SUPPLEMENTAL MATERIALS AND METHODS

Generation of AAVs

Human PNPLA3 wild type and I148M were synthesized and cloned into pUC57 shuttle plasmid (Genewiz LLC), MluI and SalI sites were introduced at 5’ and 3’ end respectively. The human PCSK9 wild type and I148M were subsequently subcloned into MluI and SalI sites of a pAAV cis plasmid that contains the liver-specific thyroxine binding globulin promoter. Luciferase driven by the same promoter was used as control. The recombinant AAV8 vectors were generated with the helper-free triple plasmid transfection method in HEK293 cells, and purified using double cesium chloride gradient centrifugation by the Viral Vector Core of University of Massachusetts Medical School. The titers were determined via digital-droplet PCR analysis.

Generation of siRNA

siRNA of placebo lipid nanoparticle (LNP) and si-hPNPLA3 were prepared as described by Gindy et al.(1). For placebo LNP, GS sequence is 5'-fluU;fluC;rG;omeA;fluC;fluC;omeG; omeA;fluU;omeA;fluU; omeA;omeA;rG; omeG;fluC;omeG;omeA;fluC;omeUs;omeU-3'. PS sequence is 5'-6amiL;dG;fluU;fluC; dG;fluC;fluC;fluU;fluU;dA;fluU;dA;fluU; fluC;dG;dG;fluU;fluC;dG;dA;omeUs;omeU;iB-3'. The core scrambled sequence is GTCGCCTTATATCGGTCGA. For si-hPNPLA3, GS sequence is 5'-fluU;fluU;fluA;fluC;omeA;fluU;omeA;omeA;omeG;omeA;fluC;omeA; fluU;fluU;omeA;fluU;fluC; fluC;fluU;omeUs;omeU-3'. PS sequence is 5'-iB;rA;rG;rG;rA;

omeU;rA;rA;omeU;rG;omeU;omeC;omeU; omeU;rA;omeU;rG;omeU;rA;rA;omeUs; omeU;iB-3'. The core targeting sequence is AGGATAATGTCTTATGTAA. LNP platform is 2'-O-me + 2'-F. siRNA stock reagents were diluted to desired concentration (0.175 mg/ml) by using Tris G diluent (10 mM tris buffer pH 7.5, 70 mM NaCl, 5% sucrose) before treatment.

Isolation of mouse hepatocytes

To determine whether human PNPLA3 was expressed in mouse hepatocytes versus hepatic stellate cells (HSCs), mice injected with PNPLA3^{I148M} were anesthetized with isoflurane. Primary mouse hepatocytes were isolated via the ethylene glycol tetra-acetic acid (EGTA)/collagenase perfusion technique, with microcannulation of the portal vein as previously described(2). Hepatocytes were cultured in collagen-coated plates with William’s E containing penicillin (100 units/ml), insulin (1.5uM), dexamethasone (0.1 μM), and thyroxine (1 μM). Primary mouse HSCs were isolated using gradient centrifugation as previously described(3), and cultured with Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum, penicillin G (100 U/mL), and streptomycin (100 μg/mL).

In vitro studies of effects of PNPLA3^{I148M} and STAT3 activation in hepatocytes on stellate cell activation:

Human HepG2 hepatoma cells which are known to carry the PNPLA3^{I148M} mutation were incubated at 37°C for 3 days in 6-well plates containing 10% fetal bovine serum, 100 IU/ml penicillin, and 100 μg/ml streptomycin. To induce fibrosis in stellate cells, the supernatants from Hep2G cultures were added to LX2 cells and incubated overnight in 6-well plates. Total RNA from cells were extracted using Trizol reagent to determine PNPLA3 ^{I148M} mRNA levels in HepG2 cells and procollagen mRNA expression in LX2 cells. For Stat3 inhibition experiments, HepG2 cells were treated with Stattic (a selective Stat3 inhibitor, Sigma Co.) at 1 μM or 5 μM for 2.5 h in normal glucose or high glucose DMEM. The media were replaced by fresh media for another 48 h. Supernatants were added to LX2 cells for overnight incubation, and HepG2 cells were collected and analyzed for Stat3, p-Stat3 and β-actin protein expression. After overnight incubation of LX2 cells in supernatant, total RNA of whole-cell lysates was extracted by using Trizol reagent to examine the effect of Stat3 inhibition on fibrosis markers.

mRNA extraction and real-time PCR

These were done as previously described (4). Liver tissues lysed in RLT lysis buffer (QIAGEN, 74104) were used for RNA isolation using RNEasy Mini Kit (QIAGEN, 74104) following the manufacturer's protocol. Total RNA yield, 260/280, and 260/230 ratios were determined using NanoDrop spectrophotometer (Thermo Scientific). Total RNA was reverse-transcribed into complementary DNA using reverse transcriptase and random primers (Invitrogen). Complementary DNA was quantified by real-time PCR using SYBR green fluorescence and TaqMan gene expression assays (Thermofisher) on a LightCycler 480 instrument (Roche Applied Science), relative to expression of Glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Primers and used were obtained from Invitrogen and Thermofisher.

Immunoblot Analysis

Briefly, 20 µg of protein were resolved by SDS-PAGE on a 4%-12% NuPAGE Novex Bis-Tris Mini Gel (Invitrogen), followed by transfer to nitrocellulose membrane and incubation with primary antibody and subsequently secondary antibody as per established protocols.

Metabolomic analyses

I. Metabolite extraction and LC-MS analysis: Two separate liquid chromatography (LC)-time of flight (ToF)-mass spectrometry (MS)-based platforms that analyzed methanol (Platform 1) and methanol/chloroform (Platform 2) extracts for lipid analyses were combined with a LC-single quadrupole-MS amino acid analysis (Platform 3) and a LC-ToF-MS platform for the analysis of polar metabolites in a methanol/H_2O extract (Platform 4)(5, 6). Identified metabolites in the methanol extract platform included fatty acids, acyl carnitines, bile acids, lysoglycerophospholipids, free sphingoid bases, N-acyl ethanolamines and oxidized fatty acids. The chloroform/methanol extract platform provided coverage over glycerolipids, cholesterol esters, sphingolipids and glycerophospholipids.

II. Metabolomics data analysis: Data were pre-processed using the TargetLynx application manager for MassLynx 4.1 software (Waters Corp., Milford, USA). Metabolites were identified prior to the analysis. Peak detection, noise reduction and data normalization were performed as previously described(7). The Shapiro-Wilk test for normality and Student's t-test for statistical significance determination between groups were performed.

Transcriptomic analysis

I. mRNA sequencing data Alignment and Annotations: This was done as described previously (8). mRNA sequence data were uploaded to a High Performance Computing system by PartekFlow® software (v7.0), adapter-trimmed and remapped to mouse genome, mm10 using STAR v2.5.2b aligner with default setting (phred: 20) for read mapping. mRNA reads were annotated to ensembl v87. Expression matrices were compared between mutant PNPLA3 versus LUC, and between mutant PNPLA3 versus wild-type PNPLA3. Statistical analyses were carried out using false discovery rate (FDR) correction through the Benjamini-Hochberg method. A default FDR <0.05 was considered statistically significant (8, 9), with a $\log_2$-fold change more than 1 (Total count >100, FDR <0.05; low expressed: 100% of samples have ≥100 reads).

II. Biological Processes and Gene Network Visualization by MetaCore: This was also performed as described previously (8). Biological pathway interactions of mRNA expressions were analyzed using MetaCore pathway analysis of differentially expressed genes (Clarivate Analytics) with $p < 0.05$ and greater than two-fold change. We performed enrichment analysis on mutant PNPLA3 versus LUC, and on mutant PNPLA3 versus wild-type PNPLA3. Functional gene networks were built based on differentially regulated mRNA gene lists as input to generate disease biomarkers and Gene Ontology terms (8, 9).

III. Integrated pathway analysis:

A joint metabolome-transcriptome analysis was performed using the integrated pathway analysis module of Metaboanalyst 4.0. The updated KEGG pathways (October 2019) were used for annotation. The data were integrated by combining queries in which genes and metabolites were pooled in to a single query and used to perform enrichment analysis. Additionally, weightage was given to the proportions of metabolites and genes at a pathway level to compute the read-out. Topology analyses using “degree centrality” i.e. the number of links that connect to a node was used to determine the impact of significantly altered pathways.

SUPPLEMENTAL REFERENCES

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SUPPLEMENTAL FIGURE LEGENDS

Supplemental Figure 1: Generation of adeno associated virus (AAV). (A-C). Human PNPLA3 wild type and mutant I148M were synthesized and cloned into pUC57 shuttle plasmid as described in the Methods section. Luciferase (LUC) driven by the same promoter was used as control. The recombinant AAV8 vectors containing LUC (A), PNPLA3WT (B) or PNPLA3I148M (C) were generated with the helper-free triple plasmid transfection method in HEK293 cells and purified by gradient centrifugation.

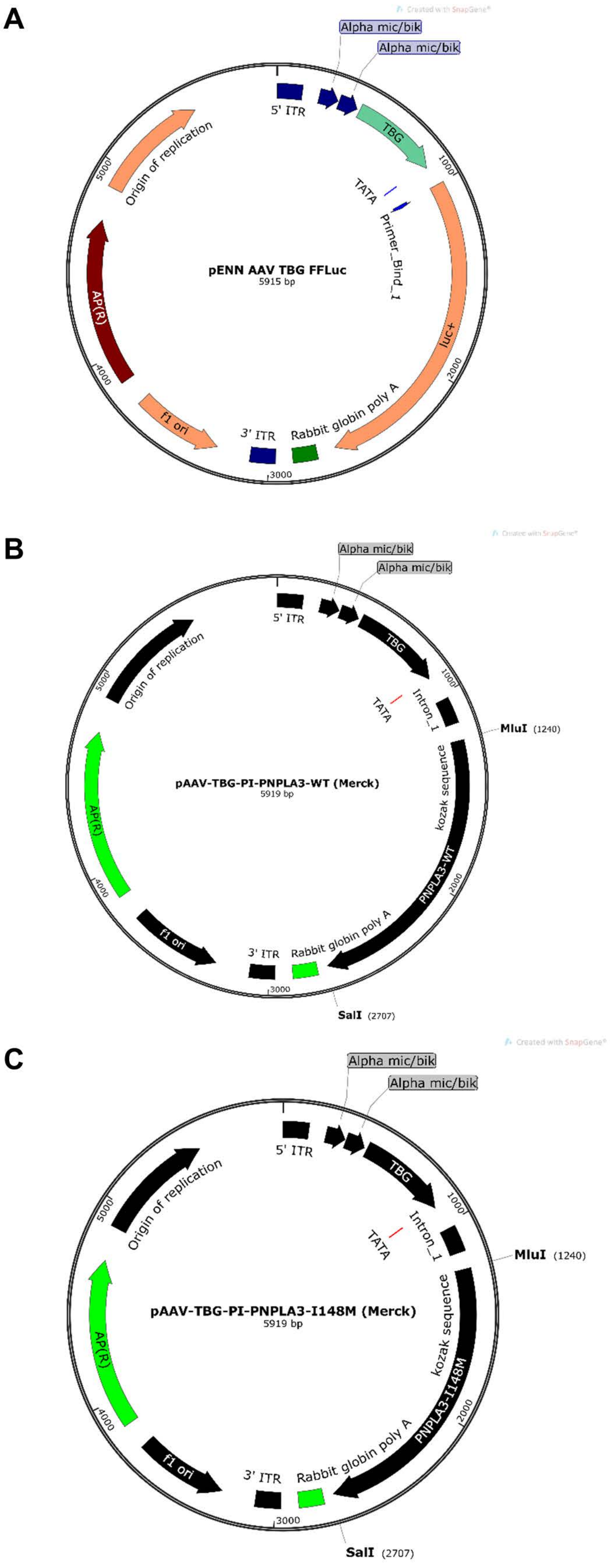
Supplemental Figure 2: **PNPLA3^{I148M} expression does not alter liver histology under conditions of chow diet.** (A) Liver tissue collected at the time of sacrifice were sectioned for histological analysis; representative Hematoxylin and eosin (H&E) stained sections of liver tissue for mice on CDNW are shown. All mice on chow diet showed similar liver histology, with histological scores of 0 for all groups (data not shown). (B) Similarly, mice on chow diet did not develop fibrosis irrespective of type of AAV construct.

Supplemental Figure 3: PNPLA3 overexpression leads to PUFA depletion with minimal effect on de novo lipogenesis. (A) Similar to PNPLA3^{I148M}, PNPLA3^{WT} (versus luc) led to PUFA depletion under conditions of chow diet (top panel) and western diet (middle panel). PNPLA3^{I148M} conferred a greater depletion of PUFA when compared to PNPLA3^{WT} (bottom panel). (B) Based on integrated pathway analyses, PNPLA3^{I148M} did not significantly alter de novo lipogenesis pathways. (C) Western blot analysis showed a mild increase in hepatic SREBP1, FASN and ACC protein expression. (D) The mRNA levels of CGI58, which has been linked to PNPLA3 TAG hydrolytic function was induced by PNPLA3^{I148M} but did not decrease significantly after silencing PNPLA3.

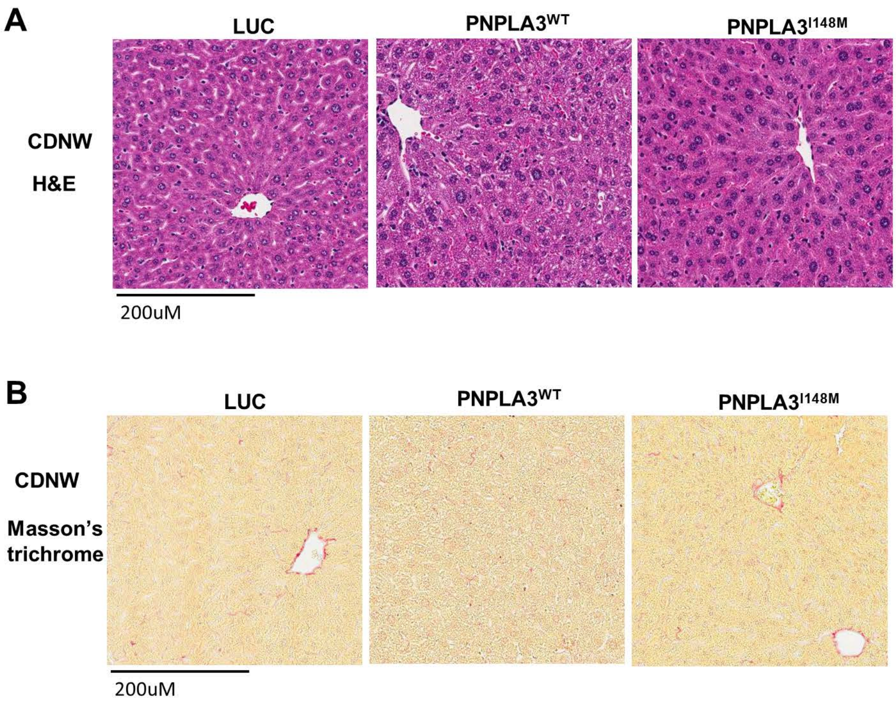
Supplemental Figure 4. PNPLA3^{I148M} under WDSW diet conditions activated innate immune system and inflammatory response pathways. (A) Top scored maps (those with the lowest p-value) based on the enrichment distribution were determined. These maps were primarily involved in immune response, including IL-6 induced innate immune response (B) and renal tubulointerstitial injury (C). Upward (red) thermometers indicate up-regulated signals and down-ward (blue) thermometers indicate down-regulated gene expression.

Supplemental Figure 5: PNPLA3^{I148M} under WDSW diet conditions induced gene ontology processes and networks involved in immune response. (A-B) The top 10 upregulated gene ontology processes (A) and process networks (B) were determined based on transcriptomic analysis of PNPLA3^{I148M} versus luc under conditions of WDSW. (C-D) The top scored networks included the STAT1-CD14 network (C) and MHC class II immune response network (D), with p = 5.46 x 10-54 and 1.85 x 10-39, respectively. Up-regulated genes are marked with red circles; down-regulated genes are indicated by blue circles.

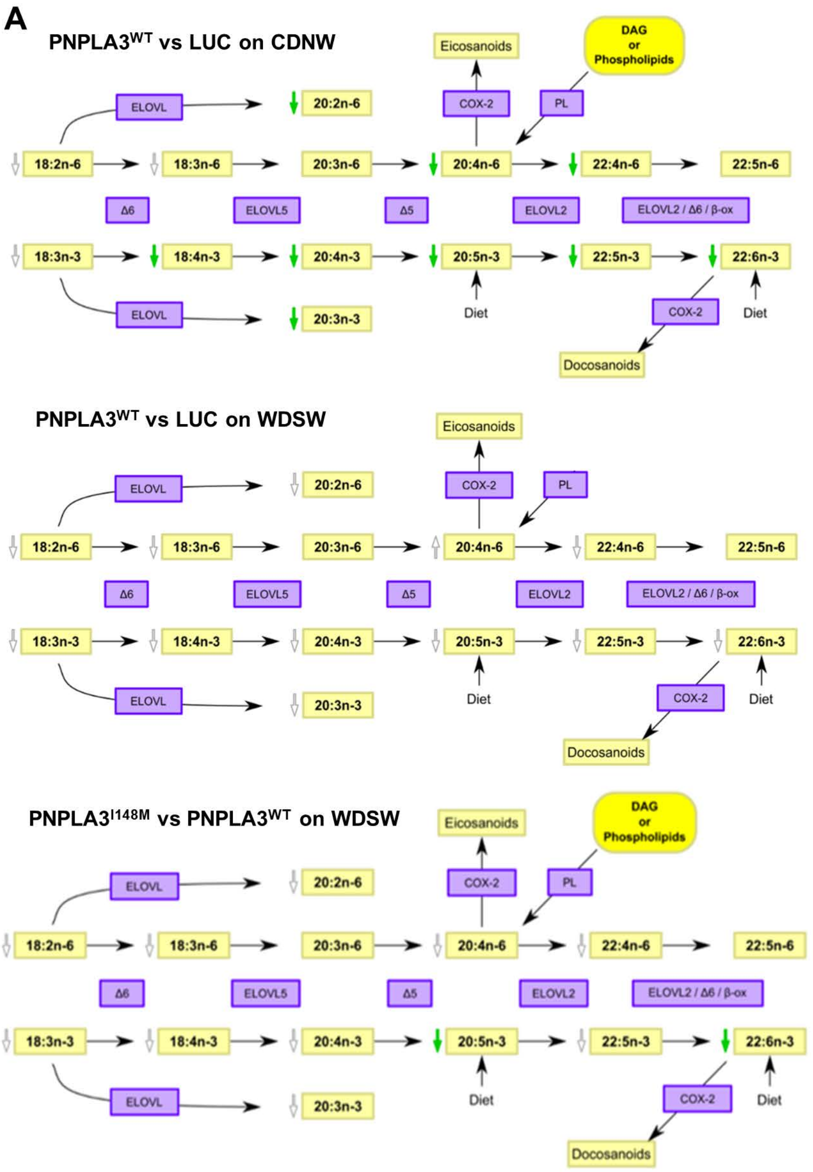
Supplementary Figure 1



Supplementary Figure 2

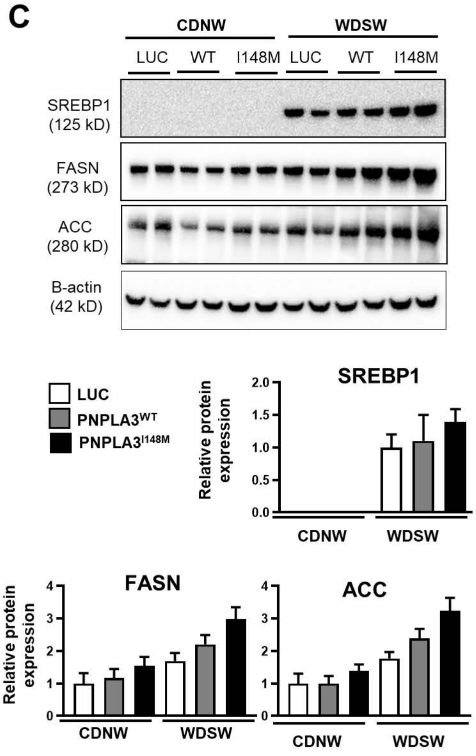


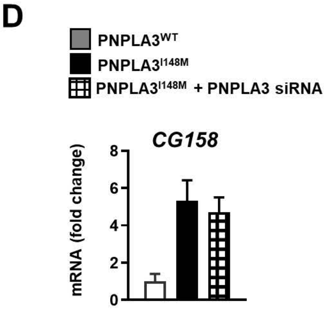
Supplementary Figure 3



B PNPLA3^{WT} vs LUC on WDSW

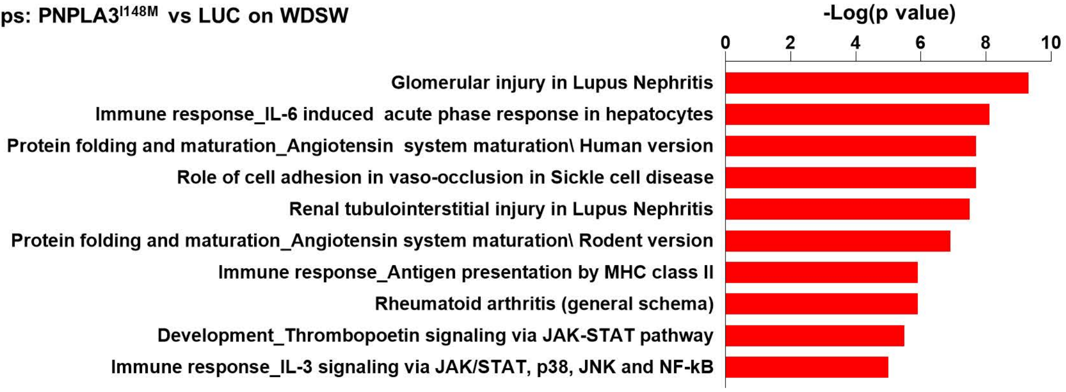
Pathway	# targets	# hits	P value	FDR	Impact
FA Biosynthesis	102	2	0.9	1	0.05
FA Degradation	129	3	0.9	1	0.07
FA Elongation	75	6	0.8	1	0.1
Unsaturated FA synthesis	81	15	8.7E-4	0.004	3



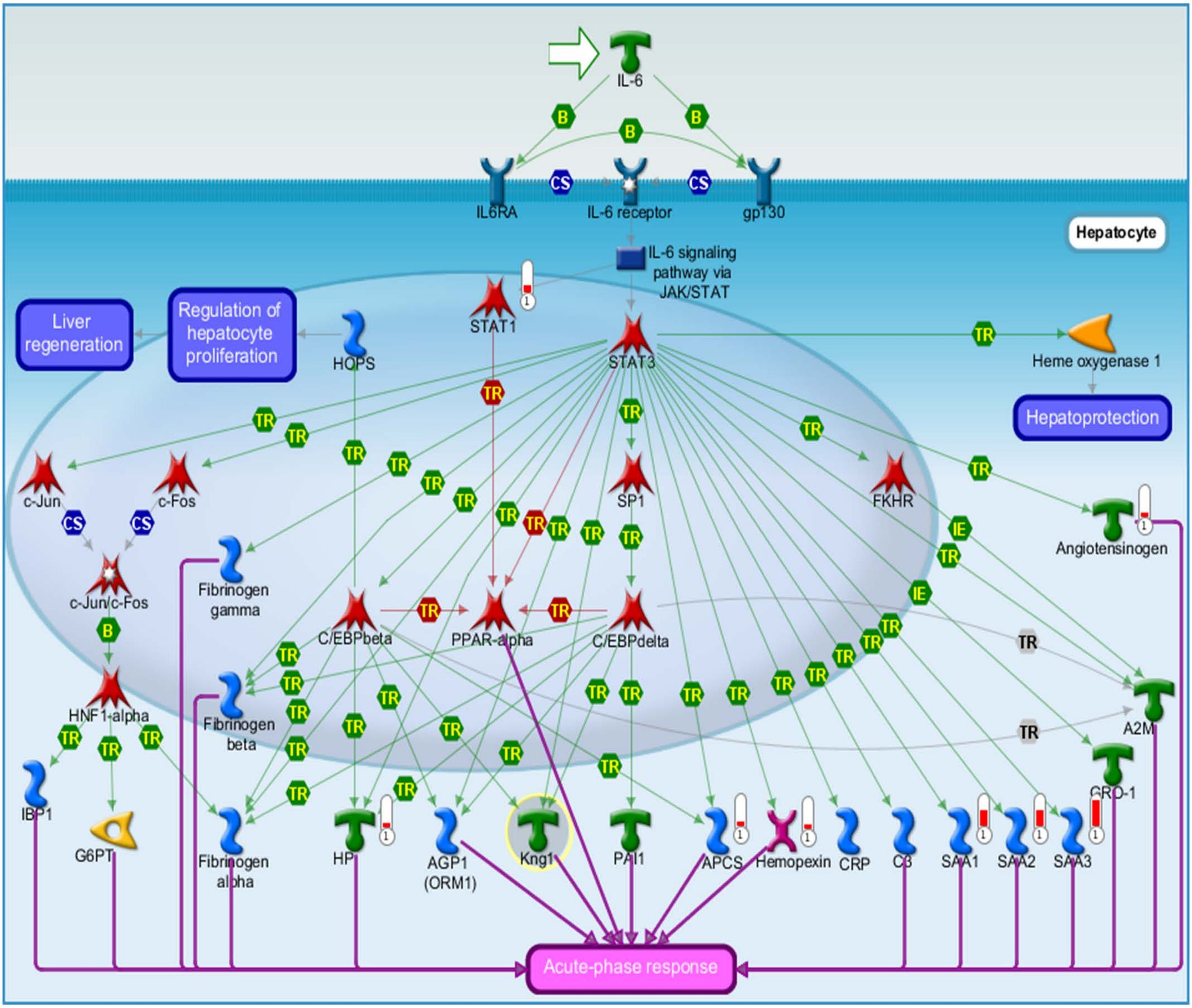


Supplementary Figure 4

A **Maps: PNPLA3^{I148M} vs LUC on WDSW**

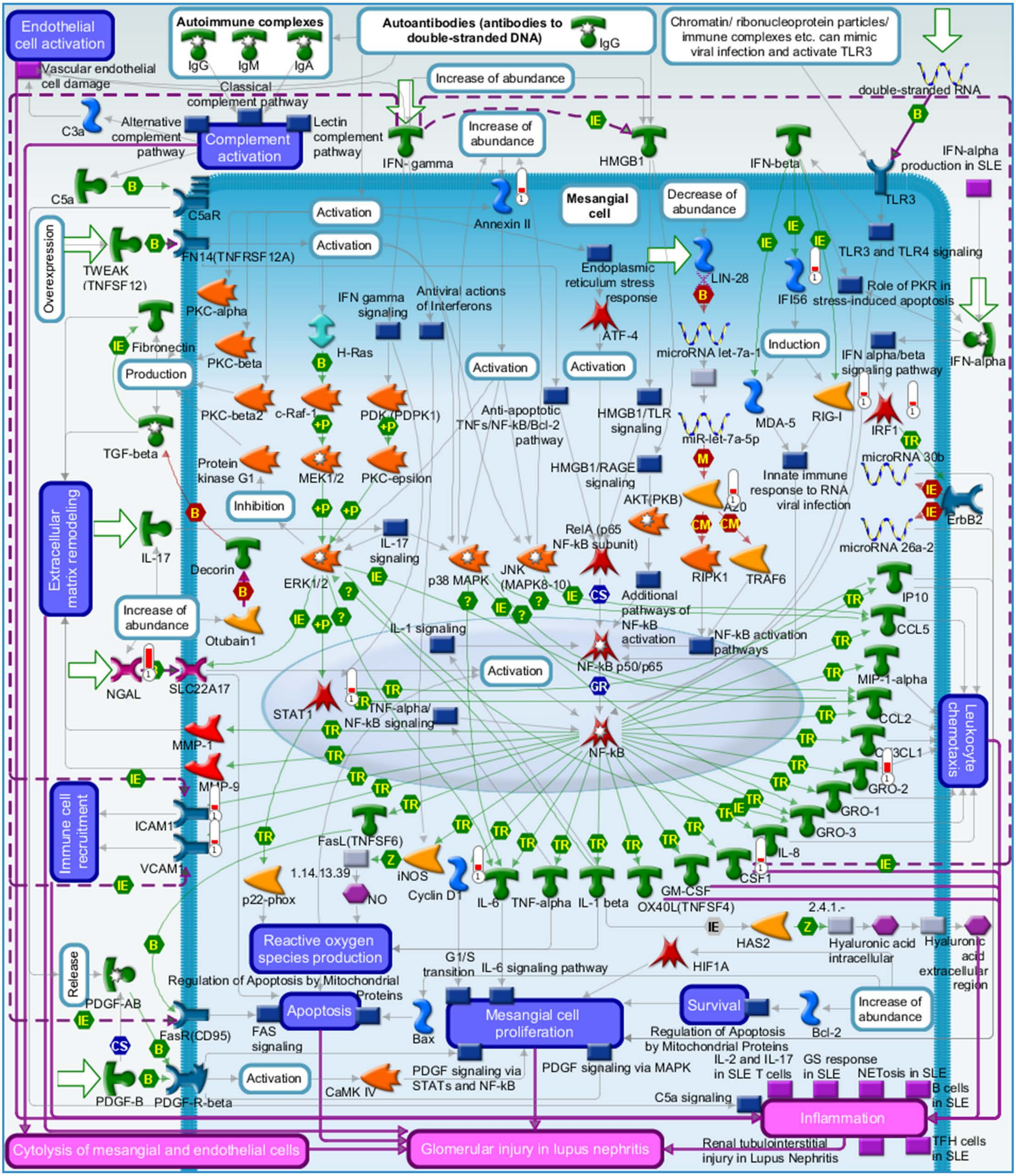


B **Map of Immune response_IL-6-induced acute-phase response in hepatocytes**

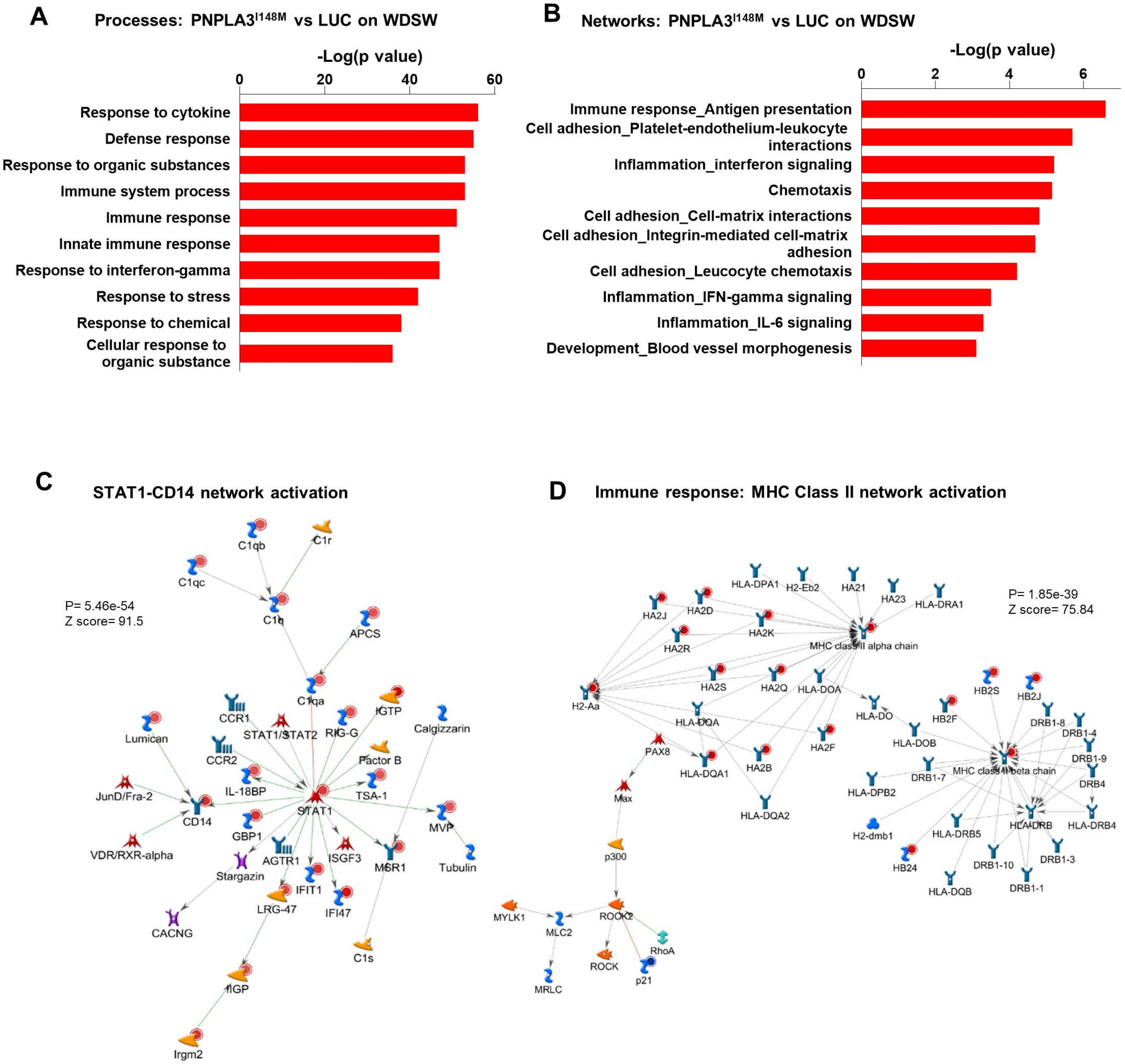


Supplementary Figure 4 continued

C **Map of Renal tubulointerstitial injury**



Supplementary Figure 5



Supplemental Table 1: PNPLA3^{I148M} vs Luc on CDNW

	Pathway	Total number of targets	Expected number of targets	Number of Hits	Raw p-value	Log10(p-value)	Holm adjust	FDR	Impact
1	Central carbon metabolism in cancer	104	1.0256	19	2.61E-19	18.583	8.54E-17	8.54E-17	0
2	Aminoacyl-tRNA biosynthesis	118	1.1637	18	7.17E-17	16.144	2.34E-14	9.63E-15	0.18557
3	ABC transporters	186	1.8343	21	8.84E-17	16.054	2.87E-14	9.63E-15	0
4	Protein digestion and absorption	141	1.3905	18	1.86E-15	14.731	6.02E-13	1.52E-13	0
5	Mineral absorption	81	0.79879	13	9.14E-13	12.039	2.95E-10	4.98E-11	0
6	Biosynthesis of unsaturated fatty acids	81	0.79879	13	9.14E-13	12.039	2.95E-10	4.98E-11	0.075758
7	Primary bile acid biosynthesis	63	0.62128	8	1.74E-07	6.7599	5.58E-05	8.12E-06	0.15957
8	Alanine, aspartate and glutamate metabolism	66	0.65087	8	2.52E-07	6.5994	8.05E-05	1.03E-05	0.57377
9	Vitamin digestion and absorption	63	0.62128	7	2.66E-06	5.5749	0.000849	8.44E-05	0
10	Glycine, serine and threonine metabolism	90	0.88754	8	2.79E-06	5.5546	0.000887	8.44E-05	0.46591
11	Purine metabolism	231	2.278	12	2.84E-06	5.5469	0.0009	8.44E-05	0.39216
12	Arginine biosynthesis	42	0.41419	6	3.18E-06	5.4974	0.001005	8.67E-05	0.4
13	Linoleic acid metabolism	78	0.76921	7	1.13E-05	4.9488	0.003544	0.000283	0.31707
14	Taurine and hypotaurine metabolism	33	0.32543	5	1.63E-05	4.7874	0.005123	0.000381	0.27586
15	Cholesterol metabolism	59	0.58183	6	2.38E-05	4.6227	0.007462	0.00052	0
16	Aldosterone synthesis and secretion	123	1.213	8	2.83E-05	4.5485	0.008823	0.000578	0
17	Nicotinate and nicotinamide metabolism	98	0.96644	7	5.01E-05	4.3003	0.015578	0.000963	0.2439
18	Phenylalanine, tyrosine and tryptophan biosynthesis	43	0.42405	5	6.12E-05	4.2135	0.01896	0.001111	0.29268
19	Leishmaniasis	74	0.72976	6	8.69E-05	4.0609	0.026856	0.001496	0.13208
20	Valine, leucine and isoleucine biosynthesis	27	0.26626	4	0.000132	3.8781	0.040781	0.002152	0.19231
21	Cysteine and methionine metabolism	115	1.1341	7	0.000138	3.8594	0.042432	0.002152	0.13592
22	Antifolate resistance	58	0.57197	5	0.000259	3.587	0.079194	0.003847	0
23	beta-Alanine metabolism	64	0.63114	5	0.000411	3.3863	0.12532	0.005842	0.11111
24	Glutathione metabolism	103	1.0157	6	0.000532	3.274	0.16175	0.00725	0.31884
25	Ferroptosis	72	0.71004	5	0.000708	3.1498	0.2146	0.00911	0.027027
26	Bile secretion	246	2.426	9	0.000724	3.1401	0.21875	0.00911	0.014085
27	Sulfur metabolism	44	0.43391	4	0.0009	3.0457	0.27094	0.010902	0
28	Fatty acid biosynthesis	77	0.75934	5	0.000962	3.0169	0.28854	0.011233	0.017442
29	Pantothenate and CoA biosynthesis	46	0.45363	4	0.001066	2.9723	0.31867	0.012018	0.16667
30	Phenylalanine metabolism	83	0.81851	5	0.001349	2.8701	0.40192	0.014701	0.12329
31	Glyoxylate and dicarboxylate metabolism	93	0.91713	5	0.002233	2.6511	0.66326	0.023557	0.079545
32	Asthma	29	0.28599	3	0.002834	2.5476	0.83887	0.028391	0
33	Inflammatory bowel disease (IBD)	60	0.5917	4	0.002865	2.5429	0.84521	0.028391	0.032258
34	Butanoate metabolism	69	0.68045	4	0.004747	2.3236	1	0.044737	0.090909
35	Toxoplasmosis	111	1.0946	5	0.004788	2.3198	1	0.044737	0.11111
36	Regulation of lipolysis in adipocytes	70	0.69031	4	0.004997	2.3013	1	0.045385	0.033333
37	Sphingolipid metabolism	73	0.7199	4	0.005799	2.2366	1	0.051251	0.36066
38	Proximal tubule bicarbonate reclamation	39	0.3846	3	0.0066	2.1805	1	0.056791	0
39	Taste transduction	121	1.1933	5	0.006873	2.1628	1	0.05763	0.11429
40	Pyrimidine metabolism	123	1.213	5	0.007356	2.1334	1	0.060136	0.18605
41	Ovarian steroidogenesis	81	0.79879	4	0.008348	2.0784	1	0.066579	0
42	Intestinal immune network for IgA production	44	0.43391	3	0.00923	2.0348	1	0.071859	0
43	Thiamine metabolism	46	0.45363	3	0.010429	1.9817	1	0.079313	0
44	D-Glutamine and D-glutamate metabolism	17	0.16765	2	0.011906	1.9242	1	0.087095	0.25
45	Th1 and Th2 cell differentiation	90	0.88754	4	0.011986	1.9213	1	0.087095	0.070423
46	Antigen processing and presentation	91	0.89741	4	0.012443	1.9051	1	0.088456	0.36842
47	Thyroid hormone synthesis	94	0.92699	4	0.013883	1.8575	1	0.096592	0
48	Fat digestion and absorption	53	0.52267	3	0.015316	1.8149	1	0.10434	0
49	Oxidative phosphorylation	149	1.4694	5	0.015931	1.7978	1	0.10439	0
50	GABAergic synapse	98	0.96644	4	0.015962	1.7969	1	0.10439	0.071429
51	Amino sugar and nucleotide sugar metabolism	157	1.5483	5	0.019527	1.7094	1	0.1252	0.074534
52	Th17 cell differentiation	106	1.0453	4	0.020682	1.6844	1	0.13006	0.028571
53	Arachidonic acid metabolism	164	1.6173	5	0.02308	1.6368	1	0.1424	0.15385
54	Retrograde endocannabinoid signaling	167	1.6469	5	0.024723	1.6069	1	0.14971	0.02381
55	Allograft rejection	64	0.63114	3	0.025204	1.5985	1	0.14985	0
56	Lysine degradation	115	1.1341	4	0.026923	1.5699	1	0.15721	0.051948
57	Graft-versus-host disease	67	0.66073	3	0.028374	1.5471	1	0.16278	0
58	Pyruvate metabolism	69	0.68045	3	0.0306	1.5143	1	0.16536	0.075472
59	alpha-Linolenic acid metabolism	69	0.68045	3	0.0306	1.5143	1	0.16536	0.11538
60	Riboflavin metabolism	28	0.27612	2	0.030848	1.5108	1	0.16536	0.20833
61	One carbon pool by folate	28	0.27612	2	0.030848	1.5108	1	0.16536	0.23333
62	Starch and sucrose metabolism	70	0.69031	3	0.031746	1.4983	1	0.16743	0.041096
63	Histidine metabolism	71	0.70017	3	0.032915	1.4826	1	0.17084	0.12903
64	Type I diabetes mellitus	73	0.7199	3	0.035319	1.452	1	0.18046	0
65	Arginine and proline metabolism	128	1.2623	4	0.037736	1.4232	1	0.18984	0.12821
66	Galactose metabolism	78	0.76921	3	0.041714	1.3797	1	0.20668	0.22535
67	Tuberculosis	195	1.923	5	0.04372	1.3593	1	0.21338	0.073529
68	Neuroactive ligand-receptor interaction	402	3.9644	8	0.04523	1.3446	1	0.2175	0.0625
69	Autoimmune thyroid disease	82	0.80865	3	0.047222	1.3259	1	0.22379	0
70	Sphingolipid signaling pathway	139	1.3708	4	0.048578	1.3136	1	0.22508	0.060976

71	Nitrogen metabolism	36	0.35502	2	0.048871	1.311	1	0.22508	0.065217
72	Viral myocarditis	88	0.86782	3	0.056117	1.2509	1	0.25145	0
73	Synaptic vesicle cycle	89	0.87768	3	0.057672	1.239	1	0.25145	0
74	Rheumatoid arthritis	89	0.87768	3	0.057672	1.239	1	0.25145	0
75	Fructose and mannose metabolism	89	0.87768	3	0.057672	1.239	1	0.25145	0.14865
76	AMPK signaling pathway	149	1.4694	4	0.059778	1.2235	1	0.2572	0.010638
77	Renin secretion	93	0.91713	3	0.064095	1.1932	1	0.27219	0.017857
78	Hematopoietic cell lineage	94	0.92699	3	0.06575	1.1821	1	0.27564	0
79	Parkinson disease	157	1.5483	4	0.069645	1.1571	1	0.28828	0.014925
80	Valine, leucine and isoleucine degradation	98	0.96644	3	0.072566	1.1393	1	0.29661	0.072917
81	African trypanosomiasis	46	0.45363	2	0.075392	1.1227	1	0.30436	0
82	Nicotine addiction	47	0.4635	2	0.078251	1.1065	1	0.31205	0.078125
83	Morphine addiction	103	1.0157	3	0.08151	1.0888	1	0.32113	0.07
84	Influenza A	169	1.6666	4	0.085914	1.0659	1	0.33445	0.044248
85	cAMP signaling pathway	240	2.3668	5	0.088733	1.0519	1	0.33762	0.040984
86	Cell adhesion molecules (CAMs)	171	1.6863	4	0.088792	1.0516	1	0.33762	0.007663
87	Citrate cycle (TCA cycle)	52	0.5128	2	0.093034	1.0314	1	0.34968	0.18182
88	Cocaine addiction	56	0.55225	2	0.10539	0.97719	1	0.39162	0.024691
89	Tyrosine metabolism	118	1.1637	3	0.11097	0.9548	1	0.40627	0.08871
90	Necroptosis	186	1.8343	4	0.11182	0.95149	1	0.40627	0.042553
91	Staphylococcus aureus infection	123	1.213	3	0.12159	0.91512	1	0.4369	0
92	Phosphonate and phosphinate metabolism	63	0.62128	2	0.12798	0.89284	1	0.4549	0
93	Glucagon signaling pathway	130	1.282	3	0.13704	0.86314	1	0.47674	0
94	Tryptophan metabolism	130	1.282	3	0.13704	0.86314	1	0.47674	0.088
95	Pentose phosphate pathway	67	0.66073	2	0.14136	0.84967	1	0.48658	0.2381
96	FoxO signaling pathway	136	1.3412	3	0.1508	0.82159	1	0.51101	0.035714
97	Long-term depression	70	0.69031	2	0.15158	0.81935	1	0.51101	0.1087
98	Sulfur relay system	19	0.18737	1	0.17175	0.7651	1	0.56885	0
99	Systemic lupus erythematosus	145	1.4299	3	0.17222	0.76392	1	0.56885	0
100	Steroid biosynthesis	77	0.75934	2	0.17596	0.75459	1	0.57538	0.091837
101	Amphetamine addiction	78	0.76921	2	0.17949	0.74596	1	0.58112	0.038462
102	Glycerophospholipid metabolism	149	1.4694	3	0.18201	0.73991	1	0.58349	0.19048
103	Cortisol synthesis and secretion	81	0.79879	2	0.19015	0.7209	1	0.60369	0
104	Epstein-Barr virus infection	232	2.2879	4	0.19604	0.70765	1	0.61447	0.055172
105	Prolactin signaling pathway	83	0.81851	2	0.19731	0.70486	1	0.61447	0.25758
106	Neomycin, kanamycin and gentamicin biosynthesis	86	0.8481	2	0.2081	0.68173	1	0.64197	0
107	Pentose and glucuronate interconversions	89	0.87768	2	0.21896	0.65964	1	0.66915	0.10294
108	Caffeine metabolism	28	0.27612	1	0.24256	0.61518	1	0.73441	0
109	Longevity regulating pathway	98	0.96644	2	0.25176	0.59901	1	0.75246	0.055556
110	Glycerolipid metabolism	99	0.9763	2	0.25542	0.59274	1	0.75246	0.051724
111	Toll-like receptor signaling pathway	99	0.9763	2	0.25542	0.59274	1	0.75246	0.072289
112	Phagosome	181	1.785	3	0.2646	0.57741	1	0.76628	0
113	Biotin metabolism	31	0.30571	1	0.2648	0.57708	1	0.76628	0.026316
114	Porphyrin and chlorophyll metabolism	183	1.8047	3	0.26994	0.56873	1	0.7743	0.012346
115	Choline metabolism in cancer	109	1.0749	2	0.29202	0.53459	1	0.82636	0
116	Autophagy - other	35	0.34516	1	0.29345	0.53247	1	0.82636	0.027778
117	AGE-RAGE signaling pathway in diabetic complications	110	1.0848	2	0.29567	0.52919	1	0.82636	0.059701
118	Vitamin B6 metabolism	37	0.36488	1	0.30736	0.51236	1	0.85174	0.025641
119	Glycosylphosphatidylinositol (GPI)-anchor biosynthesis	39	0.3846	1	0.32099	0.4935	1	0.88206	0.093023
120	Glutamatergic synapse	121	1.1933	2	0.33561	0.47416	1	0.91454	0.18571
121	Alcoholism	211	2.0808	3	0.34545	0.46161	1	0.93358	0.01
122	Selenocompound metabolism	44	0.43391	1	0.35393	0.45108	1	0.94865	0.02381
123	Lysosome	128	1.2623	2	0.3607	0.44285	1	0.95894	0
124	Insulin resistance	130	1.282	2	0.36781	0.43437	1	0.96995	0.022059
125	Platelet activation	139	1.3708	2	0.3994	0.39859	1	1	0.046512
126	Autophagy - animal	144	1.4201	2	0.41664	0.38024	1	1	0.016667
127	Herpes simplex virus 1 infection	439	4.3292	5	0.43666	0.35986	1	1	0.098485
128	Drug metabolism - other enzymes	151	1.4891	2	0.44035	0.3562	1	1	0
129	Human T-cell leukemia virus 1 infection	251	2.4753	3	0.4517	0.34515	1	1	0.007692
130	Thermogenesis	253	2.495	3	0.45685	0.34022	1	1	0
131	Vascular smooth muscle contraction	156	1.5384	2	0.45697	0.34011	1	1	0.028169
132	Amyotrophic lateral sclerosis (ALS)	62	0.61142	1	0.45991	0.33733	1	1	0.018519
133	mTOR signaling pathway	158	1.5581	2	0.46354	0.33391	1	1	0.02381
134	Basal cell carcinoma	64	0.63114	1	0.47057	0.32738	1	1	0
135	Inflammatory mediator regulation of TRP channels	162	1.5976	2	0.47654	0.3219	1	1	0.044944
136	Fatty acid elongation	69	0.68045	1	0.4963	0.30426	1	1	0.012658
137	Renal cell carcinoma	71	0.70017	1	0.50624	0.29564	1	1	0.017544
138	Cushing syndrome	172	1.6962	2	0.50819	0.29398	1	1	0
139	GnRH secretion	72	0.71004	1	0.51114	0.29146	1	1	0
140	Ether lipid metabolism	72	0.71004	1	0.51114	0.29146	1	1	0.093023
141	Serotonergic synapse	173	1.7061	2	0.51128	0.29134	1	1	0
142	Long-term potentiation	74	0.72976	1	0.52079	0.28334	1	1	0.096774
143	Ascorbate and aldarate metabolism	76	0.74948	1	0.53025	0.27552	1	1	0.018182

144	Fc epsilon RI signaling pathway	78	0.76921	1	0.53953	0.26798	1	1	0.02
145	Adipocytokine signaling pathway	78	0.76921	1	0.53953	0.26798	1	1	0.023256
146	Pancreatic cancer	78	0.76921	1	0.53953	0.26798	1	1	0.035088
147	cGMP-PKG signaling pathway	183	1.8047	2	0.54155	0.26636	1	1	0.012195
148	Propanoate metabolism	81	0.79879	1	0.55311	0.25719	1	1	0.027778
149	Folate biosynthesis	83	0.81851	1	0.56194	0.25031	1	1	0.033708
150	EGFR tyrosine kinase inhibitor resistance	83	0.81851	1	0.56194	0.25031	1	1	0.090909
151	Pertussis	86	0.8481	1	0.57486	0.24044	1	1	0
152	Chemokine signaling pathway	203	2.0019	2	0.59814	0.2232	1	1	0.03125
153	PPAR signaling pathway	92	0.90727	1	0.59958	0.22215	1	1	0.016949
154	PD-L1 expression and PD-1 checkpoint pathway in cancer	92	0.90727	1	0.59958	0.22215	1	1	0.025
155	GnRH signaling pathway	96	0.94671	1	0.61526	0.21094	1	1	0
156	Gap junction	97	0.95658	1	0.61909	0.20825	1	1	0.019231
157	Glycolysis or Gluconeogenesis	97	0.95658	1	0.61909	0.20825	1	1	0.092308
158	Fc gamma R-mediated phagocytosis	98	0.96644	1	0.62288	0.2056	1	1	0.037037
159	Fatty acid degradation	100	0.98616	1	0.63034	0.20043	1	1	0.016807
160	Viral protein interaction with cytokine and cytokine receptor	103	1.0157	1	0.64126	0.19297	1	1	0.006849
161	Ubiquinone and other terpenoid-quinone biosynthesis	103	1.0157	1	0.64126	0.19297	1	1	0.011628
162	Kaposi sarcoma-associated herpesvirus infection	221	2.1794	2	0.6445	0.19078	1	1	0.022901
163	Melanogenesis	106	1.0453	1	0.65186	0.18585	1	1	0.022727
164	Circadian entrainment	107	1.0552	1	0.65532	0.18355	1	1	0.068966
165	Parathyroid hormone synthesis, secretion and action	117	1.1538	1	0.68813	0.16233	1	1	0
166	Amoebiasis	120	1.1834	1	0.69736	0.15655	1	1	0
167	Growth hormone synthesis, secretion and action	120	1.1834	1	0.69736	0.15655	1	1	0.11111
168	C-type lectin receptor signaling pathway	124	1.2228	1	0.70924	0.14921	1	1	0.021053
169	Neurotrophin signaling pathway	126	1.2426	1	0.715	0.14569	1	1	0
170	Thyroid hormone signaling pathway	129	1.2721	1	0.72344	0.1406	1	1	0.009434
171	Osteoclast differentiation	131	1.2919	1	0.72893	0.13732	1	1	0.052632
172	Estrogen signaling pathway	142	1.4003	1	0.75723	0.12077	1	1	0.012987
173	Measles	145	1.4299	1	0.76442	0.11667	1	1	0.033708
174	Dopaminergic synapse	146	1.4398	1	0.76677	0.11533	1	1	0
175	Phospholipase D signaling pathway	159	1.568	1	0.79531	0.099466	1	1	0.014493
176	Hepatitis C	162	1.5976	1	0.80138	0.096161	1	1	0.051546
177	Hepatitis B	163	1.6074	1	0.80337	0.095086	1	1	0.022222
178	Oxytocin signaling pathway	165	1.6272	1	0.80728	0.092976	1	1	0.013158
179	JAK-STAT signaling pathway	165	1.6272	1	0.80728	0.092976	1	1	1.0556
180	RNA transport	169	1.6666	1	0.81487	0.08891	1	1	0
181	Steroid hormone biosynthesis	188	1.854	1	0.84708	0.072075	1	1	0.015228
182	Huntington disease	196	1.9329	1	0.85892	0.066048	1	1	0.014706
183	Calcium signaling pathway	202	1.992	1	0.8672	0.061883	1	1	0.014925
184	NOD-like receptor signaling pathway	215	2.1202	1	0.88351	0.053786	1	1	0.012121
185	Rap1 signaling pathway	219	2.1597	1	0.88812	0.051527	1	1	0.010638
186	Ras signaling pathway	239	2.3569	1	0.90859	0.041632	1	1	0.010417
187	Pathways in cancer	570	5.6211	3	0.92473	0.033984	1	1	0.015576
188	Endocytosis	275	2.7119	1	0.93652	0.028484	1	1	0
189	Cytokine-cytokine receptor interaction	296	2.919	1	0.94871	0.022869	1	1	0.0025
190	PI3K-Akt signaling pathway	359	3.5403	1	0.973	0.011886	1	1	0.009901
191	Human papillomavirus infection	364	3.5896	1	0.97435	0.011286	1	1	0.04375
192	Olfactory transduction	1141	11.252	1	0.99999	3.00E-06	1	1	0

Supplemental Table 2: Luc on WDSW vs Luc on CDNW

	Pathway	Total number of targets	Expected number of targets	Number of Hits	Raw p-value	Log10(p-value)	Holm adjust	FDR	Impact
1	Aminoacyl-tRNA biosynthesis	74	5.4608	18	3.36E-06	5.4742	0.000282	0.000282	0.26027
2	Valine, leucine and isoleucine biosynthesis	12	0.88553	6	9.44E-05	4.0251	0.007834	0.003964	0.63636
3	Alanine, aspartate and glutamate metabolism	61	4.5015	13	0.00035	3.4554	0.028738	0.009813	0.78333
4	Biosynthesis of unsaturated fatty acids	47	3.4683	10	0.001737	2.7602	0.14069	0.036475	0.21739
5	Arginine biosynthesis	27	1.9925	7	0.002646	2.5775	0.21164	0.044445	0.61538
6	Phenylalanine metabolism	24	1.7711	6	0.006504	2.1868	0.5138	0.091054	0.73913
7	Sphingolipid metabolism	58	4.2801	10	0.008592	2.0659	0.67014	0.1031	0.84211
8	Cysteine and methionine metabolism	71	5.2394	11	0.013288	1.8765	1	0.13953	0.62857
9	alpha-Linolenic acid metabolism	22	1.6235	5	0.019398	1.7123	1	0.18104	0.66667
10	Linoleic acid metabolism	17	1.2545	4	0.03189	1.4963	1	0.26788	1.1875
11	Phenylalanine, tyrosine and tryptophan biosynthesis	11	0.81174	3	0.041937	1.3774	1	0.32025	2
12	Glutathione metabolism	56	4.1325	8	0.050154	1.2997	1	0.35108	0.61818
13	Purine metabolism	169	12.471	18	0.067518	1.1706	1	0.43627	0.6369
14	Glycine, serine and threonine metabolism	72	5.3132	9	0.079296	1.1008	1	0.45891	0.88732
15	Pentose and glucuronate interconversions	32	2.3614	5	0.081948	1.0865	1	0.45891	0.48387
16	Nicotinate and nicotinamide metabolism	43	3.1732	6	0.09252	1.0338	1	0.48573	0.61905
17	Pantothenate and CoA biosynthesis	34	2.509	5	0.10073	0.99686	1	0.49771	0.27273
18	Taurine and hypotaurine metabolism	16	1.1807	3	0.10874	0.96363	1	0.50081	0.53333
19	Terpenoid backbone biosynthesis	36	2.6566	5	0.12147	0.91554	1	0.50081	0.51429
20	Primary bile acid biosynthesis	90	6.6415	10	0.12261	0.91149	1	0.50081	0.30337
21	Ascorbate and aldarate metabolism	17	1.2545	3	0.1252	0.90238	1	0.50081	0.4375
22	Riboflavin metabolism	9	0.66415	2	0.13843	0.85876	1	0.52857	0.625
23	Steroid biosynthesis	82	6.0512	9	0.14637	0.83455	1	0.53305	0.4321
24	Butanoate metabolism	29	2.14	4	0.16131	0.79233	1	0.53305	0.25
25	Nitrogen metabolism	10	0.73795	2	0.16499	0.78254	1	0.53305	0.33333
26	D-Glutamine and D-glutamate metabolism	10	0.73795	2	0.16499	0.78254	1	0.53305	0.44444
27	Glycerophospholipid metabolism	86	6.3463	9	0.17939	0.7462	1	0.5581	0.48235
28	Histidine metabolism	32	2.3614	4	0.20695	0.68414	1	0.62084	0.32258
29	Glyoxylate and dicarboxylate metabolism	56	4.1325	6	0.2285	0.64111	1	0.66186	0.23636
30	Glycerolipid metabolism	35	2.5828	4	0.25579	0.59212	1	0.71598	0.26471
31	Neomycin, kanamycin and gentamicin biosynthesis	4	0.29518	1	0.26423	0.57802	1	0.71598	0.66667
32	Starch and sucrose metabolism	37	2.7304	4	0.28955	0.53828	1	0.73704	0.25
33	Fructose and mannose metabolism	37	2.7304	4	0.28955	0.53828	1	0.73704	0.36111
34	Galactose metabolism	51	3.7635	5	0.3225	0.49148	1	0.77735	0.48
35	Ether lipid metabolism	39	2.878	4	0.3239	0.4896	1	0.77735	0.36842
36	beta-Alanine metabolism	44	3.247	4	0.41033	0.38687	1	0.95743	0.23256
37	Arachidonic acid metabolism	79	5.8298	6	0.53405	0.27242	1	1	0.66667
38	Phosphonate and phosphinate metabolism	10	0.73795	1	0.53611	0.27075	1	1	0.22222
39	Amino sugar and nucleotide sugar metabolism	81	5.9774	6	0.55936	0.25231	1	1	0.3
40	Citrate cycle (TCA cycle)	42	3.0994	3	0.60989	0.21475	1	1	0.39024
41	One carbon pool by folate	31	2.2876	2	0.67961	0.16774	1	1	0.3
42	Pentose phosphate pathway	47	3.4683	3	0.68648	0.16337	1	1	0.3913
43	Arginine and proline metabolism	78	5.756	5	0.69488	0.15809	1	1	0.24675
44	Ubiquinone and other terpenoid-quinone biosynthesis	17	1.2545	1	0.72958	0.13693	1	1	0.0625
45	Selenocompound metabolism	35	2.5828	2	0.74327	0.12886	1	1	0.20588
46	Sulfur metabolism	18	1.3283	1	0.74968	0.12513	1	1	0.11765
47	Pyrimidine metabolism	99	7.3057	6	0.75254	0.12347	1	1	0.28571
48	Tryptophan metabolism	84	6.1987	5	0.75604	0.12145	1	1	0.28916
49	Drug metabolism - other enzymes	69	5.0918	4	0.76251	0.11775	1	1	0.088235
50	Porphyrin and chlorophyll metabolism	53	3.9111	3	0.76296	0.1175	1	1	0.076923
51	Valine, leucine and isoleucine degradation	88	6.4939	5	0.79147	0.10156	1	1	0.12644
52	Tyrosine metabolism	88	6.4939	5	0.79147	0.10156	1	1	0.27586
53	Vitamin B6 metabolism	21	1.5497	1	0.80149	0.096104	1	1	0.05
54	Biotin metabolism	21	1.5497	1	0.80149	0.096104	1	1	0.05
55	Mucin type O-glycan biosynthesis	22	1.6235	1	0.81627	0.088168	1	1	0.14286
56	Retinol metabolism	44	3.247	2	0.84807	0.071567	1	1	0.093023
57	Glycosaminoglycan degradation	44	3.247	2	0.84807	0.071567	1	1	0.13953
58	Pyruvate metabolism	45	3.3208	2	0.85695	0.067046	1	1	0.090909
59	Glycosphingolipid biosynthesis - ganglio series	47	3.4683	2	0.8733	0.058837	1	1	0.21739
60	Propanoate metabolism	48	3.5421	2	0.88082	0.055115	1	1	0.17021
61	Lysine degradation	49	3.6159	2	0.88792	0.051625	1	1	0.083333
62	Glycosylphosphatidylinositol (GPI)-anchor biosynthesis	31	2.2876	1	0.90856	0.041645	1	1	0.13333
63	Glycosphingolipid biosynthesis - globo and isoglobo series	31	2.2876	1	0.90856	0.041645	1	1	0.13333
64	Phosphatidylinositol signaling system	74	5.4608	3	0.9206	0.035928	1	1	0.26027
65	Various types of N-glycan biosynthesis	36	2.6566	1	0.93802	0.027786	1	1	0.22857
66	Glycolysis or Gluconeogenesis	61	4.5015	2	0.94752	0.02341	1	1	0.16667
67	Drug metabolism - cytochrome P450	39	2.878	1	0.95094	0.021846	1	1	0.078947

68	Inositol phosphate metabolism	69	5.0918	2	0.96893	0.013708	1	1	0.073529
69	Fatty acid elongation	75	5.5346	2	0.97919	0.009131	1	1	0.054054
70	Fatty acid degradation	102	7.527	3	0.98478	0.006659	1	1	0.17822
71	Folate biosynthesis	60	4.4277	1	0.99053	0.004132	1	1	0.084746
72	N-Glycan biosynthesis	77	5.6822	1	0.99753	0.001075	1	1	0.026316
73	Steroid hormone biosynthesis	175	12.914	5	0.99762	0.001033	1	1	0.21839
74	Metabolism of xenobiotics by cytochrome P450	117	8.634	2	0.99891	0.000474	1	1	0.051724
75	Fatty acid biosynthesis	129	9.5195	2	0.99955	0.000197	1	1	0.023438

Supplemental Table 3: PNPLA3^{I148M} vs Luc on WDSW

	Pathway	Total number of targets	Expected number of targets	Number of Hits	Raw p-value	Log10(p-value)	Holm adjust	FDR	Impact
1	Aminoacyl-tRNA biosynthesis	74	8.3774	30	4.40E-11	10.357	3.70E-09	3.70E-09	0.61644
2	Arginine biosynthesis	27	3.0566	10	0.000427	3.37	0.035404	0.017915	0.96154
3	Linoleic acid metabolism	17	1.9245	7	0.001573	2.8033	0.12899	0.044045	1.4375
4	Nitrogen metabolism	10	1.1321	5	0.002793	2.5539	0.22627	0.056529	0.77778
5	Sphingolipid metabolism	58	6.566	14	0.004063	2.3912	0.325	0.056529	1
6	Glycerolipid metabolism	35	3.9623	10	0.004065	2.3909	0.325	0.056529	0.58824
7	Biosynthesis of unsaturated fatty acids	47	5.3208	12	0.004711	2.3269	0.36744	0.056529	0.69565
8	Amino sugar and nucleotide sugar metabolism	81	9.1698	17	0.007514	2.1242	0.57855	0.073718	0.525
9	Glutathione metabolism	56	6.3396	13	0.007898	2.1025	0.60028	0.073718	0.70909
10	Riboflavin metabolism	9	1.0189	4	0.012753	1.8944	0.95646	0.10504	1.125
11	Glycerophospholipid metabolism	86	9.7358	17	0.013756	1.8615	1	0.10504	0.58824
12	Alanine, aspartate and glutamate metabolism	61	6.9057	12	0.03702	1.4316	1	0.24618	0.71667
13	Valine, leucine and isoleucine biosynthesis	12	1.3585	4	0.038099	1.4191	1	0.24618	0.45455
14	Purine metabolism	169	19.132	26	0.058538	1.2326	1	0.35123	0.97024
15	Porphyrin and chlorophyll metabolism	53	6	10	0.069312	1.1592	1	0.38815	0.42308
16	Nicotinate and nicotinamide metabolism	43	4.8679	8	0.10509	0.97842	1	0.55174	0.7619
17	Fructose and mannose metabolism	37	4.1887	7	0.11687	0.9323	1	0.57747	0.52778
18	Phenylalanine metabolism	24	2.717	5	0.12657	0.89769	1	0.59064	0.56522
19	Pentose and glucuronate interconversions	32	3.6226	6	0.14568	0.83659	1	0.62957	0.67742
20	Drug metabolism - other enzymes	69	7.8113	11	0.1499	0.82421	1	0.62957	0.26471
21	Cysteine and methionine metabolism	71	8.0377	11	0.17251	0.76319	1	0.69003	0.37143
22	alpha-Linolenic acid metabolism	22	2.4906	4	0.23273	0.63314	1	0.88862	0.38095
23	Taurine and hypotaurine metabolism	16	1.8113	3	0.26863	0.57084	1	0.94343	0.53333
24	One carbon pool by folate	31	3.5094	5	0.26955	0.56936	1	0.94343	0.56667
25	Ascorbate and aldarate metabolism	17	1.9245	3	0.30111	0.52128	1	1	0.3125
26	D-Glutamine and D-glutamate metabolism	10	1.1321	2	0.31531	0.50127	1	1	0.44444
27	Phosphatidylinositol signaling system	74	8.3774	10	0.32444	0.48887	1	1	0.43836
28	Pantothenate and CoA biosynthesis	34	3.8491	5	0.33924	0.46949	1	1	0.33333
29	Phenylalanine, tyrosine and tryptophan biosynthesis	11	1.2453	2	0.35887	0.44506	1	1	1.2
30	Selenocompound metabolism	35	3.9623	5	0.36286	0.44026	1	1	0.35294
31	Retinol metabolism	44	4.9811	6	0.38008	0.42013	1	1	0.37209
32	Arginine and proline metabolism	78	8.8302	10	0.38801	0.41115	1	1	0.45455
33	Pyruvate metabolism	45	5.0943	6	0.40137	0.39646	1	1	0.36364
34	Butanoate metabolism	29	3.283	4	0.41978	0.37698	1	1	0.32143
35	Biotin metabolism	21	2.3774	3	0.43053	0.36599	1	1	1
36	Pentose phosphate pathway	47	5.3208	6	0.44376	0.35285	1	1	0.65217
37	Glyoxylate and dicarboxylate metabolism	56	6.3396	7	0.45169	0.34516	1	1	0.34545
38	Drug metabolism - cytochrome P450	39	4.4151	5	0.45692	0.34016	1	1	0.15789
39	Lysine degradation	49	5.5472	6	0.48555	0.31377	1	1	0.375
40	Inositol phosphate metabolism	69	7.8113	8	0.52895	0.27659	1	1	0.22059
41	Pyrimidine metabolism	99	11.208	11	0.5761	0.2395	1	1	0.55102
42	Primary bile acid biosynthesis	90	10.189	10	0.57698	0.23884	1	1	0.37079
43	Glycine, serine and threonine metabolism	72	8.1509	8	0.57976	0.23675	1	1	0.80282
44	Ubiquinone and other terpenoid-quinone biosynthesis	17	1.9245	2	0.58966	0.2294	1	1	0.1875
45	Glycosphingolipid biosynthesis - ganglio series	47	5.3208	5	0.62899	0.20136	1	1	0.3913
46	Ether lipid metabolism	39	4.4151	4	0.65994	0.1805	1	1	0.31579
47	Arachidonic acid metabolism	79	8.9434	8	0.68721	0.16291	1	1	0.64103
48	Glycosphingolipid biosynthesis - globo and isoglobo series	31	3.5094	3	0.69933	0.15532	1	1	0.26667
49	Glycosylphosphatidylinositol (GPI)-anchor biosynthesis	31	3.5094	3	0.69933	0.15532	1	1	0.33333
50	Synthesis and degradation of ketone bodies	10	1.1321	1	0.69997	0.15492	1	1	0.44444
51	Galactose metabolism	51	5.7736	5	0.70157	0.15393	1	1	0.48
52	Glycolysis or Gluconeogenesis	61	6.9057	6	0.70533	0.15161	1	1	0.33333
53	Citrate cycle (TCA cycle)	42	4.7547	4	0.71744	0.14421	1	1	0.53659
54	Histidine metabolism	32	3.6226	3	0.72013	0.14259	1	1	0.25806
55	Mucin type O-glycan biosynthesis	22	2.4906	2	0.73045	0.13641	1	1	0.2381
56	beta-Alanine metabolism	44	4.9811	4	0.75162	0.124	1	1	0.23256
57	N-Glycan biosynthesis	77	8.717	7	0.7868	0.10413	1	1	0.21053
58	Fatty acid elongation	75	8.4906	6	0.86922	0.06087	1	1	0.10811
59	Sulfur metabolism	18	2.0377	1	0.88592	0.052607	1	1	0.70588
60	Vitamin B6 metabolism	21	2.3774	1	0.92069	0.035888	1	1	0.05
61	Caffeine metabolism	21	2.3774	1	0.92069	0.035888	1	1	0.4
62	Propanoate metabolism	48	5.434	3	0.92225	0.035151	1	1	0.23404
63	Terpenoid backbone biosynthesis	36	4.0755	2	0.92745	0.032707	1	1	0.057143
64	Tryptophan metabolism	84	9.5094	6	0.92797	0.032466	1	1	0.36145
65	Starch and sucrose metabolism	37	4.1887	2	0.9343	0.029515	1	1	0.13889
66	Glycosaminoglycan degradation	44	4.9811	2	0.96763	0.01429	1	1	0.093023
67	Valine, leucine and isoleucine degradation	88	9.9623	5	0.97821	0.009569	1	1	0.2069

68	Tyrosine metabolism	88	9.9623	5	0.97821	0.009569	1	1	0.37931
69	Steroid biosynthesis	82	9.283	4	0.98795	0.005267	1	1	0.20988
70	Folate biosynthesis	60	6.7925	2	0.99403	0.0026	1	1	0.25424
71	Steroid hormone biosynthesis	175	19.811	10	0.99712	0.001253	1	1	0.21839
72	Metabolism of xenobiotics by cytochrome P450	117	13.245	4	0.99958	0.000181	1	1	0.25862
73	Fatty acid degradation	102	11.547	2	0.99995	2.28E-05	1	1	0.059406
74	Fatty acid biosynthesis	129	14.604	3	0.99998	8.68E-06	1	1	0.070312
75	Glycosphingolipid biosynthesis - lacto and neolacto series	102	11.547	1	1	1.56E-06	1	1	0.019802

Supplemental Table 4: PNPLA3^{I148M} vs PNPLA3^{WT} on WDSW

	Pathway	Total number of targets	Expected number of targets	Number of Hits	Raw p-value	Log10(p-value)	Holm adjust	FDR	Impact
1	Central carbon metabolism in cancer	104	1.8961	22	9.87E-18	17.006	3.23E-15	3.23E-15	0.098214
2	Aminoacyl-tRNA biosynthesis	118	2.1513	21	2.32E-15	14.635	7.55E-13	3.79E-13	0.25773
3	ABC transporters	186	3.3911	22	2.88E-12	11.541	9.35E-10	3.13E-10	0
4	Protein digestion and absorption	141	2.5706	18	8.33E-11	10.079	2.70E-08	6.81E-09	0
5	Mineral absorption	81	1.4768	13	2.17E-09	8.6635	7.01E-07	1.18E-07	0
6	Biosynthesis of unsaturated fatty acids	81	1.4768	13	2.17E-09	8.6635	7.01E-07	1.18E-07	0.075758
7	Alanine, aspartate and glutamate metabolism	66	1.2033	9	2.84E-06	5.5468	0.000911	0.000133	0.67213
8	Glycine, serine and threonine metabolism	90	1.6408	10	5.30E-06	5.2759	0.001695	0.000217	0.54545
9	Cholesterol metabolism	59	1.0757	8	1.07E-05	4.9701	0.003417	0.000389	0.034188
10	Primary bile acid biosynthesis	63	1.1486	8	1.76E-05	4.7551	0.005589	0.000575	0.15957
11	Linoleic acid metabolism	78	1.4221	8	8.42E-05	4.0748	0.026687	0.002334	0.73171
12	Purine metabolism	231	4.2115	14	8.57E-05	4.0673	0.027066	0.002334	0.64706
13	Arginine biosynthesis	42	0.76572	6	0.000104	3.9831	0.032752	0.002511	0.4
14	Glutathione metabolism	103	1.8778	9	0.000107	3.9687	0.03375	0.002511	0.73913
15	Vitamin digestion and absorption	63	1.1486	7	0.000142	3.8492	0.044294	0.003085	0
16	Cysteine and methionine metabolism	115	2.0966	9	0.000249	3.603	0.077831	0.005098	0.24272
17	Taurine and hypotaurine metabolism	33	0.60164	5	0.000301	3.5211	0.093684	0.005794	0.27586
18	Ferroptosis	72	1.3127	7	0.000328	3.484	0.1017	0.00596	0.027027
19	Amino sugar and nucleotide sugar metabolism	157	2.8624	10	0.000601	3.2213	0.18563	0.010295	0.26087
20	Antifolate resistance	58	1.0574	6	0.00063	3.2009	0.19393	0.010295	0
21	Phenylalanine, tyrosine and tryptophan biosynthesis	43	0.78396	5	0.001054	2.9772	0.32355	0.016411	0.29268
22	Valine, leucine and isoleucine biosynthesis	27	0.49225	4	0.001357	2.8674	0.4153	0.020173	0.19231
23	Aldosterone synthesis and secretion	123	2.2425	8	0.001839	2.7355	0.56079	0.026141	0
24	Nicotinate and nicotinamide metabolism	98	1.7867	7	0.002069	2.6843	0.62883	0.02763	0.2439
25	Sphingolipid metabolism	73	1.3309	6	0.002112	2.6752	0.64005	0.02763	1.082
26	Fat digestion and absorption	53	0.96627	5	0.002712	2.5667	0.81903	0.033554	0.045455
27	Fatty acid biosynthesis	77	1.4038	6	0.002771	2.5574	0.83392	0.033554	0.063953
28	Nitrogen metabolism	36	0.65634	4	0.004009	2.397	1	0.045454	0.1087
29	Phenylalanine metabolism	83	1.5132	6	0.004031	2.3946	1	0.045454	0.20548
30	Synaptic vesicle cycle	89	1.6226	6	0.005673	2.2462	1	0.061837	0.029412
31	beta-Alanine metabolism	64	1.1668	5	0.006133	2.2123	1	0.064698	0.11111
32	Sulfur metabolism	44	0.80219	4	0.00825	2.0835	1	0.084308	0
33	Starch and sucrose metabolism	70	1.2762	5	0.00892	2.0496	1	0.08839	0.17808
34	Pantothenate and CoA biosynthesis	46	0.83865	4	0.009642	2.0158	1	0.092735	0.16667
35	Galactose metabolism	78	1.4221	5	0.013851	1.8585	1	0.12941	0.42254
36	Oxidative phosphorylation	149	2.7165	7	0.019346	1.7134	1	0.17573	0.007299
37	Drug metabolism - other enzymes	151	2.753	7	0.020649	1.6851	1	0.18249	0.4
38	Pentose and glucuronate interconversions	89	1.6226	5	0.023225	1.634	1	0.19986	0.23529
39	Pyrimidine metabolism	123	2.2425	6	0.025035	1.6015	1	0.20991	0.31008
40	Glyoxylate and dicarboxylate metabolism	93	1.6955	5	0.02745	1.5615	1	0.22441	0.079545
41	Lysosome	128	2.3336	6	0.029682	1.5275	1	0.23673	0
42	Proximal tubule bicarbonate reclamation	39	0.71103	3	0.033765	1.4715	1	0.26289	0
43	Bile secretion	246	4.485	9	0.036476	1.438	1	0.27318	0.014085
44	Butanoate metabolism	69	1.258	4	0.037043	1.4313	1	0.27318	0.090909
45	D-Glutamine and D-glutamate metabolism	17	0.30994	2	0.037594	1.4249	1	0.27318	0.25
46	Regulation of lipolysis in adipocytes	70	1.2762	4	0.038747	1.4118	1	0.27544	0.033333
47	Renal cell carcinoma	71	1.2944	4	0.040496	1.3926	1	0.28175	0.33333
48	Choline metabolism in cancer	109	1.9872	5	0.049055	1.3093	1	0.33419	0.037736
49	Thiamine metabolism	46	0.83865	3	0.05117	1.291	1	0.34148	0
50	Salmonella infection	79	1.4403	4	0.056075	1.2512	1	0.36673	0.22917
51	Ovarian steroidogenesis	81	1.4768	4	0.060409	1.2189	1	0.38733	0
52	Endocytosis	275	5.0137	9	0.064938	1.1875	1	0.40836	0.058394
53	Peroxisome	84	1.5314	4	0.067232	1.1724	1	0.41481	0
54	Taste transduction	121	2.206	5	0.070369	1.1526	1	0.41731	0.11429
55	Phospholipase D signaling pathway	159	2.8988	6	0.070938	1.1491	1	0.41731	0.11594
56	Ras signaling pathway	239	4.3573	8	0.071466	1.1459	1	0.41731	0.44792
57	Rheumatoid arthritis	89	1.6226	4	0.079451	1.0999	1	0.44921	0
58	Arachidonic acid metabolism	164	2.99	6	0.079677	1.0987	1	0.44921	1.0085
59	Arginine and proline metabolism	128	2.3336	5	0.08482	1.0715	1	0.47011	0.16239
60	Maturity onset diabetes of the young	27	0.49225	2	0.086259	1.0642	1	0.47011	0.11765
61	Insulin resistance	130	2.3701	5	0.089216	1.0496	1	0.47361	0.088235
62	Riboflavin metabolism	28	0.51048	2	0.091817	1.0371	1	0.47361	0.20833
63	One carbon pool by folate	28	0.51048	2	0.091817	1.0371	1	0.47361	0.23333
64	Thyroid hormone synthesis	94	1.7138	4	0.092694	1.033	1	0.47361	0
65	FoxO signaling pathway	136	2.4795	5	0.1031	0.98675	1	0.50185	0.071429
66	GABAergic synapse	98	1.7867	4	0.10399	0.98299	1	0.50185	0.071429
67	Valine, leucine and isoleucine degradation	98	1.7867	4	0.10399	0.98299	1	0.50185	0.19792
68	Rap1 signaling pathway	219	3.9927	7	0.10607	0.9744	1	0.50185	0.18085
69	Glycerolipid metabolism	99	1.8049	4	0.10691	0.97097	1	0.50185	0.32759
70	Mitophagy - animal	63	1.1486	3	0.10743	0.96887	1	0.50185	0.14286

71	Sphingolipid signaling pathway	139	2.5342	5	0.11042	0.95696	1	0.50854	0.060976
72	Morphine addiction	103	1.8778	4	0.11896	0.92462	1	0.54026	0.07
73	Pentose phosphate pathway	67	1.2215	3	0.12313	0.90963	1	0.54425	0.42857
74	Autophagy - animal	144	2.6253	5	0.12316	0.90952	1	0.54425	0.066667
75	Pyruvate metabolism	69	1.258	3	0.13128	0.8818	1	0.56485	0.075472
76	alpha-Linolenic acid metabolism	69	1.258	3	0.13128	0.8818	1	0.56485	0.11538
77	Collecting duct acid secretion	35	0.6381	2	0.13327	0.87526	1	0.56597	0
78	Glycerophospholipid metabolism	149	2.7165	5	0.13656	0.86468	1	0.5725	0.35238
79	Histidine metabolism	71	1.2944	3	0.13961	0.85508	1	0.57788	0.12903
80	Bacterial invasion of epithelial cells	73	1.3309	3	0.14812	0.8294	1	0.60341	0.069767
81	cAMP signaling pathway	240	4.3756	7	0.14947	0.82545	1	0.60341	0.081967
82	Leishmaniasis	74	1.3491	3	0.15243	0.81693	1	0.60786	0.09434
83	Lysine degradation	115	2.0966	4	0.1583	0.80052	1	0.61998	0.051948
84	Parkinson disease	157	2.8624	5	0.15926	0.79789	1	0.61998	0.029851
85	Ascorbate and aldarate metabolism	76	1.3856	3	0.16118	0.7927	1	0.62006	0.090909
86	Tyrosine metabolism	118	2.1513	4	0.16881	0.77259	1	0.63923	0.14516
87	Pancreatic cancer	78	1.4221	3	0.17007	0.76937	1	0.63923	0.087719
88	Amoebiasis	120	2.1878	4	0.17596	0.75459	1	0.65384	0.035088
89	Cell cycle	123	2.2425	4	0.18686	0.72848	1	0.67823	0.12727
90	Retrograde endocannabinoid signaling	167	3.0447	5	0.18962	0.72212	1	0.67823	0.02381
91	Proteoglycans in cancer	212	3.8651	6	0.19102	0.71893	1	0.67823	0.09
92	Prolactin signaling pathway	83	1.5132	3	0.19289	0.71469	1	0.67823	0.10606
93	EGFR tyrosine kinase inhibitor resistance	83	1.5132	3	0.19289	0.71469	1	0.67823	0.19697
94	Neurotrophin signaling pathway	126	2.2972	4	0.19798	0.70339	1	0.67946	0.060976
95	Yersinia infection	126	2.2972	4	0.19798	0.70339	1	0.67946	0.13684
96	Neuroactive ligand-receptor interaction	402	7.3291	10	0.19947	0.70011	1	0.67946	0.073864
97	African trypanosomiasis	46	0.83865	2	0.20448	0.68934	1	0.68351	0
98	Neomycin, kanamycin and gentamicin biosynthesis	86	1.5679	3	0.20693	0.68417	1	0.68351	0.02381
99	Pertussis	86	1.5679	3	0.20693	0.68417	1	0.68351	0.074627
100	Nicotine addiction	47	0.85688	2	0.21118	0.67536	1	0.68994	0.078125
101	Glucagon signaling pathway	130	2.3701	4	0.2131	0.67141	1	0.68994	0
102	Regulation of actin cytoskeleton	221	4.0292	6	0.21657	0.6644	1	0.6943	0.20482
103	Fructose and mannose metabolism	89	1.6226	3	0.2212	0.65522	1	0.70226	0.14865
104	Phagosome	181	3.2999	5	0.23521	0.62855	1	0.7339	0
105	PPAR signaling pathway	92	1.6773	3	0.23566	0.62772	1	0.7339	0.18644
106	Renin secretion	93	1.6955	3	0.24051	0.61886	1	0.73467	0.017857
107	Porphyrin and chlorophyll metabolism	183	3.3364	5	0.24196	0.61625	1	0.73467	0.037037
108	Ubiquitin mediated proteolysis	138	2.516	4	0.24424	0.61217	1	0.73467	0
109	Citrate cycle (TCA cycle)	52	0.94804	2	0.24489	0.61103	1	0.73467	0.18182
110	Fc gamma R-mediated phagocytosis	98	1.7867	3	0.26503	0.57671	1	0.78785	0.12963
111	Cocaine addiction	56	1.021	2	0.27202	0.5654	1	0.80135	0.024691
112	AMPK signaling pathway	149	2.7165	4	0.28854	0.53979	1	0.84244	0.010638
113	Sulfur relay system	19	0.3464	1	0.29521	0.52986	1	0.85429	0
114	Fluid shear stress and atherosclerosis	152	2.7712	4	0.30083	0.52168	1	0.86291	0.10476
115	Legionellosis	61	1.1121	2	0.30586	0.51447	1	0.86972	0.065217
116	Phosphonate and phosphinate metabolism	63	1.1486	2	0.31933	0.49576	1	0.90019	0
117	Prostate cancer	110	2.0055	3	0.32479	0.48839	1	0.90223	0.065574
118	mTOR signaling pathway	158	2.8806	4	0.32557	0.48735	1	0.90223	0.035714
119	JAK-STAT signaling pathway	165	3.0082	4	0.3546	0.45026	1	0.96679	0.19444
120	Retinol metabolism	116	2.1149	3	0.35478	0.45004	1	0.96679	0.67797
121	Fatty acid elongation	69	1.258	2	0.35931	0.44453	1	0.97103	0.063291
122	Long-term depression	70	1.2762	2	0.3659	0.43664	1	0.98072	0.1087
123	p53 signaling pathway	71	1.2944	2	0.37245	0.42893	1	0.99018	0.046875
124	Ether lipid metabolism	72	1.3127	2	0.37899	0.42138	1	0.99942	0.2093
125	Caffeine metabolism	28	0.51048	1	0.40296	0.39473	1	1	0
126	Steroid biosynthesis	77	1.4038	2	0.4112	0.38595	1	1	0.091837
127	Amphetamine addiction	78	1.4221	2	0.41754	0.3793	1	1	0.038462
128	Glioma	78	1.4221	2	0.41754	0.3793	1	1	0.054795
129	Adipocytokine signaling pathway	78	1.4221	2	0.41754	0.3793	1	1	0.069767
130	Arrhythmogenic right ventricular cardiomyopathy (ARVC)	79	1.4403	2	0.42385	0.37278	1	1	0
131	Tryptophan metabolism	130	2.3701	3	0.42386	0.37278	1	1	0.088
132	Transcriptional misregulation in cancer	183	3.3364	4	0.4289	0.36764	1	1	0.009901
133	Biotin metabolism	31	0.56518	1	0.4351	0.36141	1	1	0.026316
134	Cortisol synthesis and secretion	81	1.4768	2	0.43637	0.36015	1	1	0
135	Necroptosis	186	3.3911	4	0.44111	0.35545	1	1	0.021277
136	Circadian rhythm	32	0.58341	1	0.44543	0.35122	1	1	0.05
137	Folate biosynthesis	83	1.5132	2	0.44874	0.34801	1	1	0.19101
138	Steroid hormone biosynthesis	188	3.4275	4	0.44921	0.34755	1	1	0.25888
139	SNARE interactions in vesicular transport	33	0.60164	1	0.45557	0.34145	1	1	0.026316
140	MAPK signaling pathway	299	5.4512	6	0.46436	0.33315	1	1	0.15323
141	Apoptosis	140	2.5524	3	0.47165	0.32638	1	1	0.072072
142	Chemical carcinogenesis	194	3.5369	4	0.47328	0.32488	1	1	0.067568
143	Autophagy - other	35	0.6381	1	0.47529	0.32304	1	1	0.027778
144	Estrogen signaling pathway	142	2.5889	3	0.481	0.31786	1	1	0.064935

145	PI3K-Akt signaling pathway	359	6.5451	7	0.48261	0.3164	1	1	0.079208
146	Colorectal cancer	89	1.6226	2	0.4849	0.31435	1	1	0.040541
147	Complement and coagulation cascades	89	1.6226	2	0.4849	0.31435	1	1	0.046154
148	Insulin signaling pathway	143	2.6071	3	0.48564	0.31368	1	1	0.12121
149	Prion diseases	37	0.67457	1	0.4943	0.30601	1	1	0
150	Vitamin B6 metabolism	37	0.67457	1	0.4943	0.30601	1	1	0.025641
151	IL-17 signaling pathway	91	1.6591	2	0.49663	0.30397	1	1	0
152	PD-L1 expression and PD-1 checkpoint pathway in cancer	92	1.6773	2	0.50242	0.29893	1	1	0.0625
153	Glycosylphosphatidylinositol (GPI)-anchor biosynthesis	39	0.71103	1	0.51263	0.29019	1	1	0.093023
154	Progesterone-mediated oocyte maturation	94	1.7138	2	0.51389	0.28913	1	1	0.025
155	Hypertrophic cardiomyopathy (HCM)	94	1.7138	2	0.51389	0.28913	1	1	0.043478
156	GnRH signaling pathway	96	1.7502	2	0.52519	0.27969	1	1	0.042553
157	Gap junction	97	1.7685	2	0.53077	0.27509	1	1	0.038462
158	Dilated cardiomyopathy (DCM)	97	1.7685	2	0.53077	0.27509	1	1	0.043478
159	Glycolysis or Gluconeogenesis	97	1.7685	2	0.53077	0.27509	1	1	0.26154
160	Longevity regulating pathway	98	1.7867	2	0.53631	0.27059	1	1	0.055556
161	Alcoholism	211	3.8469	4	0.53913	0.26831	1	1	0.02
162	Toll-like receptor signaling pathway	99	1.8049	2	0.5418	0.26616	1	1	0.048193
163	Fatty acid degradation	100	1.8232	2	0.54724	0.26182	1	1	0.058824
164	Nucleotide excision repair	43	0.78396	1	0.54733	0.26175	1	1	0
165	Selenocompound metabolism	44	0.80219	1	0.55561	0.25523	1	1	0.02381
166	Ubiquinone and other terpenoid-quinone biosynthesis	103	1.8778	2	0.56331	0.24925	1	1	0.046512
167	Inflammatory mediator regulation of TRP channels	162	2.9535	3	0.56976	0.24431	1	1	0.044944
168	Proteasome	46	0.83865	1	0.57172	0.24281	1	1	0
169	Kaposi sarcoma-associated herpesvirus infection	221	4.0292	4	0.57588	0.23967	1	1	0.091603
170	Th17 cell differentiation	106	1.9325	2	0.57897	0.23735	1	1	0.028571
171	Renin-angiotensin system	47	0.85688	1	0.57956	0.2369	1	1	0.025641
172	Tight junction	167	3.0447	3	0.59046	0.22881	1	1	0.088889
173	Pathways in cancer	570	10.392	10	0.59561	0.22504	1	1	0.084112
174	Influenza A	169	3.0811	3	0.59856	0.2229	1	1	0.035398
175	Drug metabolism - cytochrome P450	169	3.0811	3	0.59856	0.2229	1	1	0.084906
176	AGE-RAGE signaling pathway in diabetic complications	110	2.0055	2	0.5992	0.22243	1	1	0.074627
177	Fanconi anemia pathway	51	0.92981	1	0.60951	0.21502	1	1	0.12963
178	TNF signaling pathway	113	2.0602	2	0.61389	0.21191	1	1	0
179	NF-kappa B signaling pathway	113	2.0602	2	0.61389	0.21191	1	1	0.01875
180	Serotonergic synapse	173	3.1541	3	0.61444	0.21152	1	1	0
181	Type II diabetes mellitus	54	0.9845	1	0.63057	0.20027	1	1	0.064516
182	Parathyroid hormone synthesis, secretion and action	117	2.1331	2	0.63284	0.19871	1	1	0
183	Axon guidance	181	3.2999	3	0.64492	0.19049	1	1	0.10067
184	Glutamatergic synapse	121	2.206	2	0.65105	0.18638	1	1	0.18571
185	Staphylococcus aureus infection	123	2.2425	2	0.65989	0.18053	1	1	0.025641
186	Oocyte meiosis	123	2.2425	2	0.65989	0.18053	1	1	0.10588
187	C-type lectin receptor signaling pathway	124	2.2607	2	0.66424	0.17767	1	1	0.036842
188	Inflammatory bowel disease (IBD)	60	1.0939	1	0.66936	0.17434	1	1	0.032258
189	Metabolism of xenobiotics by cytochrome P450	188	3.4275	3	0.67017	0.17381	1	1	0.37363
190	Human T-cell leukemia virus 1 infection	251	4.5761	4	0.67548	0.17039	1	1	0.023077
191	HIF-1 signaling pathway	127	2.3154	2	0.67703	0.16939	1	1	0.46341
192	Amyotrophic lateral sclerosis (ALS)	62	1.1304	1	0.68136	0.16662	1	1	0.018519
193	Thermogenesis	253	4.6126	4	0.68151	0.16653	1	1	0
194	Basal cell carcinoma	64	1.1668	1	0.69294	0.15931	1	1	0
195	VEGF signaling pathway	64	1.1668	1	0.69294	0.15931	1	1	0.060606
196	Osteoclast differentiation	131	2.3883	2	0.69346	0.15898	1	1	0.13158
197	Cytosolic DNA-sensing pathway	65	1.1851	1	0.69856	0.15579	1	1	0.125
198	Endocrine and other factor-regulated calcium reabsorption	68	1.2397	1	0.71484	0.14579	1	1	0
199	RIG-I-like receptor signaling pathway	68	1.2397	1	0.71484	0.14579	1	1	0.056604
200	Platelet activation	139	2.5342	2	0.72425	0.14011	1	1	0.046512
201	Acute myeloid leukemia	71	1.2944	1	0.73024	0.13653	1	1	0.020833
202	Adherens junction	71	1.2944	1	0.73024	0.13653	1	1	0.093333
203	GnRH secretion	72	1.3127	1	0.73519	0.1336	1	1	0
204	Non-small cell lung cancer	72	1.3127	1	0.73519	0.1336	1	1	0.035714
205	Melanoma	73	1.3309	1	0.74004	0.13074	1	1	0.030303
206	Long-term potentiation	74	1.3491	1	0.74481	0.12795	1	1	0.096774
207	Systemic lupus erythematosus	145	2.6436	2	0.74561	0.12749	1	1	0.085106
208	NOD-like receptor signaling pathway	215	3.9198	3	0.75521	0.12193	1	1	0.054545
209	Fc epsilon RI signaling pathway	78	1.4221	1	0.76303	0.11746	1	1	0.02
210	Non-alcoholic fatty liver disease (NAFLD)	152	2.7712	2	0.76872	0.11423	1	1	0.058824
211	Platinum drug resistance	81	1.4768	1	0.77584	0.11023	1	1	0
212	Propanoate metabolism	81	1.4768	1	0.77584	0.11023	1	1	0.027778
213	RNA degradation	82	1.495	1	0.77995	0.10793	1	1	0
214	Vascular smooth muscle contraction	156	2.8441	2	0.7811	0.10729	1	1	0.028169
215	Human papillomavirus infection	364	6.6363	5	0.79799	0.098002	1	1	0.03125

216	Hepatitis B	163	2.9717	2	0.80137	0.096168	1	1	0.007407
217	N-Glycan biosynthesis	88	1.6044	1	0.80311	0.095226	1	1	0.037975
218	ErbB signaling pathway	88	1.6044	1	0.80311	0.095226	1	1	0.043478
219	MicroRNAs in cancer	303	5.5242	4	0.80719	0.093023	1	1	0.009132
220	Th1 and Th2 cell differentiation	90	1.6408	1	0.81027	0.091368	1	1	0.042254
221	Cardiac muscle contraction	90	1.6408	1	0.81027	0.091368	1	1	0.093023
222	Antigen processing and presentation	91	1.6591	1	0.81376	0.089504	1	1	0.026316
223	RNA transport	169	3.0811	2	0.8174	0.087564	1	1	0.074766
224	Protein processing in endoplasmic reticulum	170	3.0994	2	0.81996	0.086207	1	1	0.009434
225	Hematopoietic cell lineage	94	1.7138	1	0.82384	0.084159	1	1	0
226	Cushing syndrome	172	3.1358	2	0.82498	0.083557	1	1	0
227	mRNA surveillance pathway	95	1.732	1	0.82707	0.082456	1	1	0.053571
228	Insulin secretion	98	1.7867	1	0.83643	0.077569	1	1	0
229	cGMP-PKG signaling pathway	183	3.3364	2	0.85041	0.070373	1	1	0.012195
230	Viral protein interaction with cytokine and cytokine receptor	103	1.8778	1	0.85093	0.070109	1	1	0.013699
231	Hepatocellular carcinoma	186	3.3911	2	0.85674	0.067152	1	1	0.016949
232	Melanogenesis	106	1.9325	1	0.859	0.066007	1	1	0.022727
233	T cell receptor signaling pathway	107	1.9508	1	0.86159	0.064698	1	1	0.014085
234	Circadian entrainment	107	1.9508	1	0.86159	0.064698	1	1	0.068966
235	Chagas disease (American trypanosomiasis)	108	1.969	1	0.86414	0.063416	1	1	0.041667
236	Cellular senescence	190	3.464	2	0.8648	0.063086	1	1	0.087719
237	Toxoplasmosis	111	2.0237	1	0.8715	0.059732	1	1	0.031746
238	Tuberculosis	195	3.5552	2	0.87429	0.058345	1	1	0.022059
239	Huntington disease	196	3.5734	2	0.87611	0.05744	1	1	0.029412
240	Ribosome biogenesis in eukaryotes	116	2.1149	1	0.8829	0.05409	1	1	0
241	Focal adhesion	201	3.6645	2	0.88487	0.053119	1	1	0.064516
242	Calcium signaling pathway	202	3.6828	2	0.88655	0.052295	1	1	0.029851
243	Chemokine signaling pathway	203	3.701	2	0.88821	0.051483	1	1	0.125
244	Leukocyte transendothelial migration	119	2.1696	1	0.88925	0.050978	1	1	0.010989
245	Growth hormone synthesis, secretion and action	120	2.1878	1	0.89129	0.049983	1	1	0.063492
246	Inositol phosphate metabolism	120	2.1878	1	0.89129	0.049983	1	1	0.094118
247	Natural killer cell mediated cytotoxicity	121	2.206	1	0.89329	0.049008	1	1	0.051546
248	Pancreatic secretion	123	2.2425	1	0.89718	0.047119	1	1	0
249	Phosphatidylinositol signaling system	127	2.3154	1	0.90455	0.043566	1	1	0.27273
250	Thyroid hormone signaling pathway	129	2.3519	1	0.90804	0.041896	1	1	0.037736
251	Cytokine-cytokine receptor interaction	296	5.3965	3	0.90979	0.041057	1	1	0.015
252	Spliceosome	132	2.4066	1	0.91303	0.039516	1	1	0
253	Signaling pathways regulating pluripotency of stem cells	138	2.516	1	0.92222	0.035167	1	1	0.030612
254	Viral carcinogenesis	231	4.2115	2	0.92647	0.033168	1	1	0
255	Epstein-Barr virus infection	232	4.2297	2	0.92758	0.032649	1	1	0.02069
256	Measles	145	2.6436	1	0.93172	0.030714	1	1	0.022472
257	Dopaminergic synapse	146	2.6618	1	0.93298	0.030127	1	1	0
258	Apelin signaling pathway	146	2.6618	1	0.93298	0.030127	1	1	0.04
259	Human immunodeficiency virus 1 infection	243	4.4303	2	0.93877	0.027442	1	1	0.037313
260	Gastric cancer	154	2.8077	1	0.94226	0.025828	1	1	0.029126
261	Hepatitis C	162	2.9535	1	0.95026	0.022156	1	1	0.020619
262	Adrenergic signaling in cardiomyocytes	162	2.9535	1	0.95026	0.022156	1	1	0.028169
263	Oxytocin signaling pathway	165	3.0082	1	0.95297	0.020921	1	1	0.013158
264	Alzheimer disease	180	3.2817	1	0.96446	0.015717	1	1	0
265	Herpes simplex virus 1 infection	439	8.0036	2	0.99748	0.001098	1	1	0.030303
266	Olfactory transduction	1141	20.802	1	1	1.14E-10	1	1	0