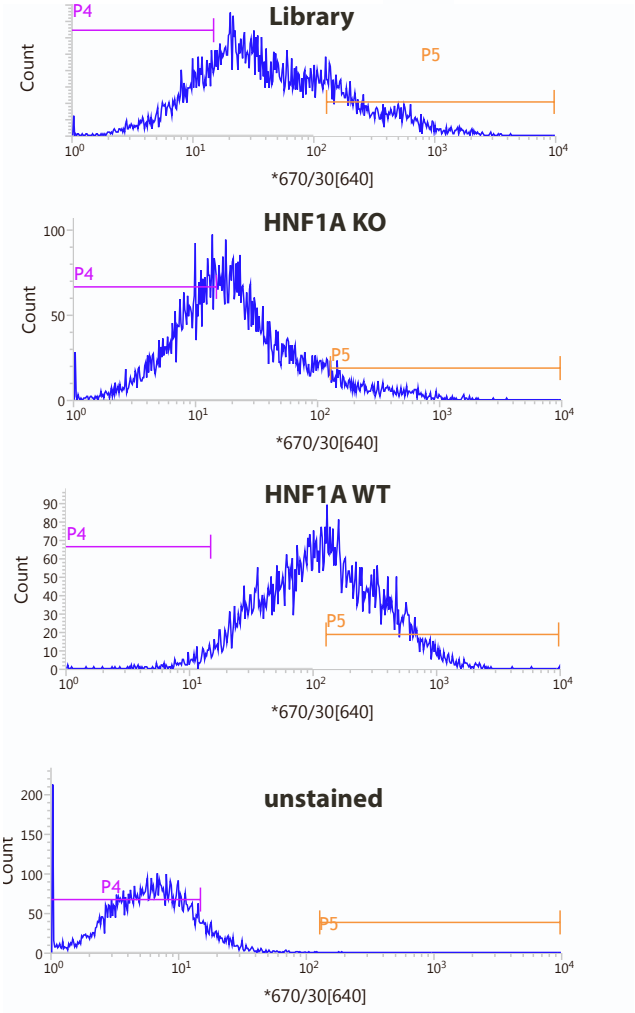


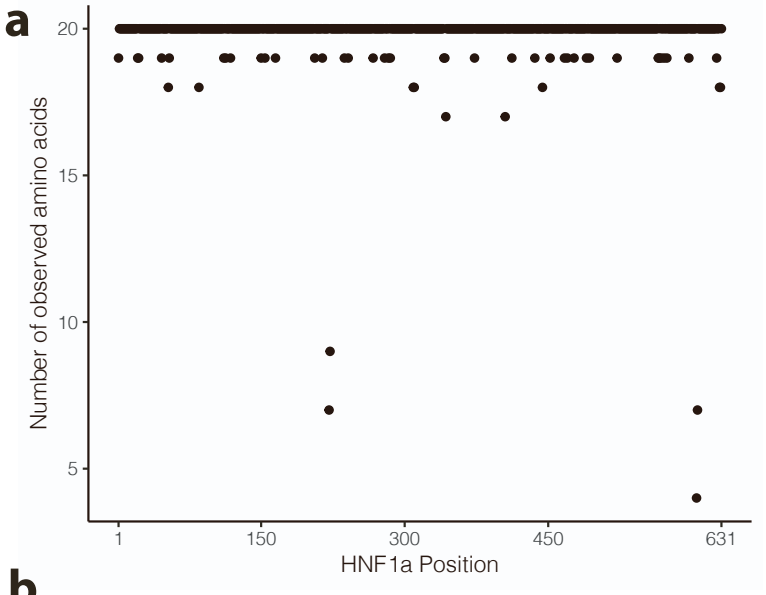
c

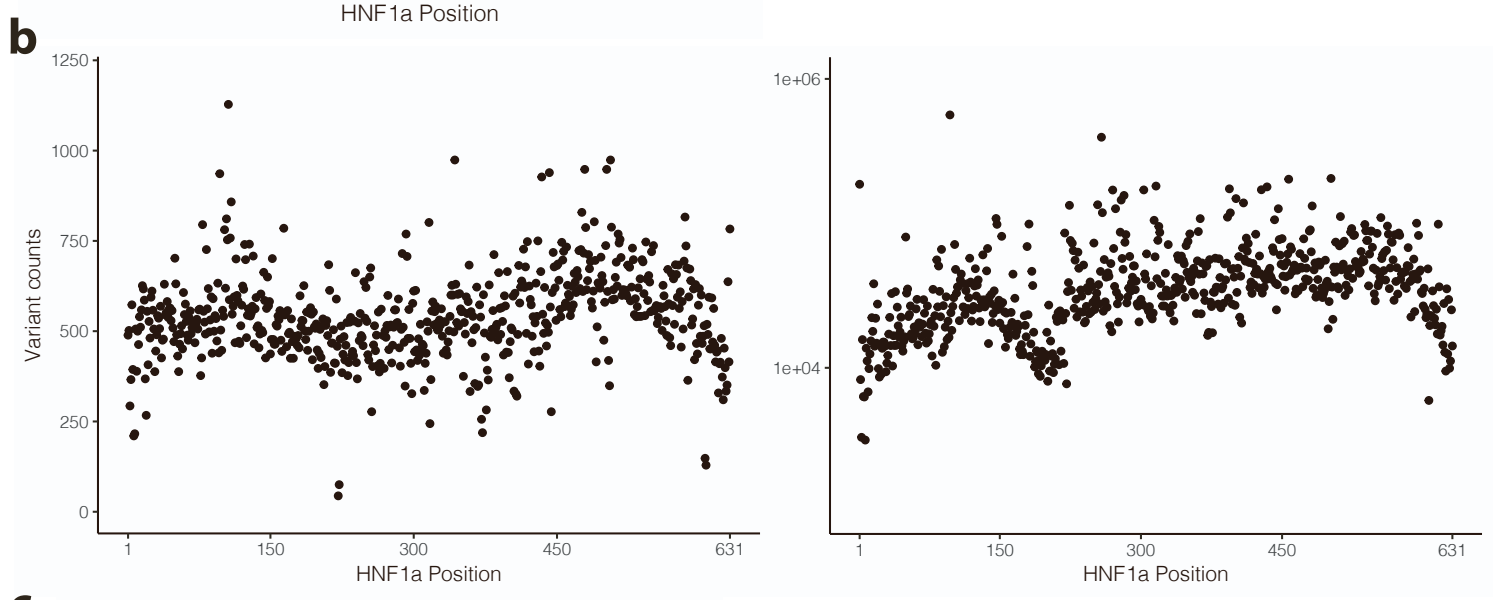
Populations: *Library*

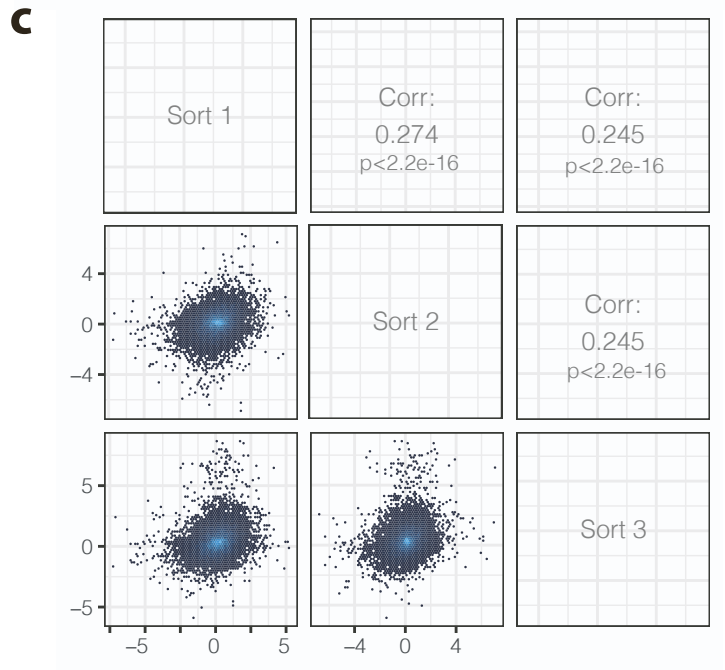
Populations	Even...	% Total	% Parent
All Events	10,000	100.00%	####
P1	9,276	92.76%	92.76%
P2	9,122	91.22%	98.34%
P3	9,097	90.97%	99.73%
P4	1,970	19.70%	21.66%
P5	2,083	20.83%	22.90%

Supplementary Figure 1. FACS sorting data for comprehensive functional testing of 11,970 HNF1A variants, Related to Figure 1

a) Forward scatter versus side scatter (FSC vs SSC) density plots describing cellular gating: the P1 gate eliminated cellular fragments and debris; the P2 and P3 gates eliminated cell doublets. **b)** Histograms of fluorescence intensity at 670 nm for HUH7 cell populations stained with APC-conjugated TM4SF4 antibody and unstained cells. 'Library' refers to HNF1A KO cells infected with the lentiviral plasmid library of 11,970 HNF1A variants. P4 and P5 show the gates for the TM4SF4 'low' and 'high' populations respectively **c)** Table showing the percentage of cells passing through gates shown in **a)** and **b)**.

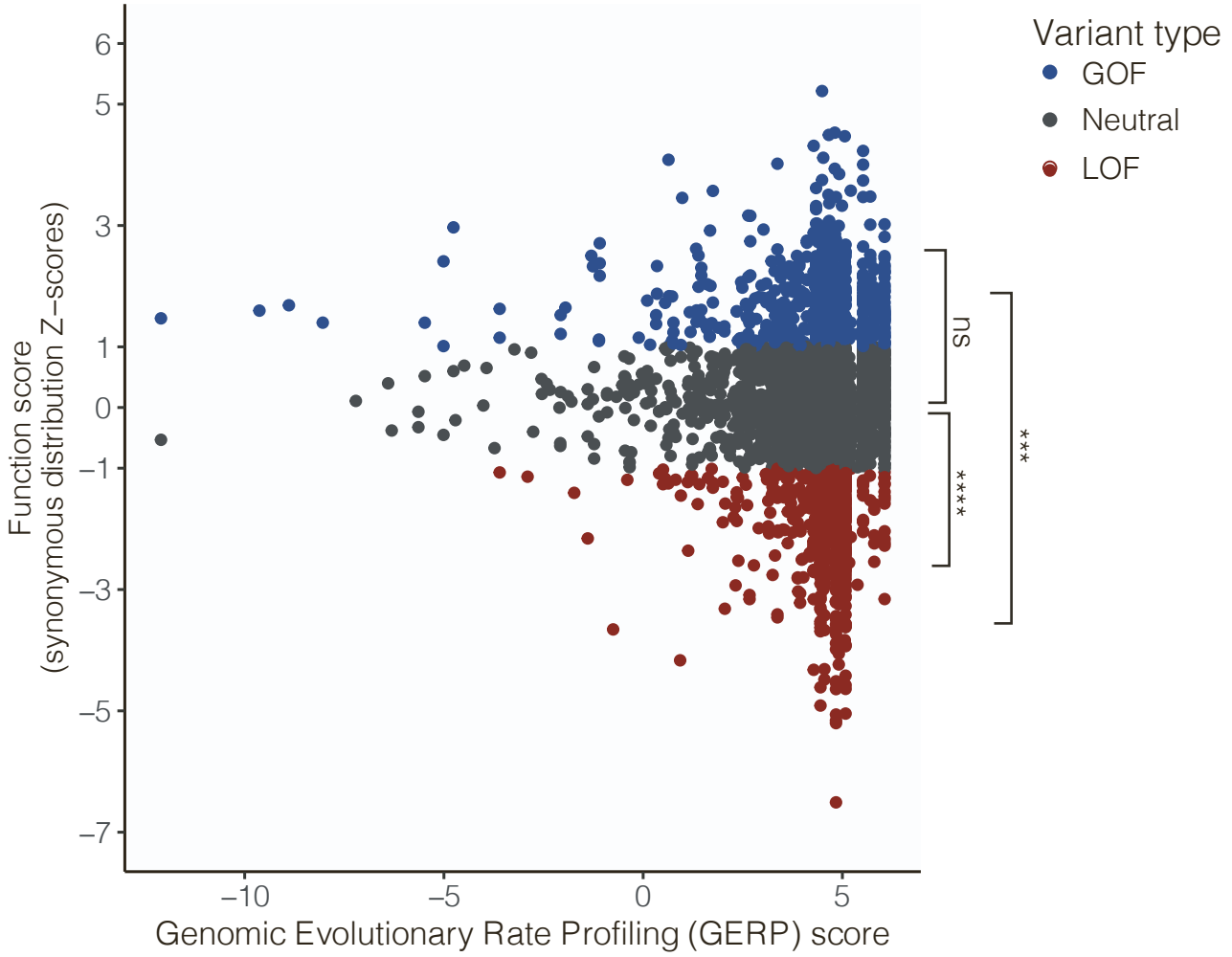






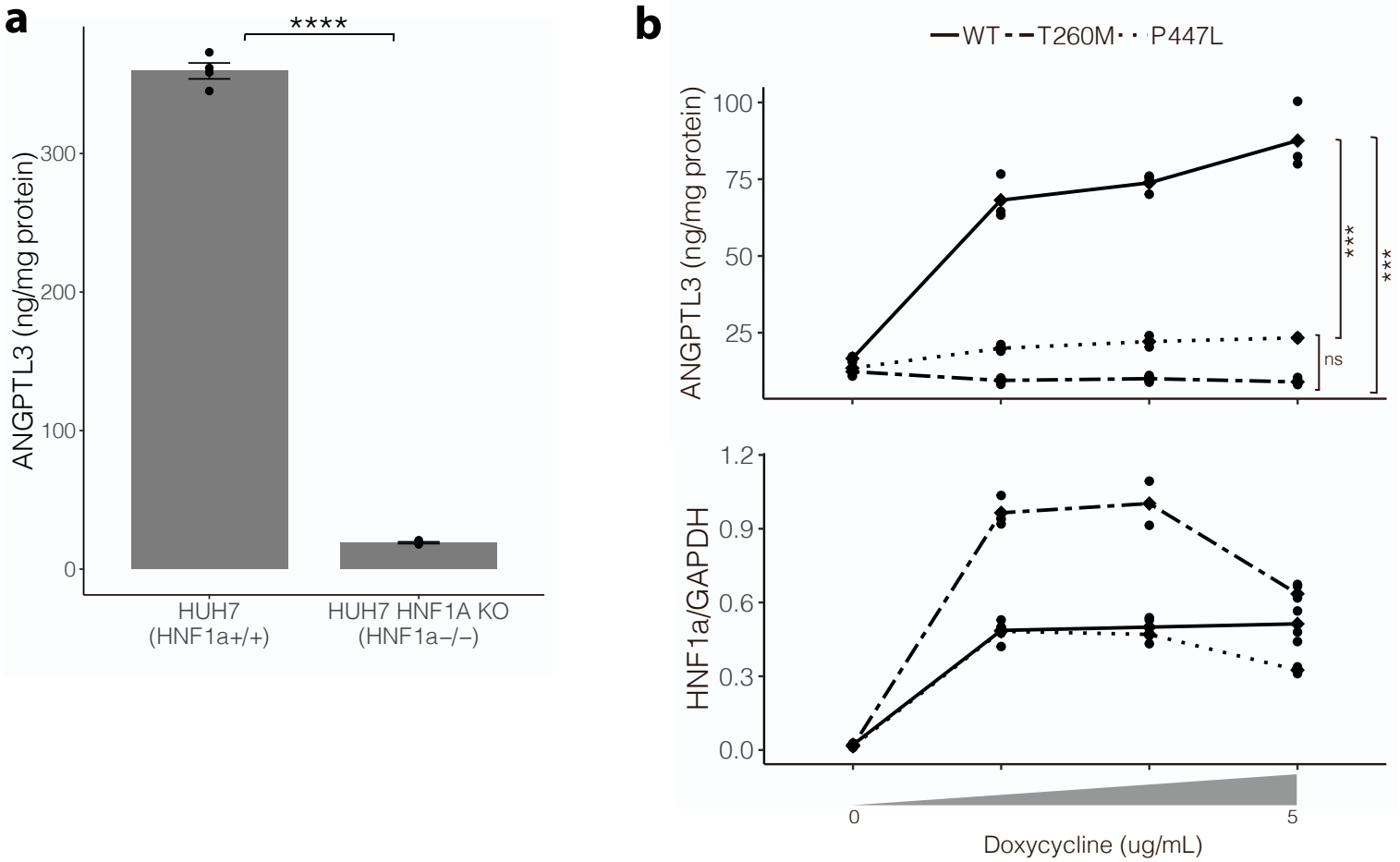
Supplementary Figure 2. HNF1A variant library completeness and balance, Related to Figure 1

a) Sequencing of the synthesized HNF1A mutagenesis library. At each position along the HNF1A primary amino acid sequence the number of observed amino acids (out of 20 possible) is shown. Amino acid positions 221, 222, 605, and 606 had low diversity. Overall the library was 99.1% percent complete, containing 11,858 of 11,970 possible variants.
b) Observed counts of HNF1A protein-coding variants per amino acid position in the (left panel) original synthesized library and (right panel) counts recovered following introduction into hepatocytes following FACS sorting. **c**) Raw log two fold changes of HNF1A variants from TM4SF4^{high} and TM4SF4^{low} sorting bins across three independent sorting experiments.

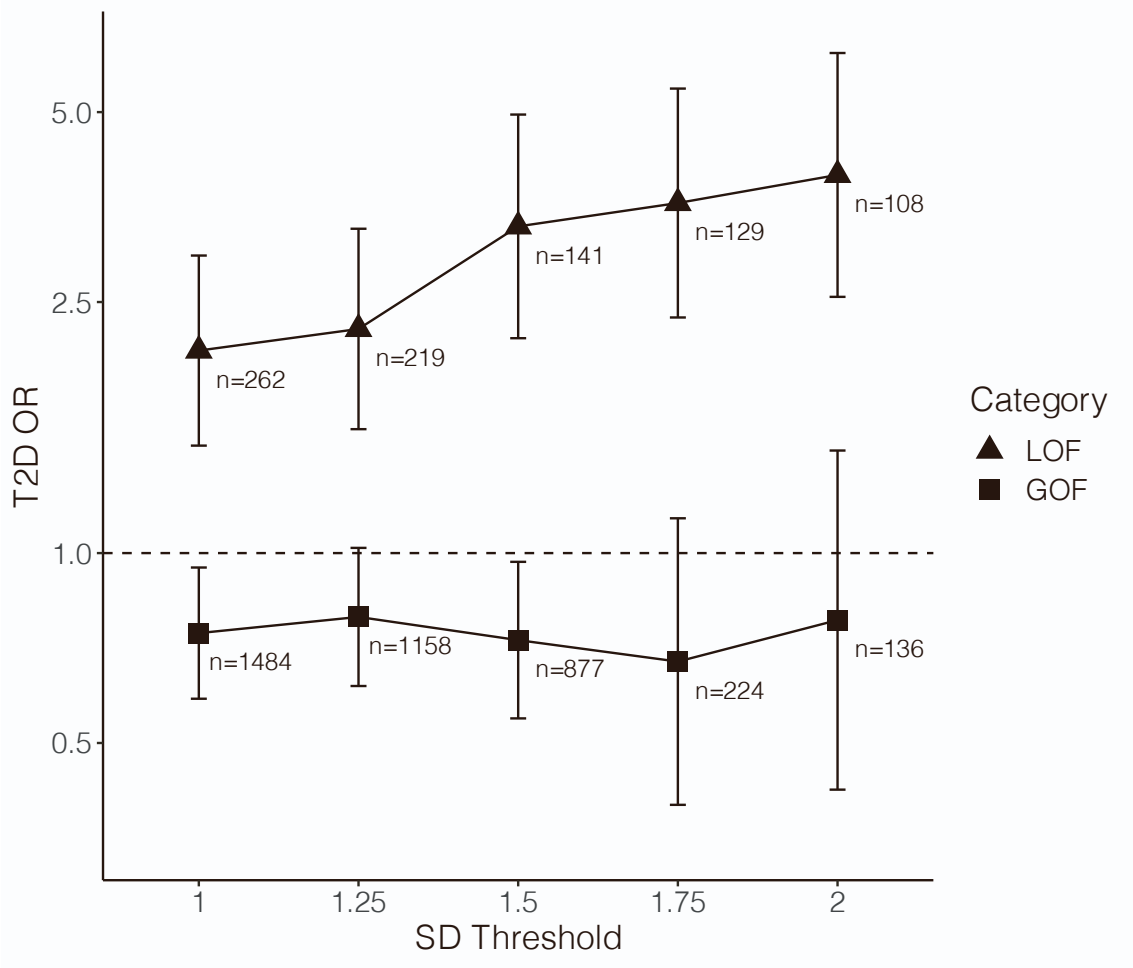


Supplementary Figure 3. HNF1A LOF variants are more evolutionarily constrained compared to GOF and neutral variants, Related to Figure 1,2.

Genomic Evolutionary Rate Profiling (GERP) scores for HNF1A variants versus the deep mutational scan function scores. Unlike GOF and neutral variants, LOF variants were depleted of low GERP scores, indicating these variants have fewer substitutions than what is expected based on the neutral rate of evolution across the phylogeny and are thus more evolutionarily constrained. (**** $p < 10^{-6}$, *** $p < 2x10^{-3}$, Wilcoxon rank sum test)

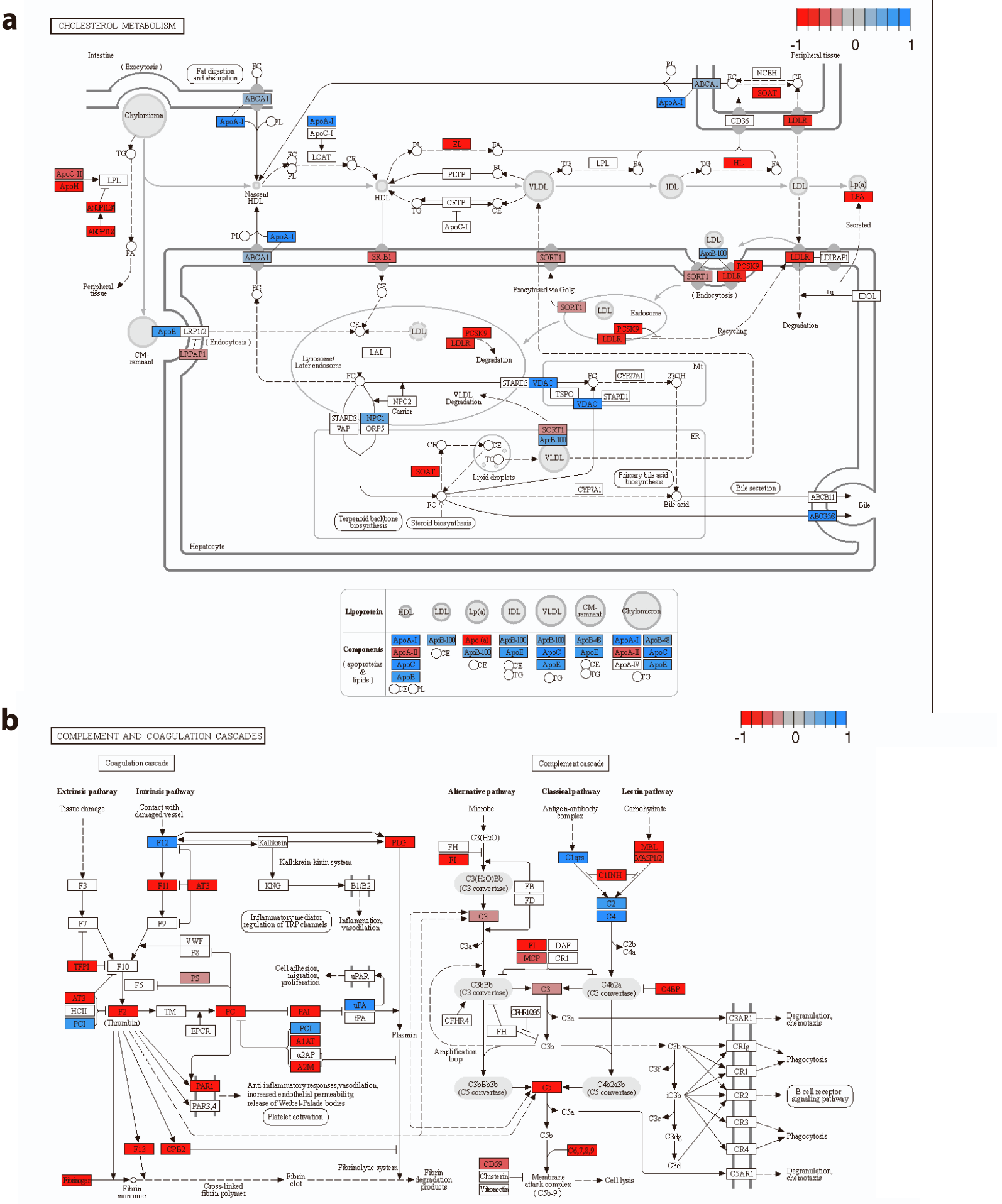


Supplementary Figure 4. HNF1A regulates the hepatic secretion of ANGPTL3, Related to Figure 2
a) Media from cultured WT and HNF1A deficient HUH7 hepatocytes was assessed for ANGPTL3 protein by ELISA 48 hours post confluency (n=3 per group, **** $p < 8.5 \times 10^{-6}$, Student's T-test). **b**) (top) Doxycycline-inducible WT and known LOF HNF1A mutant constructs were transduced into HNF1A deleted HUH7 hepatocytes and treated with doxycycline at the following concentrations: 0, 0.5, 1 and 5μg/mL (n=3 per group). ANGPTL3 secretion was measured in the media by ELISA normalized to total extracted protein. Both WT and mutant HNF1A transgenes express in a doxycycline dose dependent fashion, but the mutants fail to rescue ANGPTL3 secretion as WT(*** adjusted $p < 1.0 \times 10^{-7}$, Tukey pairwise multiple comparisons test). (bottom) The HNF1A band intensity was measured and plotted for each sample as a fraction of band intensity of endogenous GAPDH loading control.



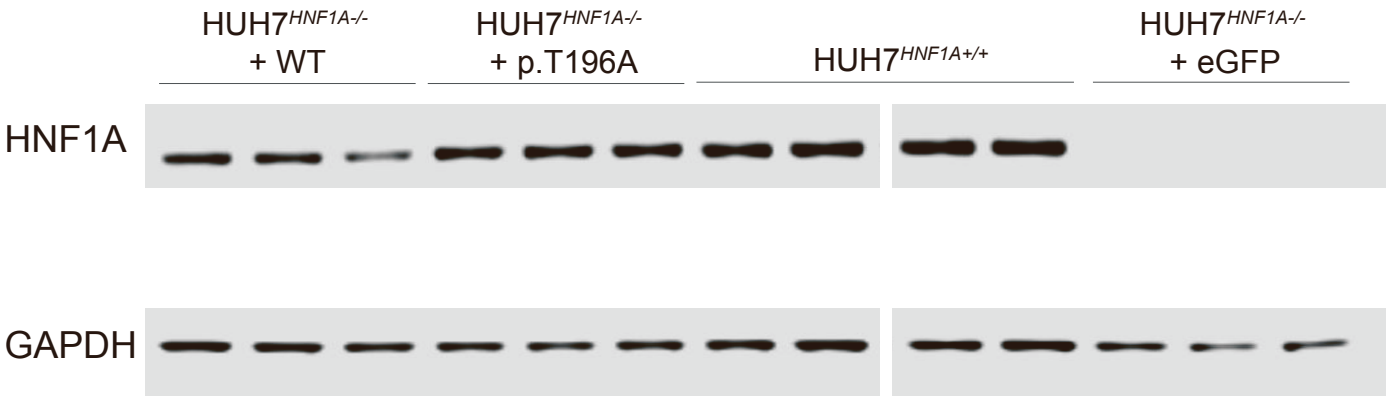
Supplementary Figure 5: Sensitivity analysis of LOF/GOF thresholding on association with T2D, Related to Figure 3.

Association of LOF and GOF HNF1A variants with T2D in the UK Biobank at varying thresholds of variant categorization. Each value along the x-axis represents the standard deviation (SD) of the function score distribution of synonymous variants used to classify variants as LOF or GOF. Odds ratios and the 95% confidence interval for association with T2D are shown on the y-axis. The number of human carriers for LOF and GOF variants at each categorization threshold is indicated. All corresponding numerical values can be found in Supplementary Table 6.



Supplementary Figure 6. Impact of HNF1A deletion on cholesterol metabolism, complement and coagulation pathways, Related to Figure 4

Genes that were differentially expressed (adjusted p<0.05) following HNF1A deletion in human hepatocytes were overlaid on the **a**) KEGG cholesterol metabolism pathway (hsa04979) and **b**) KEGG complement and coagulation cascades (hsa04610), and colored according to their log2 fold change (down regulated = red, upregulated = blue).



Supplementary Figure 7. Western blot analysis for HNF1A variant protein expression levels, Related to Figure 4

(top) HNF1A immunoblot for HNF1A null HUH7 cells electroporated with WT, p.T196A, or eGFP mRNA as well as WT HUH7 cells. (bottom) The same samples were immunoblotted for GAPDH. The HNF1A null HUH7 cells electroporated with WT and p.T196A have HNF1A expression on par with WT HUH7 cells.

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AMP-T2D

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