Table S1 Top 20 KEGG pathways enriched among upregulated genes in the liver (SAM vs. HCD)

First Category	Second Category	Pathway description	Ratio_in_ study	Ratio_in_ pop	Rich factor	Pvalue	Padjust	Pathway ID	Gene_names
Metabolism	Carbohydrate metabolism	Propanoate metabolism	14/ 1217	14/ 1217	30/ 15848	0.4667	1.04E-08	mmu00640	*Acads;Abat;Acacb;Mmut;Acss2;Ldha;Pcca;Ehhadh;Acox1;Pccb;Acox3;Acaca;Suclg1;Hadha*
Metabolism	Lipid metabolism	Biosynthesis of unsaturated fatty acids	14/ 1217	15/ 1217	34/ 15848	0.4412	8.05E-09	mmu01040	*Hsd17b12;Hsd17b4;Acnat2;Fads1;Scd2;Acot4;Elovl7;Hacd3;Acot1;Hacd4;Acox1;Acot3;Acox3;Acot2;Fads2*
Metabolism	Lipid metabolism	Steroid biosynthesis	15/ 1217	11/ 1217	20/ 15848	0.5500	4.61E-08	mmu00100	*Hsd17b7;Sqle;Cyp51;Soat1;Nsdhl;Fdft1;Msmo1;Dhcr24;Lss;Lipa;Dhcr7*
Organismal Systems	Immune system	Complement and coagulation cascades	11/ 1217	22/ 1217	91/ 15848	0.2418	1.02E-06	mmu04610	*Pros1;F13a1;Fga;Cpb2;F7;F5;Plau;Clu;Serpina1d;Fgg;C3;Itgam;Itgax;Fgb;Vsig4;C1qc;Itgb2;Serpine1;C4bp;C5ar1;Cfi;F13b*
Cellular Processes	Transport and catabolism	Lysosome	22/ 1217	27/ 1217	135/ 15848	0.2000	3.45E-06	mmu04142	*Hexb;Npc2;Litaf;Ctsc;Hyal1;Psap;Cltc;Ap3m2;Cd68;Laptm5;Ctss;Arsb;Scarb2;Ctso;Lgmn;Lipa;Ctsh;Ctsd;Sgsh;Aga;Ctsf;Manba;Fuca2;Wdr7;Ctsb;Gusb;Npc1*

Metabolism	Lipid metabolism	Fatty acid elongation	27/ 1217	11/ 1217	29/ 15848	0.3793	4.97E-06	mmu00062	*Hsd17b12;Acot4;Elovl7;Hadh;Hacd3;Hadhb;Acot1;Hacd4;Hadha;Acot3;Acot2*
Organismal Systems	Endocrine system	PPAR signaling pathway	11/ 1217	20/ 1217	89/ 15848	0.2247	1.03E-05	mmu03320	*Rxra;Acox2;Ppara;Fabp7;Scd2;Plin2;Plin5;Cyp4a14;Cyp7a1;Fads2;Acox3;Ehhadh;Acsl5;Cd36;Cyp4a32;Me1;Acox1;Cyp4a31;Sorbs1;Cpt1a*
Environmental Information Processing	Membrane transport	ABC transporters	20/ 1217	14/ 1217	51/ 15848	0.2745	2.00E-05	mmu02010	*Abcd1;Abcd2;Abcd3;Abcg8;Abca3;Abcc1;Abcc12;Abca1;Abcc3;Abca6;Abcg1;Abcb6;Abcc4;Abcg3*
Metabolism	Lipid metabolism	Fatty acid degradation	14/ 1217	14/ 1217	52/ 15848	0.2692	2.55E-05	mmu00071	*Cyp4a31;Acads;Hadh;Cyp4a14;Hadhb;Ehhadh;Aldh3a2;Acox1;Cyp4a32;Acox3;Acsl5;Acat2;Cpt1a;Hadha*
Organismal Systems	Digestive system	Cholesterol metabolism	14/ 1217	13/ 1217	50/ 15848	0.2600	7.33E-05	mmu04979	*Nceh1;Lrp1;Abca1;Soat1;Npc1;Npc2;Cyp7a1;Pcsk9;Scarb1;Cd36;Lipa;Lipg;Abcg8*
Human Diseases	Cancer: overview	Proteoglycans in cancer	13/ 1217	31/ 1217	201/ 15848	0.1542	0.000147183	mmu05205	*Wnt5b;Hpse;Met;Plcg1;Msn;Arhgef12;Ctnnb1;Fn1;Lum;Tgfb1;Hgf;Akt2;Ccnd1;Dcn;Plau;Col1a1;Sdc1;Mapk14;Vav1;Itpr1;Pik3cd;Iqgap1;Erbb3;Cttn;Pak1;Stat3;Mmp9;Flnb;Smad2;Esr1;Tlr2*
Cellular Processes	Transport and catabolism	Peroxisome	31/ 1217	17/ 1217	87/ 15848	0.1954	0.000288346	mmu04146	*Abcd1;Abcd2;Acox2;Hacl1;Abcd3;Mpv17l;Hsd17b4;Acnat2;Pmvk;Pex26;Pex19;Acox3;Ehhadh;Acsl5;Pex14;Mvk;Acox1*
Organismal Systems	Digestive system	Bile secretion	17/ 1217	18/ 1217	98/ 15848	0.1837	0.000429 49	mmu04976	*Nceh1;Hmgcr;Abcg8;Acnat2;Aqp4;Slc4a4;Ugt1a5;Ugt2b38;Scarb1;Cyp7a1;Rxra;Ugt1a1;Adcy3;Abcc3;Adcy9;Atp1a1;Abcc4;Aqp9*

Metabolism	Metabolism of other amino acids	beta-Alanine metabolism	18/ 1217	9/ 1217	32/ 15848	0.2813	0.000500762	mmu00410	*Csad;Dpys;Acads;Abat;Ehhadh;Aldh3a2;Acox1;Acox3;Hadha*
Metabolism	Metabolism of other amino acids	Taurine and hypotaurine metabolism	9/ 1217	7/ 1217	21/ 15848	0.3333	0.000689323	mmu00430	*Fmo5;Fmo2;Csad;Acnat2;Fmo4;Fmo1;Ggt6*
Metabolism	Metabolism of cofactors and vitamins	Retinol metabolism	7/ 1217	17/ 1217	95/ 15848	0.1789	0.000835005	mmu00830	*Rdh16;Cyp2c38;Cyp2b10;Ugt2b38;Cyp3a13;Cyp4a31;Ugt1a5;Rdh9;Cyp4a14;Cyp26a1;Cyp2c29;Cyp2c37;Cyp4a32;Cyp2c39;Ugt1a1;Retsat;Cyp1a2*
Metabolism	Amino acid metabolism	Valine, leucine and isoleucine degradation	17/ 1217	12/ 1217	56/ 15848	0.2143	0.000936442	mmu00280	*Acads;Mmut;Hadh;Abat;Hadhb;Ehhadh;Aldh3a2;Hadha;Pccb;Pcca;Acat2;Mccc2*
Organismal Systems	Development and regeneration	Osteoclast differentiation	12/ 1217	21/ 1217	132/ 15848	0.1591	0.001090863	mmu04380	*Pirb;Ifngr1;Btk;Sirpa;Fcgr4;Tgfbr2;Csf1r;Tnfrsf1a;Akt2;Pira12;Itpr1;Gab2;Pik3cd;Sirpb1c;Sirpb1b;Tgfb1;Lcp2;Ppp3r1;Sirpb1a;Tnfrsf11b;Mapk14*
Environmental Information Processing	Signal transduction	AMPK signaling pathway	21/ 1217	20/ 1217	123/ 15848	0.1626	0.00107591	mmu04152	*Hmgcr;Ulk1;Lepr;Acacb;Adra1a;Adipor2;Prkag2;Tbc1d1;Fbp1;Akt2;Ccnd1;Gys2;Pik3cd;Cd36;Ppp2cb;Eef2;Acaca;Scd2;Fasn;Cpt1a*
Metabolism	Amino acid metabolism	Tryptophan metabolism	20/ 1217	11/ 1217	50/ 15848	0.2200	0.001202366	mmu00380	*Cyp1b1;Maob;Ido2;Hadh;Ehhadh;Aldh3a2;Hadha;Tdo2;Dlst;Acat2;Cyp1a2*

Table S2 Top 20 KEGG pathways enriched among downregulated genes in the liver (SAM vs. HCD)

First Category	Second Category	Pathway description	Ratio_in_study	Ratio_in_pop	Rich factor	Pvalue	Padjust	Pathway ID	Gene_names
Human Diseases	Neurodegenerative disease	Prion disease	70/ 1416	263/ 15848	0.2662	2.63E-17	8.64E-15	mmu05020	*Psma7;Ndufb7;Ndufa12;Bax;Ndufs8;Cox5b;mt-Co3;Ndufs5;Cox6a1;Ndufa13;Atp5pf;mt-Cytb;C1qa;mt-Co1;Cox6b1;Atp5f1d;mt-Atp8;Cyba;Pik3ca;Mapk12;mt-Co2;Creb3l1;Ndufa11;Atp5f1e;Ndufa6;Ndufv3;Rac2;Egr1;Cacna1d;Tnf;Ndufa2;mt-Atp6;Ndufs7;Psmd1;Ndufb4;Ccl5;Uqcr11;Ncf2;Ndufa5;Ddit3;Cox7b;mt-Nd5;Mcu;Uqcrq;mt-Nd4;Ncam1;Il1a;Sdhb;mt-Nd2;Ndufa8;Hspa1a;mt-Nd1;Sem1;Atf4;C1qb;mt-Nd6;Psmb3;mt-Nd4l;Atp5pd;Ndufa3;Psmb6;Cox7c;Ncf4;C8g;Ncf1;Hspa1b;Ndufb2;Kif5b;Ndufa10;mt-Nd3*
Metabolism	Energy metabolism	Oxidative phosphorylation	42/ 1416	133/ 15848	0.3158	1.23E-13	1.35E-11	mmu00190	*Ndufb7;Ndufa12;Ndufs8;Cox5b;mt-Co3;Ndufs5;Cox6a1;Ndufa13;Atp5pf;mt-Cytb;mt-Co1;Cox6b1;mt-Co2;mt-Atp8;mt-Atp6;Sdhb;Atp5f1d;Ndufa10;Ndufa11;Atp5f1e;Ndufa6;Ndufv3;Ndufa2;Ndufs7;Ndufb4;Uqcr11;Ndufa5;Cox7b;mt-Nd5;Uqcrq;mt-Nd4;mt-Nd2;Ndufa8;mt-Nd6;mt-Nd1;Lhpp;Atp5pd;Ndufa3;Cox7c;Ndufb2;mt-Nd4l;mt-Nd3*
Human Diseases	Cardiovascular disease	Diabetic cardiomyopathy	54/ 1416	203/ 15848	0.2660	1.22E-13	2.01E-11	mmu05415	*Akt3;Ndufb7;Ndufa12;Ndufs8;Cox5b;Irs1;mt-Co3;Ndufs5;Cox6a1;Ndufa13;Atp5pf;mt-Cytb;mt-*

Human Diseases	Cancer: overview	Chemical carcinogenesis - reactive oxygen species	54/ 1416	218/ 15848	0.2477	2.72E-12	2.24E-10	mmu05208	*Co1;Cox6b1;mt-Co2;mt-Atp8;mt-Atp6;Pik3ca;Mapk12;Atp5f1d;Ndufa10;Ndufa11;Atp5f1e;Tbc1d4;Ndufv3;Ndufa2;Cyba;Ndufs7;Ncf4;Ndufb4;Uqcr11;Ncf2;Cox7b;Ndufa5;mt-Nd5;Uqcrq;mt-Nd4;Gapdh;Sdhb;mt-Nd2;Agt;Ndufa8;Ndufa6;mt-Nd1;mt-Nd6;Rac2;Atp5pd;Ndufa3;mt-Nd4l;Cox7c;Ncf1;Ndufb2;Tnni3;mt-Nd3 Akt3;Ndufb7;Mgst2;Ndufa12;Atp5pd;Ndufs8;Cox5b;mt-Co3;Ndufs5;Cox6a1;Ndufa13;Atp5pf;mt-Cytb;mt-Co1;Cox6b1;Atp5f1d;mt-Atp8;Cyba;Gstt2;Gstt1;Sdhb;Mapk12;mt-Co2;Ndufa10;Ndufa11;Atp5f1e;mt-Nd6;Ndufv3;Ndufa2;mt-Atp6;Ndufs7;Ndufb4;Uqcr11;Ncf2;Ndufa5;Fos;Nox1;mt-Nd5;Uqcrq;mt-Nd4;Pik3ca;mt-Nd2;Ndufa8;Ndufa6;mt-Nd1;Cox7b;Mgst3;Ndufa3;Cox7c;Ncf1;Map2k2;Ndufb2;mt-Nd4l;mt-Nd3*
Human Diseases	Neurodegenerative disease	Parkinson disease	58/ 1416	261/ 15848	0.2222	5.00E-11	3.29E-09	mmu05012	*Psma7;Ndufb7;Ndufa12;Bax;Ndufs8;Cox5b;mt-Co3;Ndufs5;Cox6a1;Ndufa13;Atp5f1e;mt-Cytb;mt-Co1;Cox6b1;mt-Co2;Slc39a2;mt-Atp8;mt-Atp6;Uba52;Mapt;Septin5;Sdhb;Atp5f1d;Ndufa10;Ndufa11;Dusp1;mt-Nd6;Ndufv3;Ddit3;Gnas;Ndufa2;Ndufs7;Psmd1;Ndufb4;Uqcr11;Psmb3;Ndufa5;mt-Nd5;Mcu;Uqcrq;mt-Nd4;mt-Nd2;Ndufa8;Ndufa6;mt-Nd1;Sem1;Atf4;Cox7b;mt-Nd3;Atp5pd;Ndufa3;Psmb6;Cox7c;Park7;Ndufb2;Kif5b;mt-Nd4l;Atp5pf*

Organismal Systems	Environmental adaptation	Thermogenesis	50/ 1416	224/ 15848	0.2232	9.14E-10	5.01E-08	mmu04714	*Ndufb7;Ndufa12;Adrb3;Ndufs8;Cox5b;Ndufa3;mt-Co3;Rps6kb2;Ndufs5;Cox6a1;Ndufa13;Atp5pf;mt-Cytb;mt-Co1;Cox6b1;Atp5f1d;mt-Atp8;mt-Atp6;Sdhb;Mapk12;mt-Co2;Creb3l1;Ndufa11;Atp5f1e;mt-Nd6;Ndufv3;Gnas;Ndufa2;Ndufs7;Ndufb4;Uqcr11;Cox7b;Ndufa5;mt-Nd5;Uqcrq;mt-Nd4;mt-Nd2;Ndufa8;Ndufa6;mt-Nd1;Smarcd3;Cox19;Atp5pd;Akt1s1;mt-Nd4l;Cox7c;Cox20;Ndufb2;Ndufa10;mt-Nd3*
Human Diseases	Endocrine and metabolic disease	Non-alcoholic fatty liver disease	39/ 1416	154/ 15848	0.2532	1.47E-09	6.91E-08	mmu04932	*Akt3;Ndufb7;Ndufa12;Bax;Ndufs8;Cox5b;Ndufa3;mt-Co3;Ndufs5;Cox6a1;Ndufa13;mt-Cytb;mt-Co1;Cox6b1;mt-Co2;Cox7c;Pik3ca;Mapk12;Ndufa10;Ndufa11;Ndufv3;Ddit3;Tnf;Ndufa2;Ndufs7;Ndufb4;Uqcr11;Ndufa5;Fos;Cox7b;Uqcrq;Il1a;Sdhb;Ndufa8;Ndufa6;Atf4;Irs1;Mlxipl;Ndufb2*
Human Diseases	Infectious disease: viral	Coronavirus disease - COVID-19	49/ 1416	236/ 15848	0.2076	1.67E-08	6.89E-07	mmu05171	*Fcgr3;Rpl35a;Rpl18a;Rpl22l1;Ace2;Rps17;Eif2ak2;Rps15;Syk;C1qa;Rpl5;Oas1g;Rpl12;Rpl28;Pik3ca;Mapk12;Rps16;Rpl14;Rpl36al;Rpl21;Irf3;Rps27rt;Rps29;Rpl26;Tnf;C3ar1;C1qb;Rps18;Rps25;Fos;Rpl36;Uba52;Rpl31;Rpl19;Cxcl10;Oas1b;C4a;Rpl38;Casp1;Isg15;Ccl2;Rpl35;Rpl24;Oas2;Gm2000;C8g;Stat2;Plcg2;Oas1a*
Human Diseases	Neurodegenerative disease	Huntington disease	56/ 1416	299/ 15848	0.1873	7.30E-08	2.67E-06	mmu05016	*Psma7;Ndufb7;Ap2s1;Ndufa12;Bax;Ndufs8;Cox5b;mt-Co3;Ndufs5;Cox6a1;Ndufa13;Atp5pf;mt-Cytb;mt-Co1;Cox6b1;Atp5f1d;mt-Atp8;mt-Atp6;Dnah14;Sdhb;Hip1;Creb3l1;Ndufa11;Atp5f1e;mt-Nd6;Ndufv3;Polr2i;Ndufs7;Psmd1;Ndufb4;Uqcr11;Polr2h;Cox7b;Ndufa5;mt-Co2;Polr2f;Uqcrq;mt-Nd4;mt-Nd2;Ndufa8;Ndufa6;mt-Nd1;Sem1;Psmb3;Ndufa2;mt-*

Human Diseases	Neurodegenerative disease	Alzheimer disease	65/ 1416	379/ 15848	0.1715	2.09E-07	6.89E-06	mmu05010	*Nd4l;Atp5pd;Ndufa3;Psmb6;Cox7c;mt-Nd5;Ndufb2;Gpx8;Kif5b;Ndufa10;mt-Nd3 Ndufb7;Akt3;Ndufa12;Ndufs8;Eif2ak2;Cox5b;Ndufa3;mt-Co3;Gapdh;Ndufs5;Cox6a1;Ndufa13;Atp5pf;mt-Cytb;mt-Co1;Cox6b1;Dvl1;mt-Co2;Slc39a2;mt-Atp8;mt-Atp6;Mapt;Pik3ca;Atp5f1d;Ndufa10;Ndufa11;Atp5f1e;mt-Nd6;Ndufv3;Ddit3;Tnf;Ndufa2;Ndufs7;Psmd1;Ndufb4;Psma7;Uqcr11;Cox7b;Cacna1d;Nox1;Irs3;mt-Nd5;Mcu;mt-Nd3;mt-Nd4;Il1a;Sdhb;mt-Nd2;Ndufa8;Ndufa6;mt-Nd1;Sem1;Atf4;Ndufa5;Psen2;Psmb3;Atp5pd;Irs1;Psmb6;Cox7c;Map2k2;Ndufb2;Kif5b;mt-Nd4l;Uqcrq Ndufb7;Psma7;Nxf1;Ndufa12;Bax;Srsf7;Ndufs8;Cox5b;mt-Co3;Ndufs5;Cox6a1;Ndufa13;Atp5pf;mt-Cytb;mt-Co1;Cox6b1;mt-Co2;mt-Atp8;mt-Atp6;Dnah14;Sdhb;Mapk12;Pfn1;Ndufa10;Ndufa11;Nefl;Atp5f1e;Ndufa6;Ndufv3;Ddit3;Tnf;Ndufa2;Ang4;Ndufs7;Psmd1;Ndufb4;Chchd10;Uqcr11;Ndufa5;Cox7b;mt-Nd5;Mcu;mt-Nd3;mt-Nd4;mt-Nd2;Ndufa8;mt-Nd6;mt-Nd1;Sem1;Atf4;Casp1;Psmb3;Bcl2;Atp5pd;Ndufa3;Atp5f1d;Psmb6;Cox7c;Ndufb2;Gpx8;Kif5b;mt-Nd4l;Uqcrq Rpl35a;Rpl18a;Rpl22l1;Rps17;Rps15;Rpl5;Rpl12;Rpl28;Rps16;Mrps15;Rpl36al;Rpl21;Rpl14;Rps27rt;Rps29;Rpl26;Rpl36;Mrps21;Mrpl14;Mrpl19;Rps18;Rps25;Uba52;Rpl31;Rpl19;Rpl38;Gm2000;Mrps11;Rpl35;Rpl24;Mrpl27*
Human Diseases	Neurodegenerative disease	Amyotrophic lateral sclerosis	63/ 1416	364/ 15848	0.1731	2.30E-07	6.89E-06	mmu05014	
Genetic Information Processing	Translation	Ribosome	31/ 1416	133/ 15848	0.2331	5.14E-07	1.41E-05	mmu03010	

Organismal Systems	Nervous system	Retrograde endocannabinoid signaling	31/ 1416	144/ 15848	0.2153	3.14E-06	7.95E-05	mmu04723	*Gng11;Ndufb7;Ndufa12;Ndufs8;Ndufs5;Ndufa13;Gng5;Mapk12;Ndufa10;Ndufa11;Gngt1;mt-Nd6;Ndufv3;Cacna1d;Ndufa2;Ndufs7;Cacna1a;Ndufb4;Ndufa5;mt-Nd5;mt-Nd3;mt-Nd4;mt-Nd2;Ndufa8;Ndufa6;mt-Nd1;Gngt2;Ndufa3;Ndufb2;Gng2;mt-Nd4l*
Organismal Systems	Immune system	Chemokine signaling pathway	37/ 1416	188/ 15848	0.1968	3.54E-06	8.32E-05	mmu04062	*Akt3;Gng11;Cxcl9;Rock1;Gng2;Grk4;Cxcr4;Gng5;Pik3ca;Gm13304;Gngt1;Rac2;Ccl27a;Gm10591;Ccl19;Itk;Rasgrp2;Ccl21a;Cxcl2;Ccl21b;Cxcl10;Grk1;Prex1;Pf4;Ppbp;Ccl5;Ccl3;Arrb2;Pik3r5;Gngt2;Bcar1;Ccl2;Stat2;Ncf1;Plcg2;Ccl4;Rock2*
Organismal Systems	Immune system	NOD-like receptor signaling pathway	38/ 1416	203/ 15848	0.1872	9.01E-06	0.000197638	mmu04621	*Oas1g;Defa24;Gbp2;Pycard;Gpsm3;Trpv2;Cyba;Sharpin;Mapk12;Irf3;Defa20;Defa17;Nlrp6;Tnf;Naip1;Defa22;Hsp90aa1;Ifi204;Cxcl2;Defa5;Mcu;Defa21;Oas1a;Defa42;Oas1b;Defa38;Defa29;Ccl5;Naip6;Casp1;Nlrc4;Ccl2;Bcl2;Defa2;Oas2;Stat2;Casp4;Trpm7*
Human Diseases	Infectious disease: bacterial	Staphylococcus aureus infection	26/ 1416	118/ 15848	0.2203	1.24E-05	0.000253959	mmu05150	*Fcgr3;Defa22;H2-Aa;Defa21;H2-Eb1;C1qa;Ptafr;Icam1;Fcgr1;Defa20;Krt20;Defa17;H2-DMb1;Defa42;C3ar1;C1qb;Defa24;Defa5;H2-Ab1;Defa38;C4a;Defa29;Krt18;H2-DMa;Defa2;Krt10*
Human Diseases	Cancer: overview	Transcriptional misregulation in cancer	37/ 1416	199/ 15848	0.1859	1.38E-05	0.000266653	mmu05202	*Bcl2a1d;Fli1;Bax;Defa24;Gadd45g;Pdgfa;Defa2;Cebpb;Supt3;Fcgr1;Pbx1;Slc45a3;Fut8;Defa17;Bcl2a1b;Lyl1;Defa20;Mef2c;Nfkbiz;Defa22;Gadd45b;Igf1;Maf;Rel;Ddit3;Defa5;Traf1;Defa21;Defa42;Aspscr1;Defa38;Defa29;Cebpe;Ccnt2;Bcl2a1a;Kmt2a;Runx1t1*

Organismal Systems	Immune system	Hematopoietic cell lineage	22/ 1416	94/ 15848	0.2340	2.09E-05	0.000382579	mmu04640	*Csf2ra;H2-Eb1;Il3ra;Cd7;Itga4;Siglech;Cd2;Fcgr1;H2-DMb1;Tnf;Itga6;Cd44;Gypa;Il1a;Cd22;H2-Ab1;Cd8a;Gp9;H2-DMa;H2-Aa;Itga2b;Cd59a*
Human Diseases	Cardiovascular disease	Fluid shear stress and atherosclerosis	29/ 1416	145/ 15848	0.2000	2.84E-05	0.000491813	mmu05418	*Akt3;Mgst2;Gstp2;Acvr2b;Pdgfa;Cyba;Gstt2;Icam1;Gstt1;Pik3ca;Mapk12;Dusp1;Thbd;Tnf;Mef2c;Arhgef2;Ncf2;Hsp90aa1;Fos;Nox1;Itga2b;Il1a;Mapk7;Ccl2;Bcl2;Mgst3;Rac2;Bmp4;Ncf1*
Human Diseases	Infectious disease: viral	Epstein-Barr virus infection	39/ 1416	223/ 15848	0.1749	3.50E-05	0.000576393	mmu05169	*Akt3;Bax;Gadd45g;Eif2ak2;Syk;Gm11127;H2-Q2;Oas1g;Icam1;Cd247;Pik3ca;Mapk12;Blnk;Irf3;H2-Eb1;Relb;H2-DMb1;Tnf;Gadd45b;Psmd1;Cdk6;Cd44;Ccne2;Vim;Cxcl10;H2-Ab1;Oas1b;Sem1;H2-DMa;H2-T3;Isg15;Bcl2;H2-Aa;Oas2;Entpd8;Stat2;Plcg2;Cir1;Oas1a*

Table S3 Top 20 KEGG pathways enriched among upregulated genes in the small intestine (SAM vs. HCD)

First Category	Second Category	Pathway description	Ratio_in_study	Ratio_in_pop	Rich factor	Pvalue	Padjust	Pathway ID	Gene_names
Organismal Systems	Immune system	Intestinal immune network for IgA production	9/ 247	43/ 15848	0.2093	1. 67E-08	4. 18E-06	mmu04672	*H2-DMb2;H2-Oa;Cd28;H2-Ob;Aicda;Tnfrsf13c;H2-Eb2;Tnfrsf13b;Madcam1*
Organismal Systems	Immune system	Hematopoietic cell lineage	11/ 247	94/ 15848	0.1170	2. 33E-07	2. 93E-05	mmu04640	*Cd7;Cd37;H2-DMb2;H2-Oa;Cd3g;H2-Ob;Cd3e;Cd22;H2-Eb2;Il1r2;Cd8a*
Human Diseases	Immune disease	Graft-versus-host disease	8/ 247	55/ 15848	0.1455	2. 01E-06	0. 000168	mmu05332	*Fasl;Klrd1;H2-DMb2;H2-Oa;Cd28;Gzmb;H2-Eb2;H2-Ob*
Human Diseases	Cancer: overview	Chemical carcinogenesis - DNA adducts	9/ 247	81/ 15848	0.1111	4. 61E-06	0. 000289	mmu05204	*Gstt1;Cyp2c29;Gsta4;Ugt1a6a;Ugt2b38;Ephx1;Ugt2b35;Cyp2c70;Cyp1a1*
Metabolism	Amino acid metabolism	Tryptophan metabolism	7/ 247	50/ 15848	0.1400	1. 16E-05	0. 000581	mmu00380	*Tph1;Haao;Inmt;Acat3;Cyp1a1;Il4i1;Kmo*
Human Diseases	Immune disease	Primary immunodeficiency	6/ 247	36/ 15848	0.1667	1. 78E-05	0. 000743	mmu05340	*Aicda;Tnfrsf13c;Cd3e;Cd79a;Tnfrsf13b;Cd8a*
Human Diseases	Immune disease	Allograft rejection	7/ 247	55/ 15848	0.1273	2. 20E-05	0. 000789	mmu05330	*Fasl;H2-DMb2;H2-Oa;Cd28;Gzmb;H2-Eb2;H2-Ob*
Human Diseases	Immune disease	Asthma	5/ 247	25/ 15848	0.2000	3. 64E-05	0. 001141	mmu05310	*H2-DMb2;H2-Oa;Prg2;H2-Ob;H2-Eb2*
Human Diseases	Endocrine and metabolic disease	Type I diabetes mellitus	7/ 247	62/ 15848	0.1129	4. 86E-05	0. 001356	mmu04940	*Fasl;H2-DMb2;H2-Oa;Cd28;Gzmb;H2-Eb2;H2-Ob*

Metabolism	Xenobiotics biodegradation and metabolism	Metabolism of xenobiotics by cytochrome P450	7/ 247	71/ 15848	0.0986	0. 00012	0. 002930	mmu00980	*Gstt1;Gsta4;Ugt1a6a;Ugt2b38;Ugt2b35;Cyp1a1;Ephx1*
Human Diseases	Immune disease	Autoimmune thyroid disease	7/ 247	71/ 15848	0.0986	0. 00012	0. 002930	mmu05320	*Fasl;H2-DMb2;H2-Oa;Cd28;Gzmb;H2-Eb2;H2-Ob*
Environmental Information Processing	Signaling molecules and interaction	Cell adhesion molecules	10/ 247	171/ 15848	0.0585	0. 00035	0. 007419	mmu04514	*H2-DMb2;H2-Oa;Cd28;H2-Ob;Mpz;Cd22;H2-Eb2;Madcam1;Cd8a;Cd6*
Human Diseases	Immune disease	Rheumatoid arthritis	7/ 247	86/ 15848	0.0814	0. 00039	0. 007474	mmu05323	*Ccl5;Il18;H2-DMb2;H2-Oa;Cd28;H2-Eb2;H2-Ob*
Metabolism	Lipid metabolism	Steroid hormone biosynthesis	7/ 247	90/ 15848	0.0778	0. 00051	0. 008546	mmu00140	*Cyp2c29;Ugt2b35;Hsd3b2;Ugt1a6a;Ugt2b38;Cyp2c70;Cyp1a1*
Organismal Systems	Digestive system	Vitamin digestion and absorption	4/ 247	24/ 15848	0.1667	0. 00048	0. 008583	mmu04977	*Slc19a3;Scarb1;Slc19a1;Slc46a1*
Human Diseases	Infectious disease: parasitic	Leishmaniasis	6/ 247	69/ 15848	0.0870	0. 00071	0. 011169	mmu05140	*H2-DMb2;H2-Oa;Ncf1;H2-Eb2;Prkcb;H2-Ob*
Organismal Systems	Digestive system	Bile secretion	7/ 247	98/ 15848	0.0714	0. 00085	0. 011871	mmu04976	*Car2;Ugt1a6a;Ugt2b38;Scarb1;Ugt2b35;Ephx1;Aqp8*
Metabolism	Metabolism of other amino acids	Glutathione metabolism	6/ 247	71/ 15848	0.0845	0. 00083	0. 012238	mmu00480	*Gstt1;Gsta4;Nat8f2;Nat8f6;Nat8f5;Nat8f7*
Organismal Systems	Immune system	B cell receptor signaling pathway	6/ 247	80/ 15848	0.0750	0. 00155	0. 019433	mmu04662	*Rac2;Cd79b;Cd79a;Bank1;Cd22;Prkcb*
Organismal Systems	Immune system	Antigen processing and presentation	6/ 247	80/ 15848	0.0750	0. 00155	0. 019433	mmu04612	*Klrd1;H2-DMb2;H2-Oa;H2-Ob;H2-Eb2;Cd8a*

Table S4 Top 20 KEGG pathways enriched among downregulated genes in the small intestine (SAM vs. HCD)

First Category	Second Category	Pathway description	Ratio_in_study	Ratio_in_pop	Rich factor	Pvalue	Padjust	Pathway ID	Gene_names
Metabolism	Amino acid metabolism	Arginine and proline metabolism	3/ 30	54/ 15848	0.0556	0.0001	0.0070	3/ 30	*Aoc1;Cndp2;Lap3*
Organismal Systems	Endocrine system	Renin secretion	3/ 30	75/ 15848	0.0400	0.0004	0.0092	3/ 30	*Clca4a;Clca4b;Edn2*
Metabolism	Amino acid metabolism	Histidine metabolism	2/ 30	26/ 15848	0.0769	0.0011	0.0179	2/ 30	*Aoc1;Cndp2*
Organismal Systems	Environmental adaptation	Circadian rhythm	2/ 30	34/ 15848	0.0588	0.0019	0.0229	2/ 30	*Bmal1;Npas2*
Metabolism	Lipid metabolism	Sphingolipid metabolism	2/ 30	54/ 15848	0.0370	0.0047	0.0326	2/ 30	*Sgpl1;Enpp7*
Metabolism	Amino acid metabolism	Tryptophan metabolism	2/ 30	50/ 15848	0.0400	0.0040	0.0328	2/ 30	*Aoc1;Ido1*
Human Diseases	Infectious disease: bacterial	Legionellosis	2/ 30	60/ 15848	0.0333	0.0057	0.0351	2/ 30	*Hspa1b;Hspa1a*
Organismal Systems	Aging	Longevity regulating pathway - multiple species	2/ 30	60/ 15848	0.0333	0.0057	0.0351	2/ 30	*Hspa1b;Hspa1a*
Genetic Information Processing	Folding, sorting and degradation	Protein processing in endoplasmic reticulum	3/ 30	168/ 15848	0.0179	0.0038	0.0377	3/ 30	*Hspa1b;Hspa1a;Hsph1*
Organismal Systems	Immune system	Antigen processing and presentation	2/ 30	80/ 15848	0.0250	0.0100	0.0489	2/ 30	*Hspa1b;Hspa1a*

Metabolism	Lipid metabolism	Steroid hormone biosynthesis	2/ 30	90/ 15848	0.0222	0.0125	0.0557	2/ 30	*Cyp2c55;Cyp17a1*
Metabolism	Metabolism of cofactors and vitamins	Retinol metabolism	2/ 30	95/ 15848	0.0211	0.0139	0.0566	2/ 30	*Cyp2c55;Dhrs9*
Organismal Systems	Digestive system	Pancreatic secretion	2/ 30	110/ 15848	0.0182	0.0183	0.0640	2/ 30	*Clca4a;Clca4b*
Human Diseases	Infectious disease: parasitic	Toxoplasmosis	2/ 30	109/ 15848	0.0183	0.0180	0.0678	2/ 30	*Hspa1b;Hspa1a*
Genetic Information Processing	Transcription	Spliceosome	2/ 30	131/ 15848	0.0153	0.0254	0.0828	2/ 30	*Hspa1b;Hspa1a*
Organismal Systems	Endocrine system	Estrogen signaling pathway	2/ 30	131/ 15848	0.0153	0.0254	0.0828	2/ 30	*Hspa1b;Hspa1a*
Human Diseases	Infectious disease: viral	Measles	2/ 30	143/ 15848	0.0140	0.0298	0.0860	2/ 30	*Hspa1b;Hspa1a*
Cellular Processes	Cell motility	Motor proteins	2/ 30	188/ 15848	0.0106	0.0490	0.1334	2/ 30	*Kif27;Acta1*
Metabolism	Metabolism of other amino acids	beta-Alanine metabolism	1/ 30	32/ 15848	0.0313	0.0589	0.1519	1/ 30	*Cndp2*
Human Diseases	Cardiovascular disease	Lipid and atherosclerosis	2/ 30	216/ 15848	0.0093	0.0627	0.1536	2/ 30	*Hspa1b;Hspa1a*

Table S5 Top 20 KEGG pathways enriched among upregulated metabolites in the colon (SAM vs. HCD)

First Category	Second Category	Pathway description	DA Score	Ratio_in_study	Ratio_in_pop	P_value	P_adjust	Pathway ID	Metabolites
Metabolism	Global and overview maps	Biosynthesis of cofactors	0.0323	1/14	329/4519	0.6535	0.6535	map01240	Thiamine
Metabolism	Lipid metabolism	Steroid hormone biosynthesis	0.0417	1/14	99/4519	0.2670	0.3204	map00140	5Alpha-Dihydroprogesterone
Organismal Systems	Digestive system	Bile secretion	0.0435	1/14	97/4519	0.2623	0.3313	map04976	Lithocholic Acid
Environmental Information Processing	Signal transduction	Sphingolipid signaling pathway	0.0667	1/14	15/4519	0.0456	0.2186	map04071	Sphingosine
Metabolism	Lipid metabolism	Primary bile acid biosynthesis	0.0714	1/14	47/4519	0.1363	0.2182	map00120	7A-Hydroxy-5B-Cholestan-3-One
Human Diseases	Neurodegenerative disease	Parkinson disease	0.0714	1/14	26/4519	0.0777	0.2331	map05012	Phosphate
Metabolism	Lipid metabolism	Steroid biosynthesis	0.0769	1/14	57/4519	0.1630	0.2302	map00100	24-Methylenecholesterol
Organismal Systems	Endocrine system	Parathyroid hormone synthesis, secretion and action	0.0769	1/14	10/4519	0.0306	0.3670	map04928	Phosphate

Human Diseases	Neurodegenerative disease	Pathways of neurodegeneration - multiple diseases	0.0833	1/14	32/4519	0.0948	0.1897	map05022	Phosphate
Metabolism	Lipid metabolism	Linoleic acid metabolism	0.0909	1/14	28/4519	0.0835	0.2225	map00591	13-Oxoode
Environmental Information Processing	Signaling molecules and interaction	Neuroactive ligand-receptor interaction	0.0909	1/14	53/4519	0.1525	0.2287	map04080	Palmitoylethanolamide
Organismal Systems	Digestive system	Mineral absorption	0.0909	1/14	29/4519	0.0863	0.2071	map04978	Phosphate
Metabolism	Amino acid metabolism	Tyrosine metabolism	0.1000	1/14	78/4519	0.2166	0.2888	map00350	Salidroside
Metabolism	Metabolism of cofactors and vitamins	Porphyrin metabolism	0.1111	1/14	149/4519	0.3750	0.4091	map00860	Biliverdin

Table S6 Top 20 KEGG pathways enriched among downregulated metabolites in the colon (SAM vs. HCD)

First Category	Second Category	Pathway description	DA Score	Ratio_in_study	Ratio_in_pop	P_value	P_adjust	Pathway ID	Metabolites
Organismal Systems	Nervous system	Serotonergic synapse	-0.0625	1/12	42/4519	0.1061	0.1311	map04726	5-Hydroxy-L-Tryptophan
Metabolism	Amino acid metabolism	Tryptophan metabolism	-0.0667	1/12	83/4519	0.1997	0.1997	map00380	5-Hydroxy-L-Tryptophan
Metabolism	Amino acid metabolism	Arginine and proline metabolism	-0.0833	1/12	69/4519	0.1688	0.1772	map00330	Spermidine
Organismal Systems	Digestive system	Fat digestion and absorption	-0.0833	1/12	13/4519	0.0340	0.0893	map04975	Ce(22:6(4Z,7Z,10Z,13Z,16Z,19Z))
Environmental Information Processing	Signaling molecules and interaction	Neuroactive ligand-receptor interaction	-0.0909	1/12	53/4519	0.1322	0.1461	map04080	Taurine
Metabolism	Metabolism of other amino acids	Taurine and hypotaurine metabolism	-0.1250	1/12	24/4519	0.0620	0.1183	map00430	Taurine
Organismal Systems	Endocrine system	Ovarian steroidogenesis	-0.1250	1/12	24/4519	0.0620	0.1183	map04913	Ce(22:6(4Z,7Z,10Z,13Z,16Z,19Z))

Metabolism	Carbohydrate metabolism	Galactose metabolism	-0.1667	1/12	46/4519	0.1157	0.1350	map00052	Beta-Cortol
Organismal Systems	Digestive system	Cholesterol metabolism	-0.1667	1/12	10/4519	0.0263	0.0919	map04979	Ce(22:6(4Z,7Z,10Z,13Z,16Z,19Z))
Metabolism	Metabolism of other amino acids	beta-Alanine metabolism	-0.2000	1/12	32/4519	0.0818	0.1228	map00410	Spermidine
Metabolism	Metabolism of other amino acids	Glutathione metabolism	-0.2000	1/12	38/4519	0.0965	0.1266	map00480	Spermidine
Metabolism	Energy metabolism	Sulfur metabolism	-0.2000	1/12	33/4519	0.0843	0.1180	map00920	Taurine
Environmental Information Processing	Signal transduction	Phosphatidylinositol signaling system	-0.5000	1/12	29/4519	0.0744	0.1202	map04070	Cdp-Dg(18:1(11Z)/16:1(9Z))
Human Diseases	Cardiovascular disease	Lipid and atherosclerosis	-0.5000	1/12	14/4519	0.0366	0.0854	map05417	Ce(22:6(4Z,7Z,10Z,13Z,16Z,19Z))

Table S7. Primer sequences used for real-time quantitative PCR

Gene	RefSeq Accession	Forward primer (5′→3′)	Reverse primer (5′→3′)
Ppara	NM_011144.6	CTGGCCACATCCATCCAAC	GCTCTCCTCACCGATGGACT
Cpt1a	NM_013495.2	GCCATCTGTGGGAGTATGTC	TGTAGCCTGGTGGGTTTG
Acox1	NM_015729.4	GCCCAACTGTGACTTCCATC	GCCAGGACTATCGCATGATT
Fasn	NM_007988.3	TCTGCGATGAAGAGCATGGT	GCGATTTCTGGGACTTTGTTT
Cyp7a1	NM_007824.3	TATCTAACGCTGTTTGGC	GGCTTTATGTGCGGTCT
Abca1	NM_013454.3	CCATCGTGTCTCGCCTGTT	GCTTGATCTGCCGTAACATTC
Ccl2	NM_011333	GTGGGCGTTAACTGCAT	CAGGTCCCTGTCATGCTTCT
Acox3	NM_030721.4	ACCGAACTGAGTCATGGGAG	TGAGCAGGTAGTTGCTGGTC
Gapdh	NM_008084.4	GTGAGGCCGGTGCTGAGTAT	GTGCAGGATGCATTGCTGAC