

## **SUPPLEMENTARY MATERIAL**

### **Hydroxysteroid 17-beta dehydrogenase 13 variant protects against fibrosis in subjects with non-alcoholic fatty liver disease**

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## Lipidomics analysis

Lipidomics using UHPLC-MS was performed at VTT Technical Research Centre of Finland (Espoo, Finland). Liver tissue (approximately 5 mg) was first homogenized when still frozen (Covaris, CryoPrep CP02, MA), and weighted. An aliquot (20  $\mu$ L) of an internal standard mixture containing PC(17:0/0:0), PC(17:0/17:0), PE(17:0/17:0), phosphatidylglycerol(17:0/17:0)[rac], Ceramide(d18:1/17:0), PS(17:0/17:0), phosphatidic acid(17:0/17:0) (Avanti Polar Lipids, Alabaster, AL), monoacylglycerol(17:0/0:0/0:0)[rac], DAG(17:0/17:0/0:0)[rac] and TAG(17:0/17:0/17:0) were added. The lipids were extracted using a mixture of HPLC-grade chloroform and methanol (2:1; 400  $\mu$ L). 50  $\mu$ l of 0.9% NaCl was added and the lower phase (200  $\mu$ L) was collected and 20  $\mu$ L of an internal standard mixture containing labeled PC(16:1/0:0-D<sub>3</sub>), PC(16:1/16:1-D<sub>6</sub>) and TAG(16:0/16:0/16:0-<sup>13</sup>C<sub>3</sub>) was added. The extracts were run on a Waters Q-TOF Premier mass spectrometer combined with an Acquity Ultra Performance LC™ as described earlier [1].

The column (at 50 °C) was an Acquity UPLC™ BEH C18 2.1  $\times$  100 mm with 1.7  $\mu$ m particles. The solvent system included A. ultrapure water (1% 1 M NH<sub>4</sub>Ac, 0.1% HCOOH) and B. LC/MS grade acetonitrile/isopropanol (1:1, 1% 1M NH<sub>4</sub>Ac, 0.1% HCOOH). The gradient started from 65% A / 35% B, reached 80% B in 2 min, 100% B in 7 min and remained there for 7 min. The flow rate was 0.400 ml/min and the injected amount was 2.0  $\mu$ l (Acquity Sample Organizer, at 10 °C). Reserpine was used as the lock spray reference compound. The lipid profiling was carried out using electrospray ionization mode and the data were collected at a mass range of m/z 300-1200 with a scan duration of 0.2 sec.

The data processing included alignment of peaks, peak integration, normalization and identification. Lipids were identified using an internal spectral library. The data were normalized using one or more

internal standards representative of each class of lipid present in the samples: the intensity of each identified lipid was normalized by dividing it with the intensity of its corresponding standard and multiplying it by the concentration of the standard. All monoacyl lipids except cholesterol esters, such as monoacylglycerols and monoacylglycerophospholipids, were normalized with PC(17:0/0:0), all diacyl lipids except ethanolamine phospholipids were normalized with PC(17:0/17:0), all ceramides with Cer(d18:1/17:0), all diacyl ethanolamine phospholipids with PE(17:0/17:0), and TAG and cholesterol esters with TAG(17:0/17:0/17:0). Other (unidentified) molecular species were normalized with PC(17:0/0:0) for retention times < 300 s, PC(17:0/17:0) for a retention time between 300 s and 410 s, and TAG(17:0/17:0/17:0) for longer retention times.

Quality control of the method showed that the day-to-day repeatability of control serum samples, and the relative standard deviation (RSD) for identified lipids was on average 14.1% in ESI+ mode and 9.5% in ESI- mode. The internal standards added to all samples in the study had an average RSD of 10.8% in ESI+ mode and 8.0% in ESI- mode.

- [1] Nygren H, Seppänen-Laakso T, Castillo S, Hyötyläinen T, Oresic M. Liquid Chromatography-Mass Spectrometry (LC-MS)-Based Lipidomics for Studies of Body Fluids and Tissues. In: Metz TO, ed. *Metabolic Profiling*. Totowa, NJ: Humana Press; 2010. p. 247–257.

**Supplementary Table 1. Clinical characteristics of the study subjects with liver lipidomics data according to the HSD17B13 genotype at rs72613567.**

	<b>TT (n=48)</b>	<b>TTA/TATA (n=38)</b>
Age (years)	44.9 ± 1.2	46.7 ± 1.3
Gender (% women)	72.9	68.4
BMI (kg/m <sup>2</sup> )	45.8 ± 0.8	44.6 ± 1.1
fP-Glucose (mmol/L)	5.7 (5.0 – 6.0)	5.6 (5.0 – 6.0)
fS-Insulin (mU/L)	12.1 (6.9 – 18.8)	13.4 (7.3 – 17.8)
fP-Triglycerides (mmol/L)	1.21 (0.91 – 1.53)	1.31 (0.98 – 1.71)
fP-HDL cholesterol (mmol/L)	1.12 (0.99 – 1.37)	1.06 (0.96 – 1.38)
fP-LDL cholesterol (mmol/L)	2.6 ± 0.1	2.7 ± 0.1
P-AST (IU/L)	32.9 ± 1.9	31.4 ± 1.3
P-ALT (IU/L)	38.1 ± 2.4	34.6 ± 2.4
S-Transferrin (g/l)	2.5 ± 0.1	2.6 ± 0.1
S-CDT	37.5 ± 1.6	38.2 ± 1.1
%CDT	1.5 ± 0.1	1.5 ± 0.1
GGT-CDT	3.2 ± 0.1	3.4 ± 0.1
Macrovesicular steatosis (%)	5 (0 – 30)	5 (0 – 26)
Steatosis score (%; 0/1/2/3)	33/47/9/11	32/61/8/0
Activity grade (%; 0/1/2/3/4)	86/9/5/0/0	82/11/8/0/0
Ballooning (%; 0/1/2)	95/5/0	89/11/0
Inflammation (%; 0/1/2)	86/14/0	84/16/0
Fibrosis stage (%; 0/1/2/3/4)	69/27/4/0/0	61/39/0/0/0
Subjects with significant fibrosis (F ≥ 2, %)	4.2	0.0
HSD17B13 genotype (%; TT/TTA/TATA)	100/0/0	0/95/5 *
PNPLA3 genotype (%; CC/CG/GG)	56/38/6	45/50/5
TM6SF2 genotype (%; CC/CT/TT)	81/17/2	97/3/0
MBOAT7 genotype (%; CC/CT/TT)	38/54/8	33/42/25

Data are in %, means ± SEM or median (25th-75th percentile), as appropriate. \* P ≤ 0.05.

**Supplementary Table 2. Clinical characteristics of the study subjects in hepatic gene expression analysis according to the HSD17B13 genotype at rs72613567.**

	<b>TT (n=50)</b>	<b>TTA/TATA (n=36)</b>
Age (years)	45.6 ± 1.2	48.7 ± 1.5
Gender (% women)	74.5	67.6
BMI (kg/m <sup>2</sup> )	45.8 ± 0.8	45.1 ± 1.2
fP-Glucose (mmol/L)	5.8 (5.1 – 6.5)	5.7 (5.0 – 6.1)
fS-Insulin (mU/L)	14.5 (8.3 – 19.7)	12.4 (6.4 – 15.8)
fP-Triglycerides (mmol/L)	1.16 (0.91 – 1.45)	1.31 (0.98 – 1.74)
fP-HDL cholesterol (mmol/L)	1.08 (0.92 – 1.33)	1.07 (0.96 – 1.47)
fP-LDL cholesterol (mmol/L)	2.4 ± 0.1	2.7 ± 0.1
P-AST (IU/L)	34 ± 2	32 ± 1
P-ALT (IU/L)	39 ± 3	37 ± 3
Macrovesicular steatosis (%)	10 (0 – 34)	5 (0 – 25)
Steatosis score (%; 0/1/2/3)	27/48/15/10	35/59/3/3
Activity grade (%; 0/1/2/3/4)	83/11/4/2	85/6/9/0
Ballooning (%; 0/1/2)	94/6/0	88/12/0
Inflammation (%; 0/1/2)	83/15/2	88/12/0
Fibrosis stage (%; 0/1/2/3/4)	58/33/6/2/0	59/41/0/0/0
Subjects with significant fibrosis (F ≥ 2, %)	8.3	0.0
HSD17B13 genotype (%; TT/TTA/TATA)	100/0/0	0/97/3 *
PNPLA3 genotype (%; CC/CG/GG)	53/41/6	41/53/6
TM6SF2 genotype (%; CC/CT/TT)	80/18/2	97/3/0
MBOAT7 genotype (%; CC/CT/TT)	34/56/10	35/45/19

Data are in %, means ± SEM or median (25th-75th percentile), as appropriate. \* P ≤ 0.05.

**Supplementary Table 3. Clinical characteristics of the study subjects analysed with respect to hepatic *de novo* lipogenesis according to the HSD17B13 genotype at rs72613567.**

	<b>TT (n=67)</b>	<b>TTA/TATA (n=59)</b>
Age (years)	45.8 ± 0.8	46.7 ± 0.9
Gender (% women)	58.2	54.2
BMI (kg/m <sup>2</sup> )	27.8 ± 0.5	27.6 ± 0.5
<i>De novo</i> lipogenesis (%)	7.7 ± 0.8	7.5 ± 0.8
fP-Glucose (mmol/L)	5.3 ± 0.1	5.3 ± 0.1
fP-Insulin (mU/L)	14.0 ± 1.0	12.8 ± 0.9
fP-Triglycerides (mmol/L)	1.3 ± 0.1	1.3 ± 0.1
fP-HDL cholesterol (mmol/L)	1.32 ± 0.05	1.35 ± 0.05
fP-non-HDL cholesterol (mmol/L)	3.8 ± 0.1	3.7 ± 0.1
IHTG (% <sup>1</sup> , <sup>1</sup> H-MRS)	5.3 ± 0.9	5.1 ± 0.8
HSD17B13 genotype (%TT/TTA/TATA)	100/0/0	0/80/20 *

Data are in %, means ± SEM or median (25th-75th percentile), as appropriate. \* P ≤ 0.05.

**Supplementary Table 4. Clinical characteristics of the study subjects analyzed with respect to adipose tissue lipolysis according to the HSD17B13 genotype at rs72613567.**

	<b>TT (n=40)</b>	<b>TTA/TATA (n=12)</b>
Age (years)	46 (40 – 59)	47 (42 – 59)
Gender (% women)	61	50
BMI (kg/m <sup>2</sup> )	30.1 ± 0.9	32.3 ± 2.1
fP-Glucose (mmol/L)	5.5 (5.1 – 6.0)	6.0 (5.4 – 6.3)
fS-Insulin (mU/L)	8.1 (5.7 – 13.9)	9.4 (6.4 – 14.3)
fP-Triglycerides (mmol/L)	1.02 (0.74 – 1.41)	1.53 (1.09 – 2.60)
fP-HDL cholesterol (mmol/L)	1.49 (1.25 – 1.87)	1.26 (1.10 – 1.46)
fP-LDL cholesterol (mmol/L)	3.2 (2.4 – 3.7)	3.8 (2.9 – 4.4)
P-AST (IU/L)	29 (24 – 33)	28 (20 – 38)
P-ALT (IU/L)	31 (21 – 44)	25 (14 – 52)
IHTG (% <sup>1</sup> H-MRS)	4.9 (0.8 – 12.7)	4.7 (3.5 – 12.3)
HSD17B13 genotype (%TT/TTA/TATA)	100/0/0	0/100/0 *
PNPLA3 genotype (%CC/CG/GG)	53/28/20	67/17/17
TM6SF2 genotype (%CC/CT/TT)	87/13/0	92/8/0
MBOAT7 genotype (%CC/CT/TT)	58/25/18	33/50/17

Data are in %, means ± SEM or median (25th-75th percentile), as appropriate. \* P ≤ 0.05.



**Supplementary Table 5. Clinical characteristics of the study subjects analysed with respect to hepatic glucose production and insulin sensitivity according to the HSD17B13 genotype at rs72613567.**

	<b>TT (n=62)</b>	<b>TTA/TATA (n=43)</b>
Age (years)	47.2 ± 1.3	47.9 ± 1.4
Gender (% women)	30.6	34.9
BMI (kg/m <sup>2</sup> )	28.6 ± 0.7	28.9 ± 0.8
fP-Glucose (mmol/L)	6.1 (5.5 – 8.4)	6.1 (5.6 – 8.9)
fS-Insulin (mU/L)	7.7 (5.0 – 14.3)	8.0 (5.0 – 12.5)
fP-Triglycerides (mmol/L)	1.46 (0.99 – 2.12)	1.38 (0.98 – 1.96)
fP-HDL cholesterol (mmol/L)	1.16 (1.04 – 1.45)	1.25 (1.04 – 1.53)
fP-LDL cholesterol (mmol/L)	2.9 ± 0.1	2.9 ± 0.1
P-AST (IU/L)	29 (24 – 37)	30 (25 – 46)
P-ALT (IU/L)	34 (21 – 49)	30 (23 – 49)
IHTG (% , <sup>1</sup> H-MRS)	7.8 (2.0 – 15.0)	7.0 (2.0 – 20.0)
HSD17B13 genotype (% , TT/TTA/TATA)	100/0/0	0/98/2 *
PNPLA3 genotype (% , CC/CG/GG)	61/32/6	53/42/5
TM6SF2 genotype (% , CC/CT/TT)	85/13/2	81/19/0
MBOAT7 genotype (% , CC/CT/TT)	37/44/19	40/47/14

Data are in %, means ± SEM or median (25th-75th percentile), as appropriate. \* P ≤ 0.05.

**Supplementary Table 6. Differentially expressed downregulated genes in carriers as compared to non-carriers of the HSD17B13 variant.**

Ensembl code	Gene name	logFC	qvalue
ENSG00000010818	HIVEP2	-0.255550480439627	0.00152657039895355
ENSG00000163565	IFI16	-0.376947817480197	0.00443228976469933
ENSG00000040199	PHLPP2	-0.305141389215604	0.0102064746368355
ENSG00000079387	SENP1	-0.203802034434882	0.0102064746368355
ENSG00000171467	ZNF318	-0.134392784158793	0.0131092727491285
ENSG00000153071	DAB2	-0.246470156981414	0.0131092727491285
ENSG00000136531	SCN2A	-0.790606241183511	0.0139838258805939
ENSG00000134954	ETS1	-0.235216957417972	0.014223234786406
ENSG00000178996	SNX18	-0.204356302552036	0.0145819625963922
ENSG00000038427	VCAN	-0.61554828791713	0.014758199178601
ENSG00000110395	CBL	-0.245627828137411	0.014758199178601
ENSG00000111716	LDHB	-0.214617520697295	0.014758199178601
ENSG00000070961	ATP2B1	-0.175472838207055	0.0176340337081435
ENSG00000106723	SPIN1	-0.12042925905762	0.0189143519731582
ENSG00000156675	RAB11FIP1	-0.221591760520282	0.0189143519731582
ENSG00000254087	LYN	-0.213254285012606	0.0189143519731582
ENSG00000091527	CDV3	-0.157587153199036	0.0189143519731582
ENSG00000100644	HIF1A	-0.166029060108027	0.0189143519731582
ENSG00000184384	MAML2	-0.273044575447134	0.0189143519731582
ENSG00000168615	ADAM9	-0.278675432236274	0.0189143519731582
ENSG00000148358	GPR107	-0.108238603404056	0.0189143519731582
ENSG00000269982	AC018809.2	-0.287894559941275	0.0189143519731582
ENSG00000008086	CDKL5	-0.225905330215992	0.0189143519731582
ENSG00000185753	CXorf38	-0.132922669398628	0.0189143519731582
ENSG00000143322	ABL2	-0.170189562258144	0.0189143519731582
ENSG00000012779	ALOX5	-0.407014430138333	0.0189143519731582
ENSG00000179051	RCC2	-0.223208046591564	0.0189143519731582
ENSG00000064651	SLC12A2	-0.299243544583792	0.0189143519731582
ENSG00000148158	SNX30	-0.166327572905649	0.0190669599352241
ENSG00000167703	SLC43A2	-0.368872262390875	0.0212087074410607
ENSG00000010671	BTK	-0.331119469205026	0.0214252855477724
ENSG00000104067	TJP1	-0.205497441748077	0.0214448525685946
ENSG00000187474	FPR3	-0.373738153428052	0.0271844227602903
ENSG00000095015	MAP3K1	-0.152993525859782	0.0278161001862596
ENSG00000140575	IQGAP1	-0.223777007538627	0.0278161001862596
ENSG00000171608	PIK3CD	-0.319975128367266	0.0278161001862596
ENSG00000064989	CALCRL	-0.244038740948373	0.0278161001862596
ENSG00000081237	PTPRC	-0.371832588085112	0.0294025343262216
ENSG00000169860	P2RY1	-0.253143556165753	0.0294025343262216
ENSG00000133059	DSTYK	-0.168387601193684	0.0312774488085245
ENSG00000109320	NFKB1	-0.104893316380332	0.0312974819916256

ENSG00000175356	SCUBE2	-0.60869302245801	0.0315524098170711
ENSG00000164576	SAP30L	-0.155936156599938	0.0327120380954181
ENSG00000090339	ICAM1	-0.323509125014729	0.0327120380954181
ENSG00000176390	CRLF3	-0.158860267007592	0.0330635845650014
ENSG00000083720	OXCT1	-0.333477781101549	0.0350537411657173
ENSG00000117528	ABCD3	-0.196406732199355	0.0350537411657173
ENSG00000136167	LCP1	-0.264752043349293	0.0350537411657173
ENSG00000099250	NRP1	-0.19594884187057	0.0350537411657173
ENSG00000065613	SLK	-0.125630402667988	0.0350537411657173
ENSG00000255197	AC090559.1	-0.411833997271112	0.0350537411657173
ENSG00000131323	TRAF3	-0.164757558048427	0.0350537411657173
ENSG00000110851	PRDM4	-0.121202414865969	0.0350537411657173
ENSG00000088367	EPB41L1	-0.701688782462438	0.0350537411657173
ENSG00000186517	ARHGAP30	-0.28560613965291	0.0350537411657173
ENSG00000172936	MYD88	-0.147555109576653	0.0350537411657173
ENSG00000170832	USP32	-0.152812245700867	0.0350537411657173
ENSG00000241839	PLEKHO2	-0.256934385900962	0.0350537411657173
ENSG00000147394	ZNF185	-0.336497922410945	0.0350537411657173
ENSG00000139946	PELI2	-0.263311276509494	0.0350537411657173
ENSG00000231205	ZNF826P	-0.418321072267426	0.0350537411657173
ENSG00000123338	NCKAP1L	-0.293707268316214	0.0350537411657173
ENSG00000149781	FERMT3	-0.224636376511501	0.0350537411657173
ENSG00000104856	RELB	-0.327379725822036	0.0350537411657173
ENSG00000143157	POGK	-0.125120000013575	0.0350537411657173
ENSG00000169118	CSNK1G1	-0.156957562928147	0.0350537411657173
ENSG00000164151	ICE1	-0.102622909539915	0.0351700622313922
ENSG00000143970	ASXL2	-0.182605503519094	0.0351700622313922
ENSG00000023445	BIRC3	-0.333903647301945	0.0351700622313922
ENSG00000128052	KDR	-0.328005671685864	0.0351700622313922
ENSG00000070018	LRP6	-0.282845941807	0.0351700622313922
ENSG00000164741	DLC1	-0.19918824378897	0.0351700622313922
ENSG00000163131	CTSS	-0.271339328968853	0.0351700622313922
ENSG00000120733	KDM3B	-0.0868785879794268	0.0351700622313922
ENSG00000097033	SH3GLB1	-0.106047938903209	0.0351700622313922
ENSG00000110925	CSRNP2	-0.154774146665981	0.0351700622313922
ENSG00000163947	ARHGEF3	-0.254119914692815	0.0351700622313922
ENSG00000115935	WIPF1	-0.244979675332425	0.0351700622313922
ENSG00000148498	PARD3	-0.092550771581415	0.0351700622313922
ENSG00000171475	WIPF2	-0.111833391310852	0.0351700622313922
ENSG00000123836	PFKFB2	-0.165194825870349	0.0361534250258057
ENSG00000130559	CAMSAP1	-0.161342936226375	0.0362198275167072
ENSG00000198589	LRBA	-0.131161180524386	0.0362198275167072
ENSG00000204592	HLA-E	-0.216691804631671	0.0362198275167072
ENSG00000135363	LMO2	-0.222546222353332	0.0362198275167072
ENSG00000155465	SLC7A7	-0.287422462937868	0.0362198275167072

ENSG00000132640	BTBD3	-0.150287728579633	0.0362198275167072
ENSG00000103994	ZNF106	-0.137417567976229	0.0362198275167072
ENSG00000164830	OXR1	-0.166996593462062	0.0362198275167072
ENSG00000197548	ATG7	-0.103718971312444	0.0362198275167072
ENSG00000110002	VWA5A	-0.222363309456902	0.0366528463261233
ENSG00000169641	LUZP1	-0.160454444612298	0.0366528463261233
ENSG00000026508	CD44	-0.296257876920367	0.0366528463261233
ENSG00000151491	EPS8	-0.107330749844554	0.0366528463261233
ENSG00000119314	PTBP3	-0.139711200248953	0.0366528463261233
ENSG00000113532	ST8SIA4	-0.38314182802853	0.0369966425563031
ENSG00000119772	DNMT3A	-0.156410736129803	0.0371883854080159
ENSG00000163823	CCR1	-0.427349380148316	0.0377030608608754
ENSG00000168214	RBPJ	-0.0774058611595499	0.0377030608608754
ENSG00000100368	CSF2RB	-0.416415972073712	0.0378522581170552
ENSG00000136193	SCRN1	-0.174990003912419	0.0378522581170552
ENSG00000106078	COBL	-0.133985018378513	0.0378522581170552
ENSG00000159216	RUNX1	-0.274158751581859	0.0378522581170552
ENSG00000135905	DOCK10	-0.252841818600033	0.0378522581170552
ENSG00000070190	DAPP1	-0.382570400098862	0.0383663648909273
ENSG00000110514	MADD	-0.119089128891589	0.0383663648909273
ENSG00000108960	MMD	-0.252160028386511	0.0383663648909273
ENSG00000101052	IFT52	-0.163569631827382	0.0383663648909273
ENSG00000065615	CYB5R4	-0.148063739927631	0.0384726399577028
ENSG00000145779	TNFAIP8	-0.247094373955632	0.0384726399577028
ENSG00000166068	SPRED1	-0.169300433102229	0.0384726399577028
ENSG00000159267	HLCS	-0.126193566621713	0.0385838704991444
ENSG00000163848	ZNF148	-0.118232014958586	0.03929344189352
ENSG00000092969	TGFB2	-0.430592304621376	0.03929344189352
ENSG00000171791	BCL2	-0.203694616002049	0.0400720894326787
ENSG00000101350	KIF3B	-0.115456211150512	0.0400720894326787
ENSG00000158985	CDC42SE2	-0.105482289087639	0.0400720894326787
ENSG00000182240	BACE2	-0.2528790925463	0.0400720894326787
ENSG00000116641	DOCK7	-0.150235035920572	0.0419854573635515
ENSG00000160255	ITGB2	-0.261852117283093	0.0419854573635515
ENSG00000164125	FAM198B	-0.301251651122039	0.0428083592647208
ENSG00000141968	VAV1	-0.302740693322703	0.0428083592647208
ENSG00000162511	LAPTM5	-0.253764645028454	0.0428083592647208
ENSG00000110422	HIPK3	-0.14029553604633	0.0428083592647208
ENSG00000228223	HCG11	-0.274338270884442	0.0428132884513263
ENSG00000165025	SYK	-0.27499994618794	0.0428903554415591
ENSG00000115159	GPD2	-0.151638959494685	0.0432882526689161
ENSG00000100596	SPTLC2	-0.135381971028265	0.0434344810265111
ENSG00000168394	TAP1	-0.205461400585199	0.0434344810265111
ENSG00000163513	TGFBR2	-0.158479842130195	0.0434344810265111
ENSG00000163219	ARHGAP25	-0.239873590034995	0.0434344810265111

ENSG00000143119	CD53	-0.259035330790863	0.0434344810265111
ENSG00000137845	ADAM10	-0.110390536039693	0.0435234818157893
ENSG00000168743	NPNT	-0.418560695299943	0.0435234818157893
ENSG00000038945	MSR1	-0.35425233029151	0.0437324308775064
ENSG00000113300	CNOT6	-0.120030746249939	0.0438558835507789
ENSG00000123739	PLA2G12A	-0.117196942896365	0.0440994687682717
ENSG00000116701	NCF2	-0.414596028759862	0.0441164462449184
ENSG00000085265	FCN1	-0.578619336336452	0.0446630895049579
ENSG00000144369	FAM171B	-0.358975220374996	0.0446630895049579
ENSG00000188419	CHM	-0.141941200338088	0.0454052725392483
ENSG00000184922	FMNL1	-0.281207688506106	0.0454826850442338
ENSG00000151702	FLI1	-0.175359449046143	0.0454826850442338
ENSG00000100731	PCNX1	-0.127800207402709	0.0454826850442338
ENSG00000151414	NEK7	-0.10805436850761	0.0454826850442338
ENSG00000145626	UGT3A1	-0.307668024015328	0.0454826850442338
ENSG00000143079	CTTNBP2NL	-0.171049435472015	0.0454826850442338
ENSG00000178695	KCTD12	-0.21694016565592	0.0454826850442338
ENSG00000146112	PPP1R18	-0.251145381301286	0.0454826850442338
ENSG00000175414	ARL10	-0.197608094683164	0.0454826850442338
ENSG00000009954	BAZ1B	-0.113492539944126	0.0454826850442338
ENSG00000135220	UGT2A3	-0.300895481042515	0.0454826850442338
ENSG00000154945	ANKRD40	-0.0966280983566202	0.0454826850442338
ENSG00000177485	ZBTB33	-0.175765424784998	0.0454826850442338
ENSG00000043143	JADE2	-0.167598586054375	0.0454826850442338
ENSG00000091972	CD200	-0.412489804065753	0.0455212645031174
ENSG00000170456	DENND5B	-0.143308781036254	0.0460078342800034
ENSG00000198663	C6orf89	-0.0870627585715997	0.0460078342800034
ENSG00000072736	NFATC3	-0.183175070175093	0.0463248491133958
ENSG00000102007	PLP2	-0.26248150884876	0.0467793841524275
ENSG00000185924	RTN4RL1	-0.393346612999671	0.0470031931979687
ENSG00000186174	BCL9L	-0.202718482402855	0.0475719846201044
ENSG00000092847	AGO1	-0.101932441229664	0.0484071853853374
ENSG00000066777	ARFGEF1	-0.100282656284485	0.0486349977256501
ENSG00000140749	IGSF6	-0.318612729986044	0.0496363508635229
ENSG00000188641	DPYD	-0.161128452813073	0.0496661016770657

**Supplementary Table 7. Differentially expressed upregulated genes in carriers as compared to non-carriers of the HSD17B13 variant.**

Ensembl code	Gene name	logFC	qvalue
ENSG00000140474	ULK3	0.252562706980281	0.000253437091504798
ENSG00000114735	HEMK1	0.203382625328999	0.00789603390908803
ENSG00000156463	SH3RF2	0.331416743848355	0.0114655045628418
ENSG00000077312	SNRPA	0.19879719686848	0.0114655045628418
ENSG00000132793	LPIN3	0.286309861310801	0.0139838258805939
ENSG00000117640	MTFR1L	0.0974928947129594	0.0139838258805939
ENSG00000130202	NECTIN2	0.254452140861227	0.0139838258805939
ENSG00000169696	ASPSCR1	0.217774554618623	0.0139838258805939
ENSG00000250328	MGC32805	0.324932230670449	0.0170567404398434
ENSG00000010318	PHF7	0.195413181567635	0.0189143519731582
ENSG00000213533	STIMATE	0.197299502533252	0.0189143519731582
ENSG00000164896	FASTK	0.149087510942694	0.0189143519731582
ENSG00000106400	ZNHIT1	0.144627410887437	0.0189143519731582
ENSG00000009950	MLXIPL	0.171843430639575	0.0189143519731582
ENSG00000117360	PRPF3	0.155520794570807	0.0189143519731582
ENSG00000122912	SLC25A16	0.128169577329682	0.0189143519731582
ENSG00000111077	TNS2	0.19000184084079	0.0189143519731582
ENSG00000277972	CISD3	0.13249007745208	0.0303057484535379
ENSG00000270605	AL353622.1	0.356951355154053	0.0323058188989331
ENSG00000183401	CCDC159	0.177107986621613	0.0324516634107035
ENSG00000108591	DRG2	0.192430668401204	0.0327120380954181
ENSG00000232445	AC006329.1	0.57225672845516	0.0350537411657173
ENSG00000021461	CYP3A43	0.452931131252008	0.0350537411657173
ENSG00000128654	MTX2	0.122285529233212	0.0350537411657173
ENSG00000146063	TRIM41	0.0977659253994785	0.0350537411657173
ENSG00000127527	EPS15L1	0.115520019484952	0.0350537411657173
ENSG00000131051	RBM39	0.109876377216928	0.0350537411657173
ENSG00000159377	PSMB4	0.12541657661305	0.0350537411657173
ENSG00000182796	TMEM198B	0.153908104993998	0.0350537411657173
ENSG00000101194	SLC17A9	0.217843556247413	0.0350537411657173
ENSG00000131778	CHD1L	0.222606667684858	0.0350537411657173
ENSG00000171163	ZNF692	0.148180290357041	0.0350537411657173
ENSG00000189007	ADAT2	0.179893751785141	0.0351700622313922
ENSG00000100399	CHADL	0.275943491559015	0.0351700622313922
ENSG00000010244	ZNF207	0.082836926825284	0.0351700622313922
ENSG00000184925	LCN12	0.23513604947043	0.0351700622313922
ENSG00000281344	HELLPAR	0.469805872149946	0.0351700622313922
ENSG00000115942	ORC2	0.211004499108229	0.0351700622313922
ENSG00000261061	AC092718.4	0.298773442260907	0.0351700622313922
ENSG00000186815	TPCN1	0.127181889816476	0.0351700622313922
ENSG00000169045	HNRNPH1	0.128499599265436	0.0351700622313922

ENSG00000266850	AC090912.2	0.273784314994292	0.0351700622313922
ENSG00000165995	CACNB2	0.277158731945274	0.0351700622313922
ENSG00000169903	TM4SF4	0.202826976796006	0.0352934601842154
ENSG00000025772	TOMM34	0.133333747972885	0.0362198275167072
ENSG00000041880	PARP3	0.112874213936489	0.0362198275167072
ENSG00000158473	CD1D	0.204462272875883	0.0362198275167072
ENSG00000259877	AC009113.1	0.171219248553653	0.0366528463261233
ENSG00000124839	RAB17	0.146283788011743	0.0366528463261233
ENSG00000153823	PID1	0.26736561333562	0.0366528463261233
ENSG00000268218	AC137932.3	0.327482000838927	0.0384726399577028
ENSG00000123374	CDK2	0.144954900393777	0.0384726399577028
ENSG00000234072	AC074117.1	0.156090943008878	0.0384726399577028
ENSG00000140398	NEIL1	0.134143065873963	0.0384726399577028
ENSG00000175866	BAIAP2	0.165320973226793	0.0384726399577028
ENSG00000106367	AP1S1	0.141003757149189	0.0384726399577028
ENSG00000163795	ZNF513	0.170813390763859	0.03929344189352
ENSG00000279716	AC006128.1	0.219836862017956	0.03929344189352
ENSG00000204149	AGAP6	0.221315292270943	0.03929344189352
ENSG00000205981	DNAJC19	0.107629620528967	0.03929344189352
ENSG00000163170	BOLA3	0.201464631503846	0.039877758307109
ENSG00000159199	ATP5MC1	0.144934349181368	0.0400720894326787
ENSG00000169223	LMAN2	0.132655494761782	0.0400720894326787
ENSG00000115718	PROC	0.112871998045887	0.0400720894326787
ENSG00000231609	AC007098.1	0.342103799979881	0.0400720894326787
ENSG00000132329	RAMP1	0.406111594229444	0.0420210522137169
ENSG00000273901	AC012313.9	0.248031199716779	0.0420210522137169
ENSG00000177542	SLC25A22	0.204301692154657	0.0425273546596481
ENSG00000100445	SDR39U1	0.169013845017425	0.0425273546596481
ENSG00000130254	SAFB2	0.101543350129275	0.0428083592647208
ENSG00000132275	RRP8	0.11887086265706	0.0428132884513263
ENSG00000104872	PIH1D1	0.106294678245532	0.0433397239933552
ENSG00000158882	TOMM40L	0.149738489623893	0.0433594741415914
ENSG00000123353	ORMDL2	0.165318838076669	0.0433594741415914
ENSG00000198171	DDRGK1	0.11179338641767	0.0434344810265111
ENSG00000088386	SLC15A1	0.218141121530868	0.0434344810265111
ENSG00000204576	PRR3	0.22501556452472	0.0437324308775064
ENSG00000177595	PIDD1	0.157695339960051	0.0440412424603926
ENSG00000203993	ARRDC1-AS1	0.16265163469406	0.0446630895049579
ENSG00000165471	MBL2	0.618953177032195	0.0446939540893016
ENSG00000132522	GPS2	0.19362601124249	0.0446939540893016
ENSG00000134809	TIMM10	0.218904765472307	0.0454826850442338
ENSG00000003756	RBM5	0.0917304580823693	0.0454826850442338
ENSG00000104852	SNRNP70	0.122259445860635	0.0454826850442338
ENSG00000110200	ANAPC15	0.169327451240927	0.0454826850442338
ENSG00000237149	ZNF503-AS2	0.220062087129183	0.0454826850442338

ENSG00000170271	FAXDC2	0.15449851099097	0.0454826850442338
ENSG00000215021	PHB2	0.108410194489328	0.0454826850442338
ENSG00000242265	PEG10	0.792224982648411	0.0454826850442338
ENSG00000104267	CA2	0.207713894332215	0.0454826850442338
ENSG00000129562	DAD1	0.140181939057752	0.0454826850442338
ENSG00000132507	EIF5A	0.140446150033658	0.0454826850442338
ENSG00000168397	ATG4B	0.130619387032191	0.0454826850442338
ENSG00000226699	AL360181.1	0.293527205732095	0.0454826850442338
ENSG00000162384	C1orf123	0.103200085285256	0.0454826850442338
ENSG00000103168	TAF1C	0.148365109453756	0.0467793841524275
ENSG00000095906	NUBP2	0.111902051719444	0.0467793841524275
ENSG00000179262	RAD23A	0.0993766041444736	0.0470710188796933
ENSG00000161526	SAP30BP	0.0892438978768329	0.0478558585704698
ENSG00000132716	DCAF8	0.0963598068828793	0.0480316506696637
ENSG00000074964	ARHGEF10L	0.159751367107678	0.0481683162637621
ENSG00000004534	RBM6	0.168714636463194	0.0489038268892948
ENSG00000228923	AP000355.1	0.296894259946723	0.0491766183892852
ENSG00000119705	SLIRP	0.14278553515333	0.0495983104621031
ENSG00000104859	CLASRP	0.126627401285138	0.0496363508635229
ENSG00000099840	IZUMO4	0.244458271387156	0.049862241465128
ENSG00000132394	EEFSEC	0.0897760641719469	0.049862241465128
ENSG00000204653	ASPDH	0.166888747652526	0.049862241465128



**Supplementary Table 8. Downregulated Gene Ontology pathways in carriers as compared to non-carriers of the HSD17B13 variant.**

<b>Description</b>	<b>geneID</b>	<b>Count</b>	<b>qvalue</b>
GO ACTIVATION OF IMMUNE RESPONSE	IFI16/LYN/BTK/MAP3K1/PIK3CD/PTPRC/NFKB1/TRAF3/MYD88/NCKAP1L/RELB/BIRC3/CTSS/WIPF1/WIPF2/BCL2/ITGB2/VAV1/SYK/FCN1	20	2.16390504864883e-06
GO POSITIVE REGULATION OF INNATE IMMUNE RESPONSE	IFI16/LYN/BTK/MAP3K1/NFKB1/TRAF3/MYD88/RELB/BIRC3/CTSS/HLA-E/ITGB2/VAV1/SYK/FCN1	15	4.66174538075426e-06
GO ACTIVATION OF INNATE IMMUNE RESPONSE	IFI16/LYN/BTK/MAP3K1/NFKB1/TRAF3/MYD88/RELB/BIRC3/CTSS/ITGB2/SYK/FCN1	13	1.60899007283795e-05
GO POSITIVE REGULATION OF LOCOMOTION	DAB2/ETS1/LYN/HIF1A/ADAM9/PIK3CD/PTPRC/ICAM1/NRP1/NCKAP1L/FERMT3/KDR/CCR1/TGFB2/BCL2/DOCK7/TGFBR2/ADAM10	18	1.60899007283795e-05
GO RAC GTPASE BINDING	CDKL5/RCC2/IQGAP1/EPS8/DOCK7/NCF2/FMNL1	7	1.71458245508568e-05
GO REGULATION OF INNATE IMMUNE RESPONSE	IFI16/LYN/BTK/MAP3K1/NFKB1/TRAF3/MYD88/RELB/BIRC3/CTSS/HLA-E/ITGB2/VAV1/SYK/TAP1/FCN1	16	3.48954286405353e-05
GO POSITIVE REGULATION OF DEFENSE RESPONSE	IFI16/ETS1/LYN/BTK/MAP3K1/NFKB1/TRAF3/MYD88/RELB/BIRC3/CTSS/HLA-E/ITGB2/VAV1/SYK/FCN1	16	3.89574703102597e-05
GO IMMUNE RESPONSE REGULATING CELL SURFACE RECEPTOR SIGNALING PATHWAY	LYN/BTK/MAP3K1/PIK3CD/PTPRC/NFKB1/NCKAP1L/RELB/WIPF1/WIPF2/BCL2/VAV1/SYK/FCN1/NFATC3	15	4.10062151581436e-05

GO MEMBRANE MICRODOMAIN	CBL/LDHB/ATP2B1/LYN/BTK/PTPRC/ICAM1/BIRC3/KDR/LRP6/DLC1/SPRED1/TGFBR2/RTN4RL1	14	5.54146574580176e-05
GO REGULATION OF CELL SHAPE	ICAM1/CSNK1G1/KDR/DLC1/WIPF1/WIPF2/EPS8/CDC42SE2/ITGB2/FMNL1	10	7.37178735919572e-05
GO RHO GTPASE BINDING	CDKL5/RCC2/IQGAP1/EPS8/KIF3B/DOCK7/NCF2/FMNL1	8	7.37178735919572e-05
GO B CELL RECEPTOR SIGNALING PATHWAY	LYN/BTK/PIK3CD/PTPRC/NCKAP1L/BCL2/SYK	7	7.37178735919572e-05
GO INTEGRIN MEDIATED SIGNALING PATHWAY	DAB2/ADAM9/RCC2/FERMT3/ITGB2/VAV1/SYK/ADAM10	8	9.33416630044616e-05
GO LEUKOCYTE ACTIVATION	LYN/ADAM9/BTK/PIK3CD/PTPRC/ICAM1/LCP1/RELB/HLA-E/RBPJ/BCL2/ITGB2/VAV1/SYK/TGFBR2/ADAM10	16	0.000112498324223003
GO REGULATION OF CELL ADHESION MEDIATED BY INTEGRIN	LYN/ADAM9/NCKAP1L/FERMT3/TGFB2/SYK	6	0.000143726371515479
GO SIDE OF MEMBRANE	SNX18/ATP2B1/LYN/ADAM9/ABL2/BTK/IQGAP1/PTPRC/ICAM1/TRAFF3/HLA-E/CCR1/SYK/TGFBR2/FCN1/RTN4RL1	16	0.000147479978911267
GO MYELOID LEUKOCYTE ACTIVATION	LYN/ADAM9/PIK3CD/RELB/RBPJ/SYK/TGFBR2/ADAM10	8	0.000302511799291137
GO LEUKOCYTE CELL CELL ADHESION	PIK3CD/PTPRC/ICAM1/LCP1/FERMT3/RELB/HLA-E/CD44/BCL2/ITGB2/VAV1/SYK	12	0.000303852229755125
GO LEUKOCYTE MIGRATION	LYN/PIK3CD/ICAM1/NCKAP1L/SLC7A7/CD44/EPS8/CCR1/TGFBR2/ITGB2/VAV1/SYK	12	0.000351545051677081

GO CELLULAR RESPONSE TO EXTERNAL STIMULUS	IFI16/ATP2B1/LYN/HIF1A/MAP3K1/NFKB1/ICAM1/PRDM4/MYD88/SH3GLB1/ATG7/BCL2	12	0.0003905 73558792 179
GO INTEGRIN BINDING	LYN/ADAM9/ICAM1/FERMT3/KDR/SYK/ADAM10/NPNT	8	0.0004097 23799295 624
GO PATTERN RECOGNITION RECEPTOR SIGNALING PATHWAY	BTK/MAP3K1/TRAF3/MYD88/BIRC3/CTSS/ITGB2/FCN1	8	0.0005159 11111255 387
GO CELL ADHESION MOLECULE BINDING	LYN/ADAM9/ICAM1/FERMT3/KDR/ITGB2/SYK/ADAM10/NPNT /CD200	10	0.0005262 17401501 241
GO ANCHORIN G JUNCTION	SENP1/DAB2/LYN/ADAM9/TJP1/IQGAP1/PTPRC/ICAM1/LCP1/NRP1/ZNF185/DLC1/CD44/DOCK7/ADAM10/CD200	16	0.0005283 52691765 687
GO TOLL LIKE RECEPTOR SIGNALING PATHWAY	BTK/MAP3K1/TRAF3/MYD88/BIRC3/CTSS/ITGB2	7	0.0008500 30629317 677
GO POSITIVE REGULATION OF CELL ADHESION MEDIATED BY INTEGRIN	ADAM9/NCKAP1L/TGFB2/SYK	4	0.0009693 96802216 487
GO SINGLE ORGANISM CELL ADHESION	ADAM9/PIK3CD/PTPRC/ICAM1/LCP1/FERMT3/RELB/LRP6/HLA-E/CD44/BCL2/ITGB2/VAV1/SYK/NPNT	15	0.0009693 96802216 487
GO FC RECEPTOR SIGNALING PATHWAY	LYN/BTK/MAP3K1/NFKB1/NCKAP1L/WIPF1/WIPF2/VAV1/SYK /NFATC3	10	0.0010006 44101144 68
GO CORTICAL CYTOSKELETON ORGANIZATION	EPB41L1/NCKAP1L/WIPF1/WIPF2/FMNL1	5	0.0010006 44101144 68

GO REGULATI ON OF ERYTHROC YTE DIFFERENT IATION	SENP1/ETS1/LYN/HIF1A/NCKAP1L	5	0.0010006 44101144 68
GO REGULATI ON OF CELL KILLING	PTPRC/ICAM1/HLA-E/TGFB2/VAV1/TAP1	6	0.0012186 42246319 99
GO PEPTIDYL TYROSINE AUTOPHOS PHORYLATI ON	LYN/ABL2/BTK/KDR/SYK	5	0.0014027 70817203 48
GO IMMUNE EFFECTOR PROCESS	IFI16/LYN/PIK3CD/PTPRC/ICAM1/LCP1/NCKAP1L/RELB/WIPF 1/WIPF2/ATG7/BCL2/VAV1/SYK/FCN1	15	0.0014631 45383380 07
GO PLASMA MEMBRAN E RECEPTOR COMPLEX	DAB2/LYN/TRAF3/EPS8/CSF2RB/ITGB2/SYK/TGFBR2/NPNT	9	0.0014631 45383380 07
GO PROTEIN TYROSINE KINASE ACTIVITY	LYN/ABL2/BTK/DSTYK/NRP1/KDR/CSF2RB/SYK/BAZ1B	9	0.0014631 45383380 07
GO POSITIVE REGULATI ON OF CELL ADHESION	ETS1/LYN/ADAM9/PTPRC/NCKAP1L/KDR/HLA- E/CD44/TGFB2/VAV1/SYK/TGFBR2/NPNT	13	0.0016325 63824442 47
GO B CELL HOMEOSTA SIS	LYN/HIF1A/NCKAP1L/BCL2	4	0.0016758 40856549 1
GO RECEPTOR COMPLEX	DAB2/LYN/NRP1/TRAF3/LRP6/CD44/EPS8/CSF2RB/ITGB2/SYK/ TGFBR2/NPNT	12	0.0017439 28548549 47
GO POSITIVE REGULATI ON OF EPITHELIA L CELL MIGRATIO N	ETS1/HIF1A/ADAM9/NRP1/KDR/TGFB2/TGFBR2	7	0.0017753 24157770 94

GO MYELOID CELL DIFFERENTIATION	IFI16/LYN/PIK3CD/NCKAP1L/RELB/RBPJ/RUNX1/TGFBR2/FLI1	9	0.0022408 26165480 76
GO INFLAMMATORY RESPONSE	IFI16/LYN/HIF1A/ALOX5/PIK3CD/NFKB1/ICAM1/MYD88/RELB/CCR1/RBPJ/ITGB2/SYK/NFATC3	14	0.0023236 91443458 57
GO CELL SUBSTRATE JUNCTION	SENP1/DAB2/ADAM9/IQGAP1/PTPRC/ICAM1/LCP1/NRP1/ZNF185/DLC1/CD44/DOCK7/ADAM10	13	0.0023236 91443458 57
GO NON MEMBRANE SPANNING PROTEIN TYROSINE KINASE ACTIVITY	LYN/ABL2/BTK/SYK/BAZ1B	5	0.0023236 91443458 57
GO LYMPHOCYTE ACTIVATION	BTK/PIK3CD/PTPRC/ICAM1/LCP1/RELB/HLA-E/RBPJ/BCL2/ITGB2/VAV1/SYK	12	0.0023236 91443458 57
GO REGULATION OF ERK1 AND ERK2 CASCADE	LYN/P2RY1/DSTYK/ICAM1/NRP1/KDR/CD44/CCR1/SYK/NPNT	10	0.0023236 91443458 57
GO MORPHOGENESIS OF AN EPITHELIUM	HIF1A/LCP1/NRP1/LRP6/DLC1/LUZP1/RBPJ/COBL/IFT52/TGFB2/BCL2/TGFBR2/NPNT	13	0.0023469 04399913 36
GO GRANULOCYTE MIGRATION	PIK3CD/NCKAP1L/TGFB2/ITGB2/VAV1/SYK	6	0.0025056 36293844
GO GTPASE BINDING	RAB11FIP1/CDKL5/RCC2/IQGAP1/LCP1/EPS8/KIF3B/DOCK7/NCF2/CHM/FMNL1	11	0.0025056 36293844
GO POSITIVE REGULATION OF RESPONSE TO EXTRACELLULAR STIMULUS	HIF1A/KDR/SH3GLB1/ATG7/SPTLC2	5	0.0025573 83600803 99

GO REGULATI ON OF LEUKOCYT E MEDIATED IMMUNITY	LYN/BTK/PTPRC/ICAM1/HLA-E/VAV1/SYK/TAP1	8	0.0028276 47850525 05
GO POSITIVE REGULATI ON OF MAPK CASCADE	ADAM9/MAP3K1/P2RY1/DSTYK/ICAM1/NRP1/PELI2/KDR/CD4 4/CCR1/MADD/TGFB2/SYK/NPNT	14	0.0028276 47850525 05
GO RESPONSE TO GROWTH FACTOR	CBL/ADAM9/IQGAP1/P2RY1/DSTYK/NFKB1/NRP1/PRDM4/KD R/PARD3/CD44/SPRED1/TGFB2/TGFBR2	14	0.0030340 69914609 16
GO EXTRINSIC COMPONEN T OF MEMBRAN E	SNX18/LYN/ABL2/SNX30/BTK/IQGAP1/PIK3CD/EPB41L1/SYK/ FCN1	10	0.0030661 97317839 01
GO CELL MATRIX ADHESION	ADAM9/RCC2/DLC1/CD44/BCL2/ITGB2/NPNT	7	0.0031682 06136368 83
GO LEUKOCYT E CHEMOTAX IS	PIK3CD/NCKAP1L/CCR1/TGFB2/ITGB2/VAV1/SYK	7	0.0031682 06136368 83
GO PHOSPHAT ASE BINDING	IQGAP1/TRAF3/CSRNP2/PARD3/SPRED1/BCL2/CTTNBP2NL/PP P1R18	8	0.0033325 61494963 21
GO REGULATI ON OF LEUKOCYT E MEDIATED CYTOTOXI CITY	PTPRC/ICAM1/HLA-E/VAV1/TAP1	5	0.0033885 93066855 67
GO CELL CHEMOTAX IS	PIK3CD/NRP1/NCKAP1L/CCR1/TGFB2/ITGB2/VAV1/SYK	8	0.0033885 93066855 67
GO CELL SUBSTRAT E ADHESION	ADAM9/RCC2/FERMT3/DLC1/CD44/BCL2/ITGB2/NPNT	8	0.0033885 93066855 67
GO POSITIVE REGULATI	ETS1/HIF1A/BTK/NCKAP1L/CCR1/RUNX1/SYK/TGFBR2	8	0.0033885 93066855 67

ON OF HEMOPOIESIS			
GO TRANSMEMBRANE RECEPTOR PROTEIN TYROSINE KINASE SIGNALING PATHWAY	CBL/LYN/ABL2/BTK/IQGAP1/NRP1/NCKAP1L/KDR/EP8/SPRED1/VAV1/SYK/ADAM10/NCF2	14	0.00420930597925196
GO CYTOPLASMIC SIDE OF MEMBRANE	SNX18/ATP2B1/LYN/ABL2/BTK/IQGAP1/TRAF3/SYK	8	0.00420930597925196
GO TUBE MORPHOGENESIS	HIF1A/NRP1/LRP6/DLC1/LUZP1/RBPJ/COBL/IFT52/BCL2/TGFBR2/NPNT	11	0.00427229653343965
GO CELL ADHESION MEDIATED BY INTEGRIN	ADAM9/ICAM1/NPNT	3	0.00433313772433583
GO PRODUCTION OF MOLECULAR MEDIATOR INVOLVED IN INFLAMMATORY RESPONSE	LYN/ALOX5/SYK	3	0.00433313772433583
GO RESPONSE TO EXTRACELLULAR STIMULUS	IFI16/ATP2B1/LYN/ALOX5/ICAM1/OXCT1/PRDM4/SH3GLB1/ATG7/DNMT3A/HLCS/BCL2/TGFBR2	13	0.00434765258770204
GO POSITIVE REGULATION OF ERK1 AND ERK2 CASCADE	P2RY1/DSTYK/ICAM1/NRP1/KDR/CD44/CCR1/NPNT	8	0.00457393334837671
GO NEURAL TUBE	HIF1A/LRP6/DLC1/LUZP1/COBL/IFT52	6	0.00533043102539954

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GO FC GAMMA RECEPTOR SIGNALING PATHWAY	LYN/NCKAP1L/WIPF1/WIPF2/VAV1/SYK	6	0.0055673 35526860 13
GO DENDRITIC CELL DIFFERENT IATION	LYN/RELB/RBPJ/TGFBR2	4	0.0055817 17232745 96
GO EXTRINSIC COMPONEN T OF PLASMA MEMBRAN E	SNX18/LYN/ABL2/BTK/IQGAP1/SYK/FCN1	7	0.0056516 12058238 42
GO PHOSPHATI DYLINOSIT OL 3 4 5 TRISPHOSP HATE BINDING	BTK/IQGAP1/PARD3/DAPP1	4	0.0060249 32164196 63
GO POSITIVE REGULATI ON OF EPITHELIA L TO MESENCHY MAL TRANSITIO N	DAB2/TGFB2/TGFBR2/BCL9L	4	0.0060249 32164196 63
GO EXTRINSIC COMPONEN T OF CYTOPLAS MIC SIDE OF PLASMA MEMBRAN E	SNX18/LYN/ABL2/BTK/IQGAP1/SYK	6	0.0061340 77450011 42
GO POSITIVE REGULATI ON OF B CELL DIFFERENT IATION	BTK/NCKAP1L/SYK	3	0.0061340 77450011 42



GO CYTOPLAS MIC REGION	HIF1A/CDKL5/DLC1/WIPF1/PARD3/WIPF2/EPS8/COBL/KIF3B/F MNL1	10	0.0061612 62868521 17
GO PEPTIDYL TYROSINE MODIFICAT ION	LYN/ABL2/BTK/DSTYK/KDR/CSF2RB/SYK/BAZ1B	8	0.0062811 61825589 6
GO MEMBRAN E PROTEIN PROTEOLY SIS	ADAM9/NFKB1/BACE2/ADAM10	4	0.0063232 30407280 95
GO LEUKOCYT E DIFFERENT IATION	IFI16/LYN/PIK3CD/PTPRC/RELB/RBPJ/BCL2/VAV1/SYK/TGFB R2	10	0.0065404 94213654 17
GO FC EPSILON RECEPTOR SIGNALING PATHWAY	LYN/BTK/MAP3K1/NFKB1/VAV1/SYK/NFATC3	7	0.0065404 94213654 17
GO MYELOID LEUKOCYT E MIGRATIO N	PIK3CD/NCKAP1L/TGFB2/ITGB2/VAV1/SYK	6	0.0065740 55808470 59
GO CELLULAR RESPONSE TO EXTRACEL LULAR STIMULUS	IFI16/ATP2B1/LYN/ICAM1/PRDM4/SH3GLB1/ATG7/BCL2	8	0.0065740 55808470 59
GO PHAGOCYT OSIS	LYN/NCKAP1L/WIPF1/WIPF2/CDC42SE2/VAV1/SYK/FCN1	8	0.0067308 75961665 11
GO POSITIVE REGULATI ON OF RESPONSE TO EXTERNAL STIMULUS	ETS1/HIF1A/NRP1/NCKAP1L/KDR/SH3GLB1/ATG7/CCR1/SPTL C2/ADAM10	10	0.0070540 33969112 91
GO PROTEIN AUTOPHOS PHORYLATI ON	LYN/CDKL5/ABL2/BTK/SLK/CSNK1G1/KDR/SYK	8	0.0070540 33969112 91

GO POSITIVE REGULATION OF CELL CELL ADHESION	ETS1/LYN/PTPRC/NCKAP1L/HLA-E/CD44/VAV1/SYK/TGFBR2	9	0.0072305 81699215 04
GO ANTIGEN RECEPTOR MEDIATED SIGNALING PATHWAY	LYN/BTK/PIK3CD/PTPRC/NFKB1/NCKAP1L/BCL2/SYK	8	0.0075707 13507762 04
GO POSITIVE REGULATION OF KINASE ACTIVITY	LYN/ADAM9/MAP3K1/IQGAP1/PTPRC/DSTYK/NCKAP1L/PFKFB2/MADD/MMD/TGFB2/SYK/TGFBR2	13	0.0075707 13507762 04
GO SITE OF POLARIZED GROWTH	CDKL5/IQGAP1/NRP1/PARD3/EPS8/COBL/DOCK7	7	0.0078825 74897537 29
GO EXTRACELLULAR STRUCTURE ORGANIZATION	VCAN/ICAM1/LCP1/KDR/CTSS/CD44/TGFB2/ITGB2/ADAM10/NPNT	10	0.0083416 50341088 33
GO ACTIN FILAMENT	IQGAP1/LCP1/WIPF1/WIPF2/COBL	5	0.0083416 50341088 33
GO RESPONSE TO OXYGEN LEVELS	ETS1/HIF1A/ALOX5/ICAM1/ATG7/DNMT3A/RBPJ/CYB5R4/TGFB2/BCL2	10	0.0093648 45378694 24
GO REGULATION OF TYPE I INTERFERON PRODUCTION	IFI16/NFKB1/TRAF3/MYD88/RELB/SYK	6	0.0095980 37257633 55
GO RUFFLE	CDKL5/IQGAP1/LCP1/DLC1/WIPF1/EPS8/COBL	7	0.0098469 55372380 35
GO REGULATION OF HEMOPOIESIS	SENP1/ETS1/LYN/HIF1A/BTK/NCKAP1L/CCR1/RUNX1/SYK/TGFBR2	10	0.0100234 62958592 4

GO VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR SIGNALING PATHWAY	NRP1/NCKAP1L/KDR/VAV1/NCF2	5	0.0102337 48375952 5
GO DEATH RECEPTOR BINDING	PRDM4/MYD88/MADD	3	0.0102569 53738326 4
GO NEGATIVE REGULATION OF CELL KILLING	PTPRC/HLA-E/TAP1	3	0.0102569 53738326 4
GO REGULATION OF DEPHOSPHORYLATION	IQGAP1/NCKAP1L/DLC1/CSRNP2/SPRED1/TGFB2/NPNT	7	0.0103492 80437317 1
GO POSITIVE REGULATION OF AUTOPHAGY	HIF1A/KDR/SH3GLB1/ATG7/SPTLC2	5	0.0103492 80437317 1
GO POSITIVE REGULATION OF CARBOHYDRATE METABOLIC PROCESS	HIF1A/P2RY1/NFKB1/PFKFB2/ARFGEF1	5	0.0103492 80437317 1
GO RESPONSE TO MECHANICAL STIMULUS	ETS1/HIF1A/MAP3K1/P2RY1/NFKB1/MYD88/TGFBR2/DENND5 B	8	0.0106900 23170165 6
GO POSITIVE REGULATION OF PROTEIN SECRETION	HIF1A/ADAM9/OXCT1/PFKFB2/HLA-E/TGFB2/SYK/FCN1	8	0.0109232 76583323 3
GO REGULATION OF HOMEOSTA	SENP1/ETS1/LYN/HIF1A/PTPRC/OXCT1/NCKAP1L/KDR/TGFB2 /BCL2/SYK/NEK7	12	0.0113697 62092292 6

TIC PROCESS			
GO NEGATIVE REGULATI ON OF DEPHOSPH ORYLATIO N	IQGAP1/NCKAP1L/CSRNP2/SPRED1/TGFB2	5	0.0119238 84018250 7
GO REGULATI ON OF EPITHELIA L CELL MIGRATIO N	ETS1/HIF1A/ADAM9/NRP1/KDR/TGFB2/TGFBR2	7	0.0126529 27872274 9
GO EMBRYONI C HEMOPOIE SIS	HIF1A/KDR/TGFBR2	3	0.0128250 19412156
GO MYELOID DENDRITIC CELL DIFFERENT IATION	RELB/RBPJ/TGFBR2	3	0.0128250 19412156
GO NEGATIVE REGULATI ON OF IMMUNE RESPONSE	IFI16/LYN/PTPRC/HLA-E/TGFB2/TAP1	6	0.0128250 19412156
GO REGULATI ON OF B CELL ACTIVATIO N	LYN/BTK/PTPRC/NCKAP1L/BCL2/SYK	6	0.0128250 19412156
GO POSITIVE REGULATI ON OF MYELOID CELL DIFFERENT IATION	ETS1/HIF1A/NCKAP1L/CCR1/RUNX1	5	0.0133139 00399068 9
GO RESPONSE TO CARBOHYD RATE	LYN/HIF1A/CALCRL/NFKB1/ICAM1/PFKFB2/TGFBR2	7	0.0133139 00399068 9

GO T CELL DIFFERENTIATION	PIK3CD/PTPRC/RELB/BCL2/VAV1/SYK	6	0.0135870 33534723 5
GO TUMOR NECROSIS FACTOR RECEPTOR SUPERFAMILY BINDING	TRAF3/PRDM4/MYD88/MADD	4	0.0135870 33534723 5
GO NEGATIVE REGULATION OF HYDROLASE ACTIVITY	IFI16/RCC2/IQGAP1/NCKAP1L/BIRC3/CSRNP2/CD44/TNFAIP8/SPRED1/TGFB2/ARFGEF1	11	0.0136197 60963961
GO REGULATION OF CELLULAR COMPONENT SIZE	HIF1A/CDKL5/ICAM1/NRP1/NCKAP1L/WIPF1/WIPF2/EPS8/VAV1/ARFGEF1	10	0.0136197 60963961
GO MRNA TRANSCRIPTION	HIF1A/LMO2/HIPK3	3	0.0136197 60963961
GO REGULATION OF RUFFLE ASSEMBLY	RCC2/ICAM1/COBL	3	0.0136197 60963961
GO RECEPTOR SIGNALING PROTEIN ACTIVITY	LYN/MAP3K1/SLK/KDR/TGFB2/SYK/TGFBR2	7	0.0138999 12768603 1
GO HEART DEVELOPMENT	HIF1A/CALCRL/OXCT1/NRP1/LRP6/DLC1/LUZP1/RBPJ/IFT52/TGFB2/TGFBR2/BAZ1B	12	0.0141817 34973645 1
GO MEMBRANE PROTEIN ECTODOMAIN PROTEOLYSIS	ADAM9/BACE2/ADAM10	3	0.0150548 41986328 9
GO REGULATION OF B CELL DIFFERENTIATION	BTK/NCKAP1L/SYK	3	0.0150548 41986328 9
GO REGULATION OF	HIF1A/CDKL5/ALOX5/P2RY1/ICAM1/NRP1/NCKAP1L/WIPF1/WIPF2/EPS8/VAV1/ARFGEF1	12	0.0150548 41986328 9

ANATOMICAL STRUCTURE SIZE			
GO PHAGOCYTOTIC VESICLE	RAB11FIP1/HLA-E/SYK/NCF2/FMNL1	5	0.0150548 41986328 9
GO PLASMA MEMBRANE RAFT	CBL/LRP6/DLC1/SPRED1/TGFBR2	5	0.0150548 41986328 9
GO POSITIVE REGULATION OF B CELL ACTIVATION	BTK/PTPRC/NCKAP1L/BCL2/SYK	5	0.0150548 41986328 9
GO LYMPHOCYTE HOMEOSTASIS	LYN/HIF1A/NCKAP1L/BCL2	4	0.0150548 41986328 9
GO POSITIVE REGULATION OF STEM CELL DIFFERENTIATION	DAB2/TGFB2/TGFBR2/BCL9L	4	0.0150548 41986328 9
GO REGULATION OF ADHERENS JUNCTION ORGANIZATION	RCC2/SLK/KDR/DLC1	4	0.0150548 41986328 9
GO POSITIVE REGULATION OF CELL DEVELOPMENT	DAB2/LYN/HIF1A/CDKL5/ABL2/NRP1/COBL/MMD/TGFB2/BCL2/TGFBR2/BCL9L	12	0.0150548 41986328 9
GO TUBE FORMATION	HIF1A/LRP6/DLC1/LUZP1/COBL/IFT52	6	0.0150548 41986328 9
GO ADAPTIVE IMMUNE RESPONSE	LYN/BTK/PIK3CD/ICAM1/RELB/CTSS/HLA-E/SYK/TAP1	9	0.0157670 17631212 2
GO POSITIVE REGULATION	NCKAP1L/HLA-E/SYK/TGFBR2	4	0.0157670 17631212 2

ON OF ALPHA BETA T CELL ACTIVATION			
GO POSITIVE REGULATION OF ERYTHROCYTE DIFFERENTIATION	ETS1/HIF1A/NCKAP1L	3	0.0157670176312122
GO RECEPTOR MEDIATED ENDOCYTOSIS	DAB2/GPR107/CALCRL/LRP6/ITGB2/SYK/TGFBR2/MSR1	8	0.0158934845849071
GO POSITIVE REGULATION OF LEUKOCYTE DIFFERENTIATION	BTK/NCKAP1L/CCR1/RUNX1/SYK/TGFBR2	6	0.0163385394545017
GO ANGIOGENESIS	ETS1/HIF1A/CALCRL/NRP1/KDR/RBPJ/TGFB2/SYK/TGFBR2	9	0.0166781045986848
GO REGULATION OF MYELOID CELL DIFFERENTIATION	SENP1/ETS1/LYN/HIF1A/NCKAP1L/CCR1/RUNX1	7	0.0166781045986848
GO ENDOTHELIUM DEVELOPMENT	TJP1/ICAM1/NRP1/KDR/RBPJ	5	0.0166781045986848
GO REGULATION OF CELL MATRIX ADHESION	RCC2/SLK/KDR/DLC1/BCL2	5	0.0166781045986848
GO CELL SUBSTRATE ADHERENS JUNCTION ASSEMBLY	RCC2/DLC1/BCL2	3	0.0166781045986848

GO MESENCHYMAL CELL DIFFERENTIATION	HIF1A/NRP1/LRP6/RBPJ/TGFB2/BCL2	6	0.0166781045986848
GO MORPHOGENESIS OF EMBRYONIC EPITHELIUM	HIF1A/LRP6/DLC1/LUZP1/COBL/IFT52	6	0.0166781045986848
GO POSITIVE REGULATION OF VASCULATURE DEVELOPMENT	ETS1/HIF1A/KDR/RUNX1/ITGB2/TGFBR2	6	0.0166781045986848
GO CELL GROWTH	IQGAP1/NRP1/COBL/TGFB2/BCL2/TGFBR2	6	0.0172104814816854
GO POSITIVE REGULATION OF LEUKOCYTE PROLIFERATION	LYN/PTPRC/NCKAP1L/HLA-E/BCL2/SYK	6	0.0176986913614431
GO ALPHA BETA T CELL ACTIVATION	RELB/HLA-E/BCL2/SYK	4	0.0176986913614431
GO REGULATION OF LYMPHOCYTE APOPTOTIC PROCESS	LYN/HIF1A/BTK/TGFB2	4	0.0176986913614431
GO REGULATION OF IMMUNE EFFECTOR PROCESS	LYN/BTK/PTPRC/ICAM1/TRAF3/BIRC3/HLA-E/TGFB2/VAV1/SYK/TAP1	11	0.0184023271303667
GO REGULATION OF B CELL	LYN/PTPRC/NCKAP1L/BCL2	4	0.01870560146342



PROLIFERATION			
GO CELL ACTIVATION INVOLVED IN IMMUNE RESPONSE	LYN/PIK3CD/ICAM1/LCP1/RELB/SYK	6	0.0192013851214373
GO STEM CELL DIFFERENTIATION	HIF1A/PTPRC/NRP1/LRP6/RBPJ/TGFB2/BCL2	7	0.0194072536767083
GO EPITHELIAL TO MESENCHYMAL TRANSITION	HIF1A/LRP6/RBPJ/TGFB2	4	0.0195626156821723
GO RESPONSE TO NUTRIENT	ATP2B1/ALOX5/OXCT1/PRDM4/DNMT3A/HLCS/TGFBR2	7	0.0195626156821723
GO MYELOID DENDRITIC CELL ACTIVATION	RELB/RBPJ/TGFBR2	3	0.0195626156821723
GO TRANSFORMING GROWTH FACTOR BETA RECEPTOR SIGNALING PATHWAY	CBL/ADAM9/PARD3/TGFB2/TGFBR2	5	0.0195626156821723
GO MYELOID LEUKOCYTE DIFFERENTIATION	IFI16/PIK3CD/RELB/RBPJ/TGFBR2	5	0.0203636566419501
GO REGULATION OF AUTOPHAGY	IFI16/HIF1A/ABL2/KDR/SH3GLB1/ATG7/BCL2/SPTLC2	8	0.0207196864852302
GO CONNECTIVE TISSUE DEVELOPMENT	HIF1A/OXCT1/LRP6/CD44/RUNX1/TGFB2/TGFBR2	7	0.0209037533368671

GO CELLULAR RESPONSE TO OXYGEN LEVELS	HIF1A/ICAM1/ATG7/DNMT3A/RBPJ/BCL2	6	0.0209461 95618177 2
GO SUBSTRAT E DEPENDEN T CELL MIGRATIO N	PTPRC/NRP1/FMNL1	3	0.0211261 87333362 7
GO NEGATIVE REGULATI ON OF DEFENSE RESPONSE	IFI16/ETS1/CALCRL/NFKB1/HLA-E/TAP1	6	0.0214340 94193207 9
GO POSITIVE REGULATI ON OF CELL ACTIVATIO N	LYN/BTK/PTPRC/NCKAP1L/HLA-E/BCL2/VAV1/SYK/TGFBR2	9	0.0221905 38140291 4
GO REGULATI ON OF ACTIN FILAMENT BASED PROCESS	ABL2/ICAM1/NCKAP1L/DLC1/WIPF1/WIPF2/EPS8/TGFB2/ARF GEF1	9	0.0221905 38140291 4
GO CARTILAGE DEVELOPM ENT	HIF1A/LRP6/CD44/RUNX1/TGFB2/TGFBR2	6	0.0233641 42681975 2
GO LEUKOCYT E HOMEOSTA SIS	LYN/HIF1A/NCKAP1L/BCL2	4	0.0233654 85496392 2
GO REGULATI ON OF CELL CELL ADHESION	ETS1/LYN/PTPRC/NCKAP1L/FERMT3/HLA- E/CD44/VAV1/SYK/TGFBR2	10	0.0240539 80089845 7
GO NEURAL TUBE DEVELOPM ENT	HIF1A/LRP6/DLC1/LUZP1/COBL/IFT52	6	0.0245683 05793880 6

GO DEVELOPMENTAL GROWTH INVOLVED IN MORPHOGENESIS	IQGAP1/NRP1/LRP6/COBL/TGFBR2	5	0.0268415700809074
GO REGULATION OF REACTIVE OXYGEN SPECIES METABOLIC PROCESS	HIF1A/ICAM1/BCL2/ITGB2/SYK/TGFBR2	6	0.0268415700809074
GO POSITIVE REGULATION OF SMOOTH MUSCLE CELL MIGRATION	NRP1/BCL2/DOCK7	3	0.0269274092061115
GO PROTEIN COMPLEX INVOLVED IN CELL ADHESION	LYN/ITGB2/NPNT	3	0.0269274092061115
GO REGULATION OF PROTEIN SECRETION	RAB11FIP1/LYN/HIF1A/ADAM9/OXCT1/PFKFB2/HLA-E/TGFB2/SYK/FCN1	10	0.0280319710590896
GO INNATE IMMUNE RESPONSE ACTIVATING CELL SURFACE RECEPTOR SIGNALING PATHWAY	LYN/NFKB1/RELB/SYK/FCN1	5	0.0284152017967018
GO LYMPHOCYTE DIFFERENTIATION	PIK3CD/PTPRC/RELB/RBPJ/BCL2/VAV1/SYK	7	0.0289388639090284
GO CELLULAR RESPONSE TO GLUCOSE	IFI16/SH3GLB1/BCL2	3	0.0289495330221689

STARVATION			
GO REGULATION OF ACTIN FILAMENT LENGTH	ICAM1/NCKAP1L/WIPF1/WIPF2/EPS8/ARFGEF1	6	0.0293602 73928732
GO MYD88 DEPENDENT TOLL LIKE RECEPTOR SIGNALING PATHWAY	BTK/MAP3K1/MYD88	3	0.0313844 77030769 1
GO REGULATION OF EPITHELIAL TO MESENCHYMAL TRANSITION	DAB2/TGFB2/TGFBR2/BCL9L	4	0.0324906 45087111 5
GO ANTIGEN PROCESSING AND PRESENTATION	ICAM1/RELB/CTSS/HLA-E/KIF3B/TAP1/NCF2	7	0.0329436 56216358 7
GO POSITIVE REGULATION OF HOMEOSTATIC PROCESS	ETS1/HIF1A/OXCT1/NCKAP1L/TGFB2/SYK/NEK7	7	0.0331777 10065961 1
GO WOUND HEALING	ETS1/LYN/HIF1A/P2RY1/LCP1/FERMT3/TGFB2/VAV1/SYK/TGFB2/C6orf89	11	0.0331777 10065961 1
GO SIGNAL TRANSDUCTION BY PROTEIN PHOSPHORYLATION	LYN/MAP3K1/NFKB1/SLK/KDR/CSF2RB/SPRED1/TGFB2/SYK/TGFB2	10	0.0331777 10065961 1
GO REGULATION OF ALPHA BETA T CELL ACTIVATION	NCKAP1L/HLA-E/SYK/TGFBR2	4	0.0331777 10065961 1

GO REGULATI ON OF CELL JUNCTION ASSEMBLY	RCC2/SLK/KDR/DLC1	4	0.0331777 10065961 1
GO POSITIVE REGULATI ON OF CELL MORPHOGE NESIS INVOLVED IN DIFFERENT IATION	DAB2/CDKL5/NRP1/TGFB2/TGFBR2/BCL9L	6	0.0337020 57657421 2
GO NEGATIVE REGULATI ON OF OSSIFICATI ON	HIF1A/CCR1/RBPJ/BCL2	4	0.0346091 47143379 4
GO REGULATI ON OF SMALL GTPASE MEDIATED SIGNAL TRANSDUC TION	ARHGAP30/DLC1/ARHGEF3/MADD/TGFB2/VAV1/ARHGAP25/ ARFGEF1	8	0.0350534 51118342 2
GO ADHERENS JUNCTION ASSEMBLY	RCC2/DLC1/BCL2	3	0.0350534 51118342 2
GO CELLULAR RESPONSE TO BIOTIC STIMULUS	LYN/HIF1A/ADAM9/NFKB1/ICAM1/SYK	6	0.0350534 51118342 2
GO REGULATI ON OF LYMPHOCY TE MEDIATED IMMUNITY	BTK/PTPRC/HLA-E/VAV1/TAP1	5	0.0353271 60887319 9
GO I KAPPAB KINASE NF KAPPAB SIGNALING	BTK/NFKB1/RELB/BIRC3	4	0.0353271 60887319 9

GO POSITIVE REGULATI ON OF TYPE I INTERFERO N PRODUCTI ON	IFI16/NFKB1/MYD88/SYK	4	0.0353271 60887319 9
GO REGULATI ON OF NATURAL KILLER CELL MEDIATED IMMUNITY	HLA-E/VAV1/TAP1	3	0.0372447 92648919 7
GO PHOSPHATI DYLINOSIT OL PHOSPHAT E BINDING	SNX18/BTK/IQGAP1/PARD3/DAPP1	5	0.0372447 92648919 7
GO RESPONSE TO INTERLEUK IN 1	ETS1/HIF1A/NFKB1/ICAM1/MYD88	5	0.0372447 92648919 7
GO ENDOTHELI AL CELL DIFFERENT IATION	TJP1/ICAM1/NRP1/RBPJ	4	0.0382481 61953607 6
GO RESPONSE TO FIBROBLAS T GROWTH FACTOR	CBL/IQGAP1/DSTYK/CD44/SPRED1	5	0.0382481 61953607 6
GO CELL LEADING EDGE	ATP2B1/CDKL5/IQGAP1/LCP1/SLK/DLC1/WIPF1/EPS8/COBL	9	0.0391965 27935072
GO NEGATIVE REGULATI ON OF LYMPHOCY TE MEDIATED IMMUNITY	PTPRC/HLA-E/TAP1	3	0.0391965 27935072
GO CELLULAR RESPONSE TO	HIF1A/CALCRL/NFKB1/ICAM1	4	0.0411497 86229666 7

CARBOHYD RATE STIMULUS			
GO REGULATI ON OF CELLULAR RESPONSE TO GROWTH FACTOR STIMULUS	DAB2/HIF1A/DSTYK/RBPJ/TGFBR2/NPNT/BCL9L	7	0.0411497 86229666 7
GO PROTEIN PHOSPHAT ASE BINDING	IQGAP1/TRAF3/PARD3/BCL2/CTTNBP2NL	5	0.0411497 86229666 7
GO GLIAL CELL MIGRATIO N	VCAN/P2RY1/TGFB2	3	0.0411497 86229666 7
GO POSITIVE REGULATI ON OF ALPHA BETA T CELL DIFFERENT IATION	NCKAP1L/SYK/TGFBR2	3	0.0411497 86229666 7
GO POSITIVE REGULATI ON OF B CELL PROLIFERA TION	PTPRC/NCKAP1L/BCL2	3	0.0411497 86229666 7
GO REGULATI ON OF PROTEIN POLYMERI ZATION	ICAM1/NCKAP1L/WIPF1/WIPF2/EP8/ARFGEF1	6	0.0417968 78600447 2
GO FOREBRAIN DEVELOPM ENT	PHLPP2/ETS1/HIF1A/NRP1/LRP6/DLC1/BTBD3/RBPJ/DOCK7	9	0.0418154 77158061 6
GO POSITIVE REGULATI ON OF CHEMOTAX IS	NRP1/NCKAP1L/KDR/CCR1/ADAM10	5	0.0418154 77158061 6

GO REGULATI ON OF CELL SUBSTRAT E ADHESION	RCC2/SLK/KDR/DLC1/BCL2/NPNT	6	0.0423701 27598852 6
GO ACTIN FILAMENT BINDING	ABL2/LCP1/WIPF1/WIPF2/FMNL1	5	0.0428907 98858835 6
GO NEGATIVE REGULATI ON OF INNATE IMMUNE RESPONSE	IFI16/HLA-E/TAP1	3	0.0431370 10762343 9
GO REGULATI ON OF LEUKOCYT E DIFFERENT IATION	LYN/BTK/NCKAP1L/CCR1/RUNX1/SYK/TGFBR2	7	0.0432725 55024913 8
GO RESPONSE TO TUMOR NECROSIS FACTOR	ADAM9/NFKB1/ICAM1/TRAF3/BIRC3/ADAM10/NPNT	7	0.0440807 10827947 3
GO RESPONSE TO ALCOHOL	ETS1/ATP2B1/HIF1A/ICAM1/OXCT1/LRP6/EP8/DNMT3A/TGF BR2	9	0.0442437 00325604 6
GO DEVELOPM ENTAL CELL GROWTH	IQGAP1/NRP1/COBL/TGFBR2	4	0.0442437 00325604 6
GO DIENCEPHA LON DEVELOPM ENT	ETS1/NRP1/LRP6/RBPJ	4	0.0442437 00325604 6
GO RESPONSE TO DRUG	LYN/HIF1A/ICAM1/OXCT1/ABCD3/NCKAP1L/DNMT3A/TGFB2 /BCL2/TGFBR2	10	0.0443508 31326301 9
GO NEGATIVE REGULATI ON OF NATURAL KILLER CELL	HLA-E/TAP1	2	0.0445045 27666124 7



MEDIATED IMMUNITY			
GO TRACHEA MORPHOGENESIS	LRP6/TGFBR2	2	0.0445045 27666124 7
GO NEGATIVE REGULATION OF GROWTH	HIF1A/CRLF3/NRP1/PRDM4/TGFB2/BCL2/TGFBR2	7	0.0446931 67882417 1
GO REGULATION OF OSSIFICATION	HIF1A/CCR1/RBPJ/TGFB2/BCL2/NPNT	6	0.0447418 66970874 5
GO EXTRACELLULAR MATRIX DISASSEMBLY	LCP1/CTSS/CD44/ADAM10	4	0.0449982 36529548 7
GO BLOOD VESSEL MORPHOGENESIS	ETS1/HIF1A/CALCRL/NRP1/KDR/RBPJ/TGFB2/SYK/TGFBR2	9	0.0449982 36529548 7
GO CELL CORTEX	DLC1/WIPF1/PARD3/WIPF2/EPS8/COBL/FMNL1	7	0.0457376 04208765
GO POSITIVE REGULATION OF GROWTH	CDKL5/NRP1/RBPJ/TGFB2/BCL2/TGFBR2/ADAM10	7	0.0457376 04208765
GO REGULATION OF LEUKOCYTE APOPTOTIC PROCESS	LYN/HIF1A/BTK/TGFB2	4	0.0463326 01133550 9
GO EXTERNAL SIDE OF PLASMA MEMBRANE	ADAM9/PTPRC/ICAM1/CCR1/TGFBR2/FCN1/RTN4RL1	7	0.0463701 96564807 4
GO CELLULAR RESPONSE TO MECHANICAL STIMULUS	HIF1A/MAP3K1/NFKB1/MYD88	4	0.0472603 73994806 3

GO RUFFLE MEMBRANE	CDKL5/LCP1/DLC1/EPS8	4	0.0472603 73994806 3
GO POSITIVE REGULATION OF SECRETION	HIF1A/ADAM9/P2RY1/OXCT1/PFKFB2/HLA-E/TGFB2/SYK/FCN1	9	0.0472603 73994806 3
GO REGULATION OF CHEMOTAXIS	LYN/NRP1/NCKAP1L/KDR/CCR1/ADAM10	6	0.0472603 73994806 3
GO RESPONSE TO TOXIC SUBSTANCE	ETS1/LYN/HIF1A/KDM3B/DNMT3A/CYB5R4/BCL2	7	0.0472603 73994806 3
GO GUANYL NUCLEOTIDE EXCHANGE FACTOR ACTIVITY	ARHGEF3/CSF2RB/DOCK10/MADD/DOCK7/VAV1/DENND5B/ARFGEF1	8	0.0472603 73994806 3
GO CELL SUBSTRATE JUNCTION ASSEMBLY	RCC2/DLC1/BCL2	3	0.0473458 07154604 2
GO MYELOID CELL ACTIVATION INVOLVED IN IMMUNE RESPONSE	LYN/PIK3CD/SYK	3	0.0473458 07154604 2
GO CELL JUNCTION ASSEMBLY	RCC2/TJP1/DLC1/PARD3/BCL2	5	0.0473458 07154604 2
GO REGULATION OF PHOSPHATASE ACTIVITY	NCKAP1L/CSRNP2/SPRED1/TGFB2/NPNT	5	0.0473458 07154604 2
GO POSITIVE REGULATION OF LYMPHOCYTE	BTK/NCKAP1L/SYK/TGFBR2	4	0.0473458 07154604 2

DIFFERENTIATION			
GO ASYMMETRIC CELL DIVISION	PARD3/DOCK7	2	0.0473458 07154604 2
GO CARDIOBLAST DIFFERENTIATION	RBPJ/TGFB2	2	0.0473458 07154604 2
GO CELLULAR RESPONSE TO LIPOPROTEIN PARTICLE STIMULUS	ITGB2/SYK	2	0.0473458 07154604 2
GO PATHWAY RESTRICTED SMAD PROTEIN PHOSPHORYLATION	TGFB2/TGFBR2	2	0.0473458 07154604 2
GO ACTIN CYTOSKELETON	ABL2/IQGAP1/LCP1/ZNF185/FERMT3/DLC1/WIPF1/WIPF2/COBL/CTTNBP2NL	10	0.0483942 84709250 2
GO REGULATION OF HOMOTYPIC CELL CELL ADHESION	LYN/PTPRC/NCKAP1L/HLA-E/CD44/VAV1/SYK/TGFBR2	8	0.0483942 84709250 2
GO CELL JUNCTION ORGANIZATION	RCC2/TJP1/DLC1/PARD3/TGFB2/BCL2	6	0.0483942 84709250 2
GO REGULATION OF RAS PROTEIN SIGNAL TRANSDUCTION	DLC1/ARHGEF3/MADD/TGFB2/VAV1/ARFGEF1	6	0.0483942 84709250 2
GO PROTEIN SERINE THREONINE KINASE ACTIVITY	CDKL5/MAP3K1/DSTYK/SLK/CSNK1G1/TGFB2/HIPK3/SYK/TGFBR2/NEK7	10	0.0485765 21316902 6

GO NEGATIVE REGULATI ON OF GTPASE ACTIVITY	RCC2/IQGAP1/ARFGEF1	3	0.0487243 00781014 8
GO KINASE REGULATO R ACTIVITY	IQGAP1/NCKAP1L/LRP6/MADD/SPRED1/RTN4RL1	6	0.0490593 64958055 4
GO RECEPTOR METABOLI C PROCESS	CALCRL/SH3GLB1/ITGB2/SYK	4	0.0497552 59963609
GO B CELL ACTIVATIO N	BTK/PIK3CD/PTPRC/RBPJ/BCL2	5	0.0497552 59963609
GO MIDBODY	RCC2/IQGAP1/SH3GLB1/KIF3B/C6orf89	5	0.0497552 59963609
GO EXOCYTOSI S	RAB11FIP1/LYN/PIK3CD/CCR1/SCRN1/TGFB2/SYK/ARFGEF1	8	0.0497552 59963609

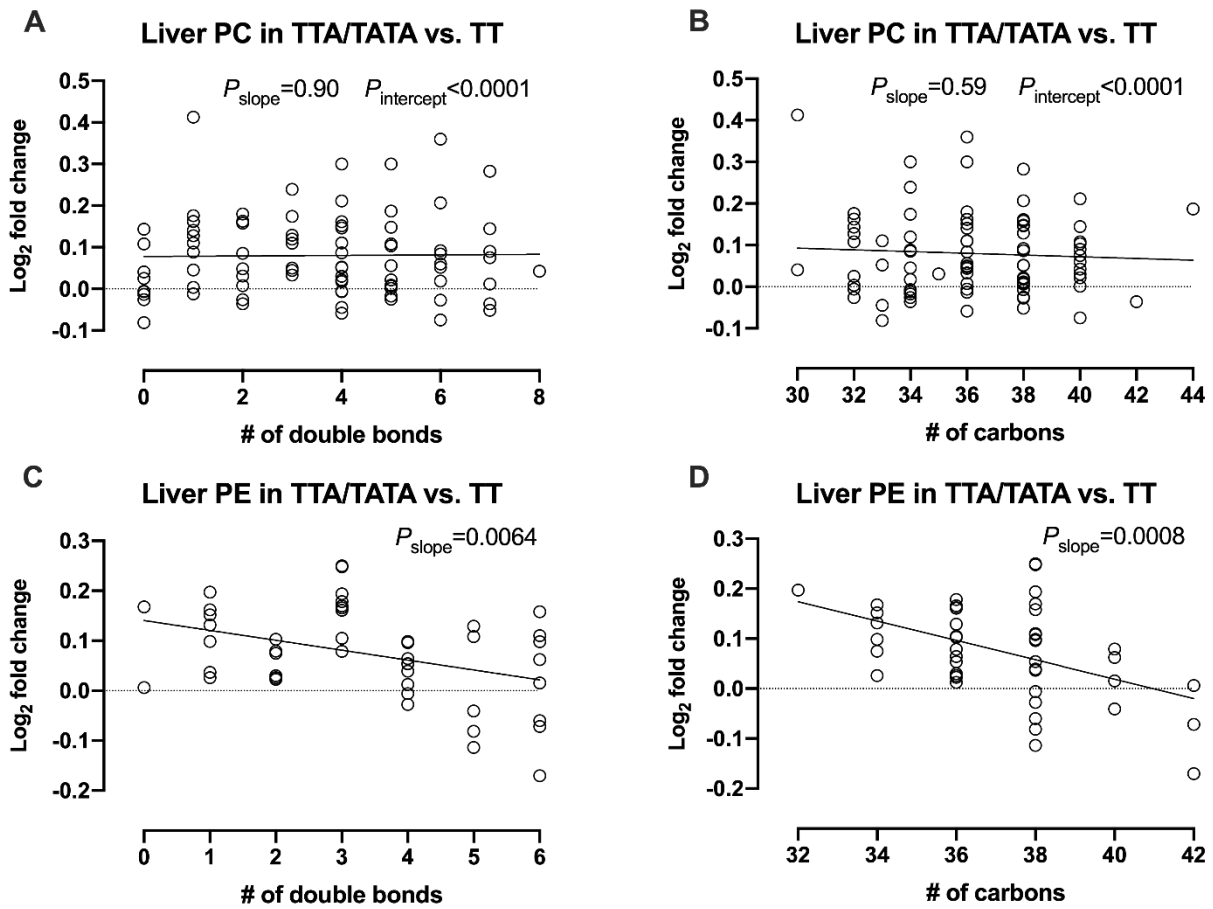
**Supplementary Table 9. Upregulated Gene Ontology pathways in carriers as compared to non-carriers of the HSD17B13 variant.**

<b>Description</b>	<b>geneID</b>	<b>Count</b>	<b>qvalue</b>
GO PROTEIN TARGETING TO MITOCHONDRION	MTX2/TOMM34/DNAJC19/TOMM40L/TIMM10	5	0.00406638544931212
GO PROTEIN LOCALIZATION TO MITOCHONDRION	MTX2/TOMM34/DNAJC19/TOMM40L/TIMM10	5	0.00889075167487519

**Supplementary Table 10. Gene specific primers used in qPCR analyses.**

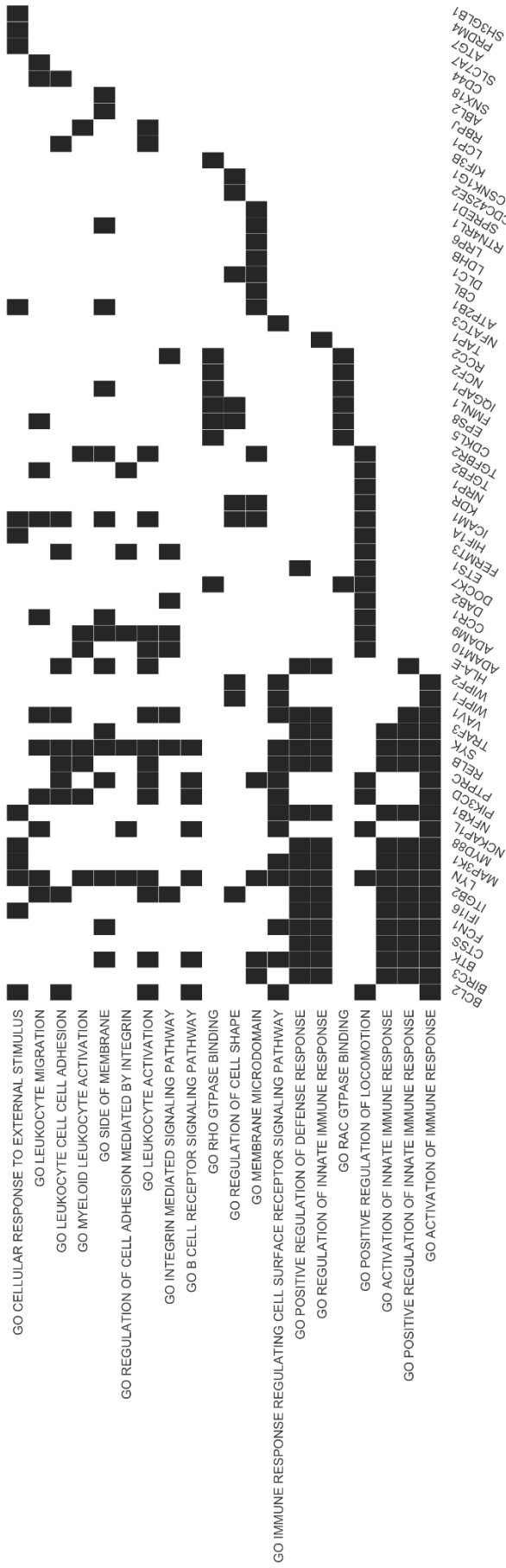
<b>Gene</b>	<b>Primer Sequence (F-forward, R-reverse)</b>
ALOX5-F	ACAAGCCCTTCTACAACGACT
ALOX5-R	AGCTGGATCTCGCCCAGTT
PLA2G12A-F	TGCAGTGACGGATCTAAGCCT
PLA2G12A-R	GTCAGGGAAGGGATACCAATGT
HIF1A-F	GAACGTCGAAAAGAAAAGTCTCG
HIF1A-R	CCTTATCAAGATGCGAACTCACA
TGFB2-F	CAGCACACTCGATATGGACCA
TGFB2-R	CCTCGGGCTCAGGATAGTCT
TRAF3-F	CTCACAAGTGCAGCGTCCAG
TRAF3-R	GCTCCACTCCTTCAGCAGGT
ABCB4-F	CAGTACTGGTGCACCTTCTACAAGACTT
ABCB4-R	TGCAATTAAAGCCAACCTGGTT
LPIN3-F	GGAGGAAACCCAAGCAGAAAG
LPIN3-R	AGGGATAGCTCACTCTCAGCG
PLCD3-F	CCAGAACCACTCTCAGCATCCA
PLCD3-R	GCCATTGTTGAGCACGTAGTCAG
PLD4-F	AACATGGACTGGCGGTCTCTGA
PLD4-R	CCAGTAGGTCTGGAAGGTCTTC
PCYT1A-F	CTCCACATCAGACATCATCACC
PCYT1A-R	TTACTTTGTCAACCCTCTCCTG
CHPT1-F	CACCGAAGAGGCACCATACTG
CHPT1-R	CCCTAAAGGGGAACAAGAGTTTG
CEPT1-F	ATGTGGAGATTCTCACCCGGA
CEPT1-R	TCTTCTAGCCGCTTTAGTTGGT
PEMT-F	GGGGTTCGCTGGAACCTTC
PEMT-R	GAGCCACTATGTAGGTGAGGG
COL3A1-F	TGGTCTGCAAGGAATGCCTGGA
COL3A1-R	TCTTTCCTGGGACACCATCAG

$\beta$ -ACTIN-F	GACAGGATGCAGAAGGAGAT
$\beta$ -ACTIN-R	TGATCCACATCTGCTGGAAGG
36B4-F	CATGCTCAACATCTCCCCTTCTCC
36B4-R	GGGAAGGTGTAATCCGTCTCCACAG



**Supplementary Figure 1. Hepatic phospholipids in carriers of the HSD17B13 gene variant as compared to non-carriers according to number of double bonds and carbons.** Linear regression between the number of double bonds (A, C) or carbons (B, D) in liver phosphatidylcholines (PC) (A-B) and liver phosphatidylethanolamines (PE) (C-D) and fold change of mean concentrations of respective lipids in the TTA/TATA (n=38) vs. TT group (n=48) (*solid line*). Each circle denotes an individual lipid species. The intercepts and slopes denote deviation of this regression line from 0 (*dashed line*).





**Supplementary Figure 2. Genes in the downregulated pathways in the livers of carriers of the HSD17B13 gene variant.** Y-axis denotes the downregulated Gene Ontology (GO) pathways and the x-axis the individual genes in these pathways in the liver of carriers of the HSD17B13 variant (n=36) as compared to non-carriers (n=50).