Fatty Acid Desaturase 1 (*FADS1*) Gene Polymorphisms Control Human Hepatic Lipid Composition

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Methods and Materials

Lipidomic Analysis

Targeted lipidomic analysis of 357 lipids (**Table S2**) was conducted using an automated electrospray ionization (ESI)-tandem mass spectrometry approach according to a protocol described previously (Kilaru et al., 2010). Data acquisition was performed based on a modified procedure by Devaiah et al. (Devaiah et al., 2006). Briefly, hepatic lipid extracts were dissolved in chloroform/methanol (9:1) prior to analysis. Precise amounts of internal standards for various PCs, lysoPCs, PEs, lysoPEs, PAs, (phytanoyl) PAs, PSs, (phytanoyl) PSs and PIs were added. A triple quadrupole MS/MS system (API 4000, Applied Biosystems, Foster City, CA) was used to acquire mass spectra. Unfractionated samples were introduced by continuous infusion into the Turbo V ESI source using an autosampler (LC Mini PAL, CTC Analytics AG, Zwingen, Switzerland) fitted with the required injection loop for the acquisition time. A series of spectra were produced by sequential precursor and neutral loss scans of the extracts produced, with each spectrum revealing a set of lipid species containing a common head group fragment. Positive mode was used to detect lipid species.

After mass spectrometry analysis, the data were then smoothed, and the background of each spectrum was subtracted. The peaks were further centroided and integrated using custom script and Applied Biosystems Analyst software. Peaks for the target lipids in these spectra were then identified, followed by data correction for isotopic overlap, and molar amounts calculation by comparing to the internal standards in the same lipid class. To correct for chemical or instrumental noise, a sample containing only internal standard mixture was also run through the same series of scans, in which the molar amounts of each lipid metabolite detected were subtracted from the molar amounts of each metabolite calculated from the experimental sample spectra. The data were adjusted to account for the fraction of sample analyzed and normalized to the sample total protein content measured as above. Data were reported as nmol or lmol of each detected lipid metabolite/mg protein.

Western Blotting

Protein samples used for Western blotting were isolated from the liver tissue using AllPrep Extraction Kit (Qiagen, CA, USA). The following antibodies were used: FADS1 (ab126706) and GAPDH (ab37168) from Abcam (Cambridge, MA, USA). The protein extracts concentrations were determined using BCA assay (Thermo Fisher Scientific, Rockford, IL, USA). All protein samples were diluted in loading buffer and heated at 90^0C for 10 mins. Samples were then subjected to separation on SDS-PAGE and transferred to polyvinyl difluoride membranes. The membranes were incubated with the specific antibodies and the proteins of interest were detected by species-specific horseradish-peroxidase (HRP)-conjugated immunoglobulin and then visualized using enhanced chemilumuniscence (Thermo Fisher Scientific, Rockford, IL, USA). Protein bands were visualized by exposed to the CL-XPosure film (Thermal Fisher Scientific) for 1 min. Films were then scanned and the area density of the protein band was quantified using ImageJ (Schneider et al., 2012). The FADS1/GAPDH ratios were used for further analysis. Proteins of the HepG2 cell line were loaded on each gel, and the protein ratios in HepG2 cells were used as an internal control to normalize the ratios obtained for each liver sample.

Data Analysis and Statistics

We performed an integrated analysis to understand the role of *FADS* polymorphisms as well as *FADS* genes in regulating hepatic lipid composition. Tests were focused on: 1) associations between these SNPs and mRNA expression of *FADS* genes (*FADS1*, *FADS2* and *FADS3*), hepatic content of 169 lipid species, 14,196 pair-wise ratios of these lipid species, and total hepatic fat content (HFC); 2) Locus-wide (+/-500kb region) mapping of *cis*-eQTLs for *FADS* genes, to evaluate the effect of remaining *cis*-SNPs within the locus; 3) Genome-wide mapping of quantitative trait loci (QTL) for hepatic content of the individual lipids and lipid ratios identified in step 1 to further verify the effects of remaining SNPs among the entire genome. A flowchart describing study design along with key observations is shown in **Fig S2**.

All analyses were conducted using a linear regression model, by assuming the allelic effect to be an additive mode. Prior to QTL mapping, gene expression levels, individual lipid levels and total fat content were log transformed (+log10). Residual variances were calculated by controlling covariates including age, gender, body mass index (BMI), race and alcohol intake status (yes or no). A conditional analysis was also conducted to test whether the *PNPLA3* gene polymorphism (rs738409) (Romeo et al., 2008) may confound the associations between *FADS* SNPs and individual lipids and HFC.

A total of 464,626 SNPs were included in the genome-wide association analysis, after removing those who have >5% missing rate, minor allele frequency (MAF) <0.05, or failed the Hardy-Weinberg Equilibrium (HWE) test at the threshold 0.001. Bonferroni correction was used to correct the potential multiple testing for each experiment, i.e. the association between 6 SNPs and mRNA levels of 3 *FADS* genes (corrected significance p=0.017), between SNPs and the levels of 169 individual lipids (corrected significance $p=3\times10^{-4}$), between SNPs and 14,196 lipid ratios (corrected significance $p=3.5\times10^{-6}$), locus-wide eQTL mapping [for 2,177 imputed SNPs (further described below), corrected significance $p=2.3\times10^{-5}$] and GWAS analyses (464,626 SNPs, $p=1\times10^{-7}$). Given the high LD levels (r^2>0.8) between all 6 SNPs among the *FADS* locus (**Fig S1**), *p* values for the associations with these SNPs were not further corrected for these 6 tests.

For locus-wide eQTL mapping, we used both originally genotyped and imputed SNP information within the region (hg19, Chr11: 61,071,142-62,159,006). To further validate the eQTL mapping results, we also conducted a similar mapping in an additional Asian liver eQTL dataset recently published (Wang et al., 2014). Imputed data with 1000 Genome data as a reference in both our dataset and the Asian dataset was performed in the previously published analysis and was kindly provided by Wang et al. (Wang et al., 2014). The imputed data further underwent a quality control (QC) process by filtering out the SNPs with low imputation quality (≤30%) and minor allele frequency (<5%). After this process, information for 2,177 and 1,619 SNPs respectively in our dataset and the Asian dataset was remained for further analyses.

To further verify the association between SNP genotypes and FADS1 protein levels, the FADS1/GAPDH ratios were log transformed and correlated with the SNP genotype (rs174556 as an example), by using the same model presented above for mRNA analysis.

To further evaluate the causal effect of the six core SNPs and their LD proxies on *FADS1* gene transcription, we performed an enrichment analysis by investigating the distribution of these SNPs in transcription factor binding sites (TFBS) identified in the ENCODE project. We performed this by comparing the number of SNPs located in the TFBS between the SNPs that are in the LD block and those that are not but with a similar MAF (≥0.25). A Chi-Square test was used and the significance level was set at $p<0.05$.

Statistical analyses were performed using PLINK (http://pngu.mgh.harvard.edu/~purcell/plink) (Purcell et al., 2007) or SAS v9.3 (SAS Institute Inc. NC, USA) and data were plotted using R or Graphpad Prism 6.0 (Graphpad Software, CA, USA).

Figure Legends

Fig S1. Linkage disequilibrium structure and recombination hotspots across the *FADS* gene locus. Shown here is the LD level (r^2) across all SNPs at the locus genotyped in 1000 Genome (Caucasian population, CEU) centered to rs174556.

Fig S2. Illustration of the study design.

Fig S3. Frequency distribution of hepatic fat content (HFC) in the livers. Showing here is the relative HFC normalized by total protein content.

Fig S4. SNP-centric Zoomplot showing LD structure centered at rs174537 and the associations between imputed SNPs across the FADS gene locus and A) *FADS1* expression, B) *FADS2* expression and C) *FADS3* expression in our liver samples cohort.

Fig S5. SNP-centric Zoomplot showing LD structure centered at rs174537 and the associations between imputed SNPs and A-B) *FADS1* expression as represented by two different probes; C-D) *FADS2* expression represented by two different probes; and E) *FADS3* expression in a set of published Han Chinese liver sample cohort (Wang *et al*, 2014).

Fig S1.

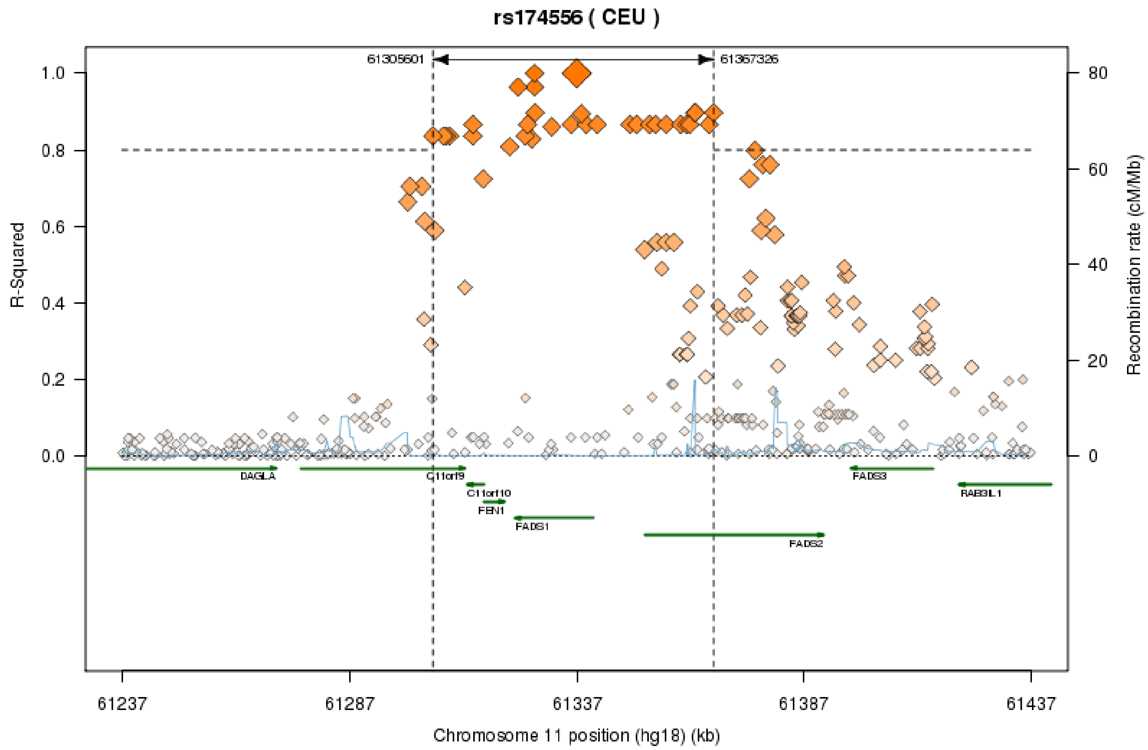
rs174556 (CEU)
61305601
61367326
R-Squared
Recombination rate (cM/Mb)
1.0
0.8
0.6
0.4
0.2
0.0
80
60
40
20
0
DAGLA
C11orf9
C11orf10
FEN1
FADS1
FADS2
FADS3
RAB3IL1
61237
61287
61337
61387
61437
Chromosome 11 position (hg18) (kb)

Fig S2

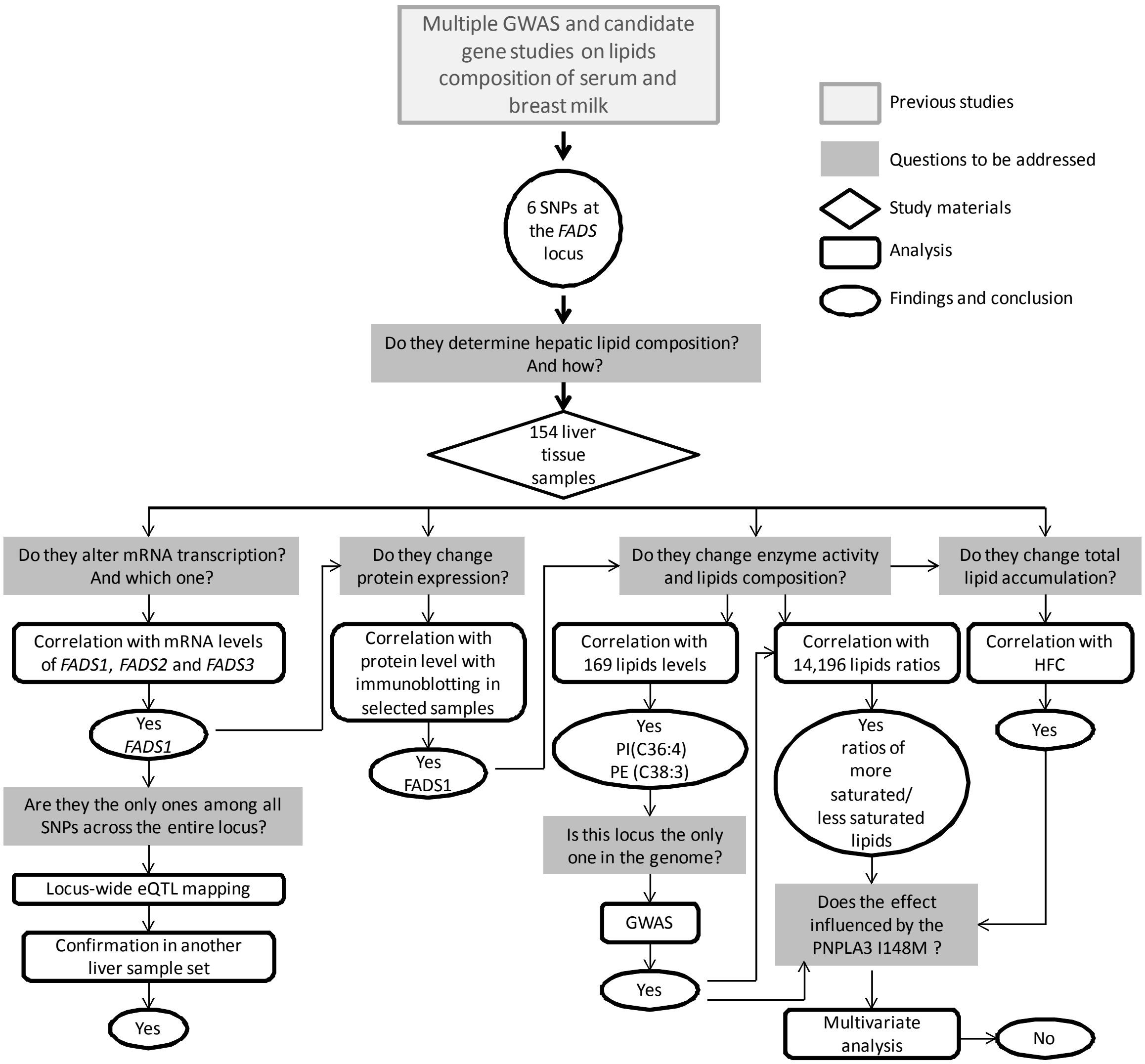
Multiple GWAS and candidate gene studies on lipids composition of serum and breast milk
Previous studies
Questions to be addressed
Study materials
Analysis
Findings and conclusion
6 SNPs at the FADS locus
Do they determine hepatic lipid composition? And how?
154 liver tissue samples
Do they alter mRNA transcription? And which one?
Do they change protein expression?
Do they change enzyme activity and lipids composition?
Do they change total lipid accumulation?
Correlation with mRNA levels of FADS1, FADS2 and FADS3
Correlation with protein level with immunoblotting in selected samples
Correlation with 169 lipids levels
Correlation with 14,196 lipids ratios
Correlation with HFC
Yes FADS1
Yes FADS1
Yes PI(C36:4) PE (C38:3)
Yes ratios of more saturated/ less saturated lipids
Yes
Are they the only ones among all SNPs across the entire locus?
Is this locus the only one in the genome?
Does the effect influenced by the PNPLA3 I148M ?
Locus-wide eQTL mapping
GWAS
Confirmation in another liver sample set
Yes
Multivariate analysis
No
Yes

Fig S3.

Number of sample

0.00 0.05 0.10 0.15 0.20 0.25 0.30 0.35 0.40 0.45 0.50 0.55 0.60

Fig S4

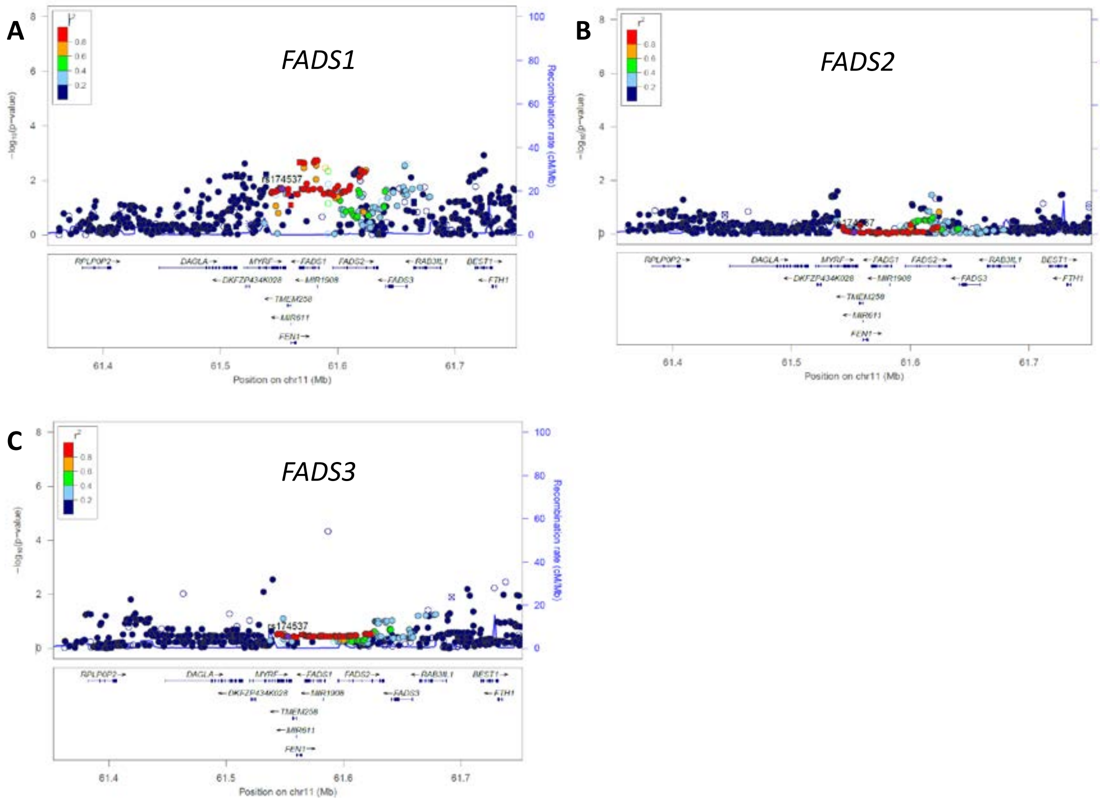
A
FADS1
B
FADS2
C
FADS3
rs174537
Recombination rate (cM/Mb)
−log10(p-value)
Position on chr11 (Mb)
61.4
61.5
61.6
61.7
RPLP0P2
DAGLA
MYRF
FADS1
FADS2
RAB3IL1
BEST1
DKFZP434K028
MIR1908
FADS3
FTH1
TMEM258
MIR611
FEN1

Fig S5

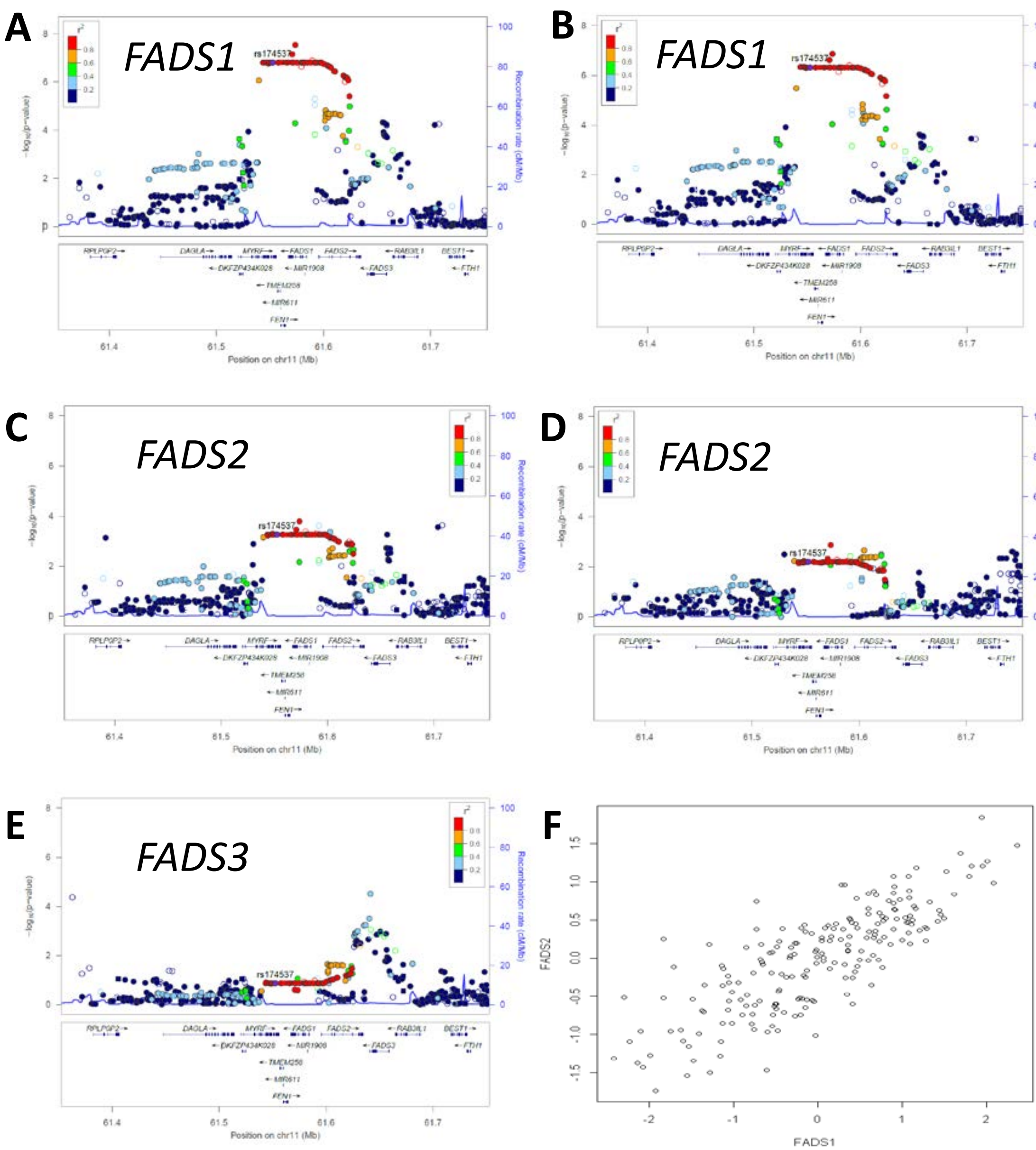
A
FADS1
B
FADS1
C
FADS2
D
FADS2
E
FADS3
F
FADS2
FADS1
Position on chr11 (Mb)
Recombination rate (cM/Mb)
rs174537

Table S1. Summary of studies and traits associated with *FADS1* SNPs in our study.

SNP	Location	Allele	Position	Associated traits	References
rs1535	61354548	A/G	*FADS2* Intronic	Blood LDL cholesterol levels	Sabatti et al, 2009
				Circulating sphingolipid levels	Hicks et al, 2009
				Blood HDL cholesterol levels	Zabaneh et al, 2010
				Blood HDL cholesterol levels	Lettre et al, 2011
				Plasma phospholipids levels	Lemaitre et al, 2011
				Blood polyunsaturated fatty acid levels during pregnancy	Steer et al, 2012
				DHA status in infants	Harslof et al, 2013
rs102275	61314379	A/G	*TMEM258* Intronic	Blood HDL cholesterol and triglycerides levels	Kathiresan et al, 2008
				Blood LDL cholesterol levels	Sabatti et al, 2009
				Circulating sphingolipid levels	Hicks et al, 2009
				Crohn's disease	Franke et al, 2010
				Blood HDL cholesterol levels	Zabaneh et al, 2010
				Plasma phospholipids n-3 fatty acids levels	Lemaitre et al, 2011
				Circulating phospholipids levels and ratios	Demirkan et al, 2012
rs174537	61309256	G/T	*FADS1* Intronic	Blood LDL cholesterol levels	Sabatti et al, 2009
				Plasma polyunsaturated fatty acids levels	Tanaka et al, 2009
				Circulating sphingolipid levels	Hicks et al, 2009
				Serum polyunsaturated fatty acid levels	Mathias et al, 2010
				Serum lipids, CAD risk	Kwak et al, 2011
				Colostrum long chain polyunsaturated levels	Morales et al, 2011
				Plasma phospholipids n-3 fatty acids levels	Lemaitre et al, 2011
				Serum phospholipid polyunsaturated fatty acid levels	Kim et al, 2011
				Serum arachidonic acid levels	Sergeant et al, 2012
				Age associated serum phospholipid PUFA	Hong et al, 2013
				CAD risk in Chinese Han Population	Li et al, 2013
rs174546	61326406	C/T	*FADS1* 3'-UTR	Blood LDL cholesterol levels	Sabatti et al, 2009

				Circulating sphingolipid levels	Hicks et al, 2009
				Erythrocyte membrane and plasma phospholipid PUFA levels	Rzehak et al, 2010
				Serum fatty acid ratios	Bokor et al, 2010
				Plasma total and HDL cholesterol levels	Lu et al, 2010
				Serum polyunsaturated fatty acid levels	Mathias et al, 2010
				Plasma triglycerides-, HDL- , LDL- and total cholesterol levels	Teslovich et al, 2010
				n-6 polyunsaturated fatty acid composition in erythrocyte membranes	Zietemann et al, 2010
				Blood HDL cholesterol levels	Zabaneh et al, 2010
				Serum total and non-HDL cholesterol levels	Dumont et al, 2011
				Plasma phospholipids n-3 fatty acids levels	Lemaitre et al, 2011
				Plasma triglycerides levels in Chinese population	Zhang et al, 2011
				Plasma total and HDL-cholesterol in 2-year old infants	Molto-Puigmarti et al, 2013
rs174556	61337211	C/T	*FADS1* Intronic	Serum phospholipids fatty acids levels	Schaeffer et al, 2006
				Erythrocyte membrane and serum phospholipid fatty acids	Malerba et al, 2008
				Blood LDL cholesterol levels	Sabatti et al, 2009
				Circulating sphingolipid levels	Hicks et al, 2009
				Plasma polyunsaturated fatty acids levels	Tanaka et al, 2009
				Serum polyunsaturated fatty acid levels	Mathias et al, 2010
				Blood HDL cholesterol levels	Zabaneh et al, 2010
				CAD risk	Qin et al, 2011
				Erythrocyte membrane and plasma phospholipid PUFA levels	Rzehak et al, 2010
				Acute coronary syndrome in Chinese Han population	Song et al, 2013
				Plasma total and HDL-cholesterol in 2-year old infants	Molto-Puigmarti et al, 2013
rs174576	61360086	A/C	*FADS2* Intronic	Blood triglycerides and HDL-cholesterol levels	Barber et al, 2010
				Plasma polyunsaturated fatty acid levels	Tanaka et al, 2009
				Plasma phospholipids n-3 fatty acid levels	Lemaitre et al, 2011

Note: HDL: high density lipoprotein; LDL: low density lipoprotein; PUFA: polyunsaturated fatty acid; CAD: coronary artery disease.

Table S2. Lipids profiled in the study (total number of lipids=357).

Mass	Compound Formula	Compound Name	Mass	Compound Formula	Compound Name
LysoPC			**PG**		
494.3	C24H48O7PN	LPC(16:1)	710.5	C36H69O10P	PG(30:1)
496.3	C24H50O7PN	LPC(16:0)	712.5	C36H71O10P	PG(30:0)
518.3	C26H48O7PN	LPC(18:3)	736.5	C38H71O10P	PG(32:2)
520.3	C26H50O7PN	LPC(18:2)	738.5	C38H73O10P	PG(32:1)
522.3	C26H52O7PN	LPC(18:1)	740.5	C38H75O10P	PG(32:0)
524.4	C26H54O7PN	LPC(18:0)	760.5	C40H71O10P	PG(34:4)
542.3	C28H48O7PN	LPC(20:5)	762.5	C40H73O10P	PG(34:3)
544.3	C28H50O7PN	LPC(20:4)	764.5	C40H75O10P	PG(34:2)
546.3	C28H52O7PN	LPC(20:3)	766.5	C40H77O10P	PG(34:1)
548.4	C28H54O7PN	LPC(20:2)	768.5	C40H79O10P	PG(34:0)
550.4	C28H56O7PN	LPC(20:1)	788.5	C42H75O10P	PG(36:4)
552.4	C28H58O7PN	LPC(20:0)	790.5	C42H77O10P	PG(36:3)
568.3	C30H50O7PN	LPC(22:6)	792.5	C42H79O10P	PG(36:2)
570.3	C30H52O7PN	LPC(22:5)	794.6	C42H81O10P	PG(36:1)
PC			812.5	C44H75O10P	PG(38:6)
676.5	C36H70O8PN	PC(28:1)	814.5	C44H77O10P	PG(38:5)
704.5	C38H74O8PN	PC(30:1)	**LPG**		
706.5	C38H76O8PN	PC(30:0)	481.3	C22H43O9P	LPG(16:1)
730.5	C40H76O8PN	PC(32:2)	483.3	C22H45O9P	LPG(16:0)
732.5	C40H78O8PN	PC(32:1)	505.3	C24H43O9P	LPG(18:3)
734.6	C40H80O8PN	PC(32:0)	507.3	C24H45O9P	LPG(18:2)
754.5	C42H76O8PN	PC(34:4)	509.3	C24H47O9P	LPG(18:1)
756.5	C42H78O8PN	PC(34:3)	**ePS**		
758.6	C42H80O8PN	PC(34:2)	746.5	C40H76O9PN	ePS(34:2)
760.6	C42H82O8PN	PC(34:1)	748.5	C40H78O9PN	ePS(34:1)
762.6	C42H84O8PN	PC(34:0)	772.5	C42H78O9PN	ePS(36:3)
778.5	C44H76O8PN	PC(36:6)	774.6	C42H80O9PN	ePS(36:2)
780.5	C44H78O8PN	PC(36:5)	776.6	C42H82O9PN	ePS(36:1)
782.6	C44H80O8PN	PC(36:4)	778.6	C42H84O9PN	ePS(36:0)
784.6	C44H82O8PN	PC(36:3)	794.5	C44H76O9PN	ePS(38:6)
786.6	C44H84O8PN	PC(36:2)	796.5	C44H78O9PN	ePS(38:5)
788.6	C44H86O8PN	PC(36:1)	798.6	C44H80O9PN	ePS(38:4)
790.6	C44H88O8PN	PC(36:0) or ePC(38:7)	800.6	C44H82O9PN	ePS(38:3)
806.6	C46H80O8PN	PC(38:6)	802.6	C44H84O9PN	ePS(38:2)
808.6	C46H82O8PN	PC(38:5)	804.6	C44H86O9PN	ePS(38:1)
810.6	C46H84O8PN	PC(38:4)	824.6	C46H82O9PN	ePS(40:5)
812.6	C46H86O8PN	PC(38:3)	826.6	C46H84O9PN	ePS(40:4)

814.6	C46H88O8PN	PC(38:2)	828.6	C46H86O9PN	ePS(40:3)
816.6	C46H90O8PN	PC(38:1)	830.6	C46H88O9PN	ePS(40:2)
818.7	C46H92O8PN	PC(38:0) or ePC(40:7)	**PA**		
830.6	C48H80O8PN	PC(40:8)	658.4	C35H61O8P	PA(32:4)
832.6	C48H82O8PN	PC(40:7)	660.4	C35H63O8P	PA(32:3)
834.6	C48H84O8PN	PC(40:6)	662.4	C35H65O8P	PA(32:2)
836.6	C48H86O8PN	PC(40:5)	664.5	C35H67O8P	PA(32:1)
838.6	C48H88O8PN	PC(40:4)	666.5	C35H69O8P	PA(32:0)
840.6	C48H90O8PN	PC(40:3)	686.4	C37H65O8P	PA(34:4)
842.7	C48H92O8PN	PC(40:2)	688.5	C37H67O8P	PA(34:3)
852.5	C50H78O8PN	PC(42:11)	690.5	C37H69O8P	PA(34:2)
854.6	C50H80O8PN	PC(42:10)	692.5	C37H71O8P	PA(34:1)
856.6	C50H82O8PN	PC(42:9)	710.4	C39H65O8P	PA(36:6)
858.6	C50H84O8PN	PC(42:8)	712.5	C39H67O8P	PA(36:5)
860.6	C50H86O8PN	PC(42:7)	714.5	C39H69O8P	PA(36:4)
862.6	C50H88O8PN	PC(42:6)	716.5	C39H71O8P	PA(36:3)
864.6	C50H90O8PN	PC(42:5)	718.5	C39H73O8P	PA(36:2)
866.7	C50H92O8PN	PC(42:4)	738.5	C41H69O8P	PA(38:6)
868.7	C50H94O8PN	PC(42:3)	740.5	C41H71O8P	PA(38:5)
870.7	C50H96O8PN	PC(42:2)	742.5	C41H73O8P	PA(38:4)
878.6	C52H80O8PN	PC(44:12)	744.5	C41H75O8P	PA(38:3)
880.6	C52H82O8PN	PC(44:11)	746.5	C41H77O8P	PA(38:2)
882.6	C52H84O8PN	PC(44:10)	764.5	C43H71O8P	PA(40:7)
884.6	C52H86O8PN	PC(44:9)	766.5	C43H73O8P	PA(40:6)
886.6	C52H88O8PN	PC(44:8)	768.5	C43H75O8P	PA(40:5)
888.6	C52H90O8PN	PC(44:7)	**SM and DSM**		
890.7	C52H92O8PN	PC(44:6)	701.5	C39H77N2O6P	SM(16:1)
892.7	C52H94O8PN	PC(44:5)	703.6	C39H79N2O6P	SM(16:0)
894.7	C52H96O8PN	PC(44:4)	705.6	C39H81N2O6P	DSM(16:0)
896.7	C52H98O8PN	PC(44:3)	729.6	C41H81N2O6P	SM(18:1)
898.7	C52H100O8PN	PC(44:2)	731.6	C41H83N2O6P	SM(18:0)
PE			733.6	C41H85N2O6P	DSM(18:0)
634.4	C33H64O8PN	PE(28:1)	785.6	C45H89N2O6P	SM(22:1)
636.5	C33H66O8PN	PE(28:0)	787.7	C45H91N2O6P	SM(22:0)
662.5	C35H68O8PN	PE(30:1)	789.7	C45H93N2O6P	DSM(22:0)
664.5	C35H70O8PN	PE(30:0)	813.7	C47H93N2O6P	SM(24:1)
688.5	C37H70O8PN	PE(32:2)	815.7	C47H95N2O6P	SM(24:0)
690.5	C37H72O8PN	PE(32:1)	817.7	C47H97N2O6P	DSM(24:0)
692.5	C37H74O8PN	PE(32:0)	**ePC**		
712.5	C39H70O8PN	PE(34:4)	714.5	C40H76O7PN	ePC(32:3)
714.5	C39H72O8PN	PE(34:3)	716.6	C40H78O7PN	ePC(32:2)

716.5	C39H74O8PN	PE(34:2)	718.6	C40H80O7PN	ePC(32:1)
718.5	C39H76O8PN	PE(34:1)	720.6	C40H82O7PN	ePC(32:0)
720.5	C39H78O8PN	PE(34:0)	740.6	C42H78O7PN	ePC(34:4)
736.5	C41H70O8PN	PE(36:6)	742.6	C42H80O7PN	ePC(34:3)
738.5	C41H72O8PN	PE(36:5)	744.6	C42H82O7PN	ePC(34:2)
740.5	C41H74O8PN	PE(36:4)	746.6	C42H84O7PN	ePC(34:1)
742.5	C41H76O8PN	PE(36:3)	748.6	C42H86O7PN	ePC(34:0)
744.5	C41H78O8PN	PE(36:2)	766.6	C44H80O7PN	ePC(36:5)
746.6	C41H80O8PN	PE(36:1)	768.6	C44H82O7PN	ePC(36:4)
748.6	C41H82O8PN	PE(36:0)	770.6	C44H84O7PN	ePC(36:3)
764.5	C43H74O8PN	PE(38:6)	772.6	C44H86O7PN	ePC(36:2)
766.5	C43H76O8PN	PE(38:5)	774.6	C44H88O7PN	ePC(36:1)
768.5	C43H78O8PN	PE(38:4)	776.6	C44H90O7PN	ePC(36:0)
770.6	C43H80O8PN	PE(38:3)	792.6	C46H82O7PN	ePC(38:6)
772.6	C43H82O8PN	PE(38:2)	794.6	C46H84O7PN	ePC(38:5)
774.6	C43H84O8PN	PE(38:1)	796.6	C46H86O7PN	ePC(38:4)
776.6	C43H86O8PN	PE(38:0)	798.6	C46H88O7PN	ePC(38:3)
788.5	C45H74O8PN	PE(40:8)	800.6	C46H90O7PN	ePC(38:2)
790.5	C45H76O8PN	PE(40:7)	802.7	C46H92O7PN	ePC(38:1)
792.5	C45H78O8PN	PE(40:6)	804.7	C46H94O7PN	ePC(38:0) or PC(38:7)
794.6	C45H80O8PN	PE(40:5)	820.6	C48H86O7PN	ePC(40:6)
796.6	C45H82O8PN	PE(40:4)	822.6	C48H88O7PN	ePC(40:5)
798.6	C45H84O8PN	PE(40:3)	824.6	C48H90O7PN	ePC(40:4)
800.6	C45H86O8PN	PE(40:2)	826.7	C48H92O7PN	ePC(40:3)
812.5	C47H74O8PN	PE(42:10)	828.7	C48H94O7PN	ePC(40:2)
814.5	C47H76O8PN	PE(42:9)	**LysoPE**		
816.5	C47H78O8PN	PE(42:8)	452.3	C21H42O7PN	LPE(16:1)
818.6	C47H80O8PN	PE(42:7)	454.3	C21H44O7PN	LPE(16:0)
820.6	C47H82O8PN	PE(42:6)	476.3	C23H42O7PN	LPE(18:3)
822.6	C47H84O8PN	PE(42:5)	478.3	C23H44O7PN	LPE(18:2)
824.6	C47H86O8PN	PE(42:4)	480.3	C23H46O7PN	LPE(18:1)
826.6	C47H88O8PN	PE(42:3)	500.3	C25H42O7PN	LPE(20:5)
828.6	C47H90O8PN	PE(42:2)	502.3	C25H44O7PN	LPE(20:4)
836.5	C49H74O8PN	PE(44:12)	504.3	C25H46O7PN	LPE(20:3)
838.5	C49H76O8PN	PE(44:11)	506.3	C25H48O7PN	LPE(20:2)
840.5	C49H78O8PN	PE(44:10)	508.3	C25H50O7PN	LPE(20:1)
842.6	C49H80O8PN	PE(44:9)	510.3	C25H52O7PN	LPE(20:0)
844.6	C49H82O8PN	PE(44:8)	526.3	C27H44O7PN	LPE(22:6)
846.6	C49H84O8PN	PE(44:7)	528.3	C27H46O7PN	LPE(22:5)
848.6	C49H86O8PN	PE(44:6)	**PE-Cer**		
850.6	C49H88O8PN	PE(44:5)	659.5	C36H71O6PN2	PE-Cer(16:1)

852.6	C49H90O8PN	PE(44:4)	661.5	C36H73O6PN2	PE-Cer(16:0)
854.7	C49H92O8PN	PE(44:3)	687.5	C38H75O6PN2	PE-Cer(18:1)
856.7	C49H94O8PN	PE(44:2)	689.5	C38H77O6PN2	PE-Cer(18:0)
ePE			773.6	C44H89O6PN2	PE-Cer(24:0)
672.5	C37H70O7PN	ePE(32:3)	**PS**		
674.5	C37H72O7PN	ePE(32:2)	734.5	C38H72O10PN	PS(32:1)
676.5	C37H74O7PN	ePE(32:1)	736.5	C38H74O10PN	PS(32:0)
678.5	C37H76O7PN	ePE(32:0)	756.5	C40H70O10PN	PS(34:4)
698.5	C39H72O7PN	ePE(34:4)	758.5	C40H72O10PN	PS(34:3)
700.5	C39H74O7PN	ePE(34:3)	760.5	C40H74O10PN	PS(34:2)
702.5	C39H76O7PN	ePE(34:2)	762.5	C40H76O10PN	PS(34:1)
704.6	C39H78O7PN	ePE(34:1)	764.5	C40H78O10PN	PS(34:0)
706.6	C39H80O7PN	ePE(34:0)	780.5	C42H70O10PN	PS(36:6)
724.5	C41H74O7PN	ePE(36:5)	782.5	C42H72O10PN	PS(36:5)
726.5	C41H76O7PN	ePE(36:4)	784.5	C42H74O10PN	PS(36:4)
728.6	C41H78O7PN	ePE(36:3)	786.5	C42H76O10PN	PS(36:3)
730.6	C41H80O7PN	ePE(36:2)	788.5	C42H78O10PN	PS(36:2)
732.6	C41H82O7PN	ePE(36:1)	790.6	C42H80O10PN	PS(36:1)
734.6	C41H84O7PN	ePE(36:0)	792.6	C42H82O10PN	PS(36:0)
750.5	C43H76O7PN	ePE(38:6)	806.5	C44H72O10PN	PS(38:7)
752.6	C43H78O7PN	ePE(38:5)	808.5	C44H74O10PN	PS(38:6)
754.6	C43H80O7PN	ePE(38:4)	810.5	C44H76O10PN	PS(38:5)
756.6	C43H82O7PN	ePE(38:3)	812.5	C44H78O10PN	PS(38:4)
758.6	C43H84O7PN	ePE(38:2)	814.6	C44H80O10PN	PS(38:3)
760.6	C43H86O7PN	ePE(38:1)	816.6	C44H82O10PN	PS(38:2)
762.6	C43H88O7PN	ePE(38:0)	818.6	C44H84O10PN	PS(38:1)
778.6	C45H80O7PN	ePE(40:6)	820.6	C44H86O10PN	PS(38:0)
780.6	C45H82O7PN	ePE(40:5)	832.5	C46H74O10PN	PS(40:8)
782.6	C45H84O7PN	ePE(40:4)	834.5	C46H76O10PN	PS(40:7)
784.6	C45H86O7PN	ePE(40:3)	836.5	C46H78O10PN	PS(40:6)
786.6	C45H88O7PN	ePE(40:2)	838.6	C46H80O10PN	PS(40:5)
PI			840.6	C46H82O10PN	PS(40:4)
848.5	C43H75O13P	PI(34:4)	842.6	C46H84O10PN	PS(40:3)
850.5	C43H77O13P	PI(34:3)	844.6	C46H86O10PN	PS(40:2)
852.5	C43H79O13P	PI(34:2)	846.6	C46H88O10PN	PS(40:1)
854.5	C43H81O13P	PI(34:1)	854.5	C48H72O10PN	PS(42:11)
872.5	C45H75O13P	PI(36:6)	856.5	C48H74O10PN	PS(42:10)
874.5	C45H77O13P	PI(36:5)	858.5	C48H76O10PN	PS(42:9)
876.5	C45H79O13P	PI(36:4)	860.5	C48H78O10PN	PS(42:8)
878.5	C45H81O13P	PI(36:3)	862.6	C48H80O10PN	PS(42:7)
880.6	C45H83O13P	PI(36:2)	864.6	C48H82O10PN	PS(42:6)

882.6	C45H85O13P	PI(36:1)	866.6	C48H84O10PN	PS(42:5)
900.5	C47H79O13P	PI(38:6)	880.5	C50H74O10PN	PS(44:12)
902.5	C47H81O13P	PI(38:5)	882.5	C50H76O10PN	PS(44:11)
904.6	C47H83O13P	PI(38:4)	884.5	C50H78O10PN	PS(44:10)
906.6	C47H85O13P	PI(38:3)	886.6	C50H80O10PN	PS(44:9)
908.6	C47H87O13P	PI(38:2)	888.6	C50H82O10PN	PS(44:8)
910.6	C47H89O13P	PI(38:1)	890.6	C50H84O10PN	PS(44:7)
912.6	C47H91O13P	PI(38:0)	892.6	C50H86O10PN	PS(44:6)
924.5	C49H79O13P	PI(40:8)	894.6	C50H88O10PN	PS(44:5)
926.5	C49H81O13P	PI(40:7)	896.6	C50H90O10PN	PS(44:4)
928.6	C49H83O13P	PI(40:6)	898.6	C50H92O10PN	PS(44:3)
930.6	C49H85O13P	PI(40:5)	900.7	C50H94O10PN	PS(44:2)
932.6	C49H87O13P	PI(40:4)			
934.6	C49H89O13P	PI(40:3)			
936.6	C49H91O13P	PI(40:2)			
938.6	C49H93O13P	PI(40:1)			
940.7	C49H95O13P	PI(40:0)			
948.5	C51H79O13P	PI(42:10)			
950.5	C51H81O13P	PI(42:9)			
952.6	C51H83O13P	PI(42:8)			
954.6	C51H85O13P	PI(42:7)			
956.6	C51H87O13P	PI(42:6)			
958.6	C51H89O13P	PI(42:5)			
960.6	C51H91O13P	PI(42:4)			
962.6	C51H93O13P	PI(42:3)			
964.7	C51H95O13P	PI(42:2)			
972.5	C53H79O13P	PI(44:12)			
974.5	C53H81O13P	PI(44:11)			
976.6	C53H83O13P	PI(44:10)			
978.6	C53H85O13P	PI(44:9)			
980.6	C53H87O13P	PI(44:8)			
982.6	C53H89O13P	PI(44:7)			
984.6	C53H91O13P	PI(44:6)			
986.6	C53H93O13P	PI(44:5)			
988.7	C53H95O13P	PI(44:4)			
990.7	C53H97O13P	PI(44:3)			
992.7	C53H99O13P	PI(44:2)			

Table S3. Association between *FADS* polymorphisms and lipid ratios.

SNP	ID	Molecule	Ratio*	Beta	R^2	p-value
rs174576	C44H80O8PN/C47H85O13P	PC(36:4)/PI(38:3)	D/S	-2.17	0.17	1.72E-07
	C44H82O8PN/C46H82O8PN	PC(36:3)/PC(38:5)	S/D	0.43	0.17	1.05E-07
	C47H83O13P/C47H85O13P	PI(38:4)/PI(38:3)	D/S	-1.94	0.22	8.65E-10
	C46H84O8PN/C46H86O8PN	PC(38:4)/PC(38:3)	D/S	-0.86	0.16	2.99E-07
	C43H76O8PN/C47H85O13P	PE(38:5)/PI(38:3)	D/S	-1.13	0.17	1.09E-07
	C46H82O8PN/C46H86O8PN	PC(38:5)/PC(38:3)	D/S	-0.49	0.15	4.82E-07
	C46H82O8PN/C47H85O13P	PC(38:5)/PI(38:3)	D/S	-0.51	0.18	4.51E-08
	C47H85O13P/C45H76O8PN	PI(38:3)/PE(40:5)	S/D	0.38	0.16	2.53E-07
	C47H85O13P/C47H81O13P	PI(38:3)/PI(38:5)	S/D	0.44	0.17	1.08E-07
	C47H85O13P/C44H78O8PN	PI(38:3)/PC(36:5)	S/D	1.31	0.17	1.38E-07
	C47H85O13P/C45H79O13P	PI(38:3)/PI(36:4)	S/D	0.55	0.19	1.77E-08
	C47H85O13P/C49H85O13P	PI(38:3)/PI(40:5)	S/D	0.90	0.20	4.47E-09
	C47H85O13P/C43H80O7PN	PI(38:3)/ePE(38:4)	S/D	1.49	0.16	2.47E-07
	C47H85O13P/C43H82O8PN	PI(38:3)/PE(38:2)	D/S	1.98	0.16	2.55E-07
	C47H85O13P/C49H87O13P	PI(38:3)/PI(40:4)	S/D	4.54	0.17	5.47E-08
	C43H80O8PN/C45H79O13P	PE(38:3)/PI(36:4)	S/D	0.28	0.20	7.13E-09
	C43H80O8PN/C43H80O7PN	PE(38:3)/ePE(38:4)	S/D	0.70	0.15	4.74E-07
rs1535	C44H80O8PN/C47H85O13P	PC(36:4)/PI(38:3)	D/S	-2.11	0.16	3.78E-07
	C44H82O8PN/C46H82O8PN	PC(36:3)/PC(38:5)	S/D	0.43	0.17	1.27E-07
	C47H83O13P/C47H85O13P	PI(38:4)/PI(38:3)	D/S	-1.88	0.21	3.08E-09
	C43H76O8PN/C47H85O13P	PE(38:5)/PI(38:3)	D/S	-1.10	0.16	2.80E-07
	C46H82O8PN/C47H85O13P	PC(38:5)/PI(38:3)	D/S	-0.49	0.17	1.06E-07
	C47H85O13P/C47H81O13P	PI(38:3)/PI(38:5)	S/D	0.43	0.16	2.97E-07
	C47H85O13P/C44H78O8PN	PI(38:3)/PC(36:5)	S/D	1.28	0.16	2.42E-07
	C47H85O13P/C45H79O13P	PI(38:3)/PI(36:4)	S/D	0.54	0.18	3.11E-08
	C47H85O13P/C49H85O13P	PI(38:3)/PI(40:5)	S/D	0.86	0.18	1.81E-08
	C47H85O13P/C43H80O7PN	PI(38:3)/ePE(38:4)	S/D	1.51	0.17	1.48E-07
	C47H85O13P/C43H82O8PN	PI(38:3)/PE(38:2)	D/S	1.93	0.15	5.03E-07
	C47H85O13P/C49H87O13P	PI(38:3)/PI(40:4)	S/D	4.59	0.18	3.54E-08
	C43H80O8PN/C45H79O13P	PE(38:3)/PI(36:4)	S/D	0.28	0.19	2.14E-08
	C43H80O8PN/C43H80O7PN	PE(38:3)/ePE(38:4)	S/D	0.70	0.15	4.49E-07
rs174546	C44H80O8PN/C47H85O13P	PC(36:4)/PI(38:3)	D/S	-2.11	0.16	3.78E-07
	C44H82O8PN/C46H82O8PN	PC(36:3)/PC(38:5)	S/D	0.43	0.17	1.27E-07
	C47H83O13P/C47H85O13P	PI(38:4)/PI(38:3)	D/S	-1.88	0.21	3.08E-09
	C43H76O8PN/C47H85O13P	PE(38:5)/PI(38:3)	D/S	-1.10	0.16	2.80E-07
	C46H82O8PN/C47H85O13P	PC(38:5)/PI(38:3)	D/S	-0.49	0.17	1.06E-07
	C47H85O13P/C47H81O13P	PI(38:3)/PI(38:5)	S/D	0.43	0.16	2.97E-07
	C47H85O13P/C44H78O8PN	PI(38:3)/PC(36:5)	S/D	1.28	0.16	2.42E-07
	C47H85O13P/C45H79O13P	PI(38:3)/PI(36:4)	S/D	0.54	0.18	3.11E-08
	C47H85O13P/C49H85O13P	PI(38:3)/PI(40:5)	S/D	0.86	0.19	1.81E-08
	C47H85O13P/C43H80O7PN	PI(38:3)/ePE(38:4)	S/D	1.51	0.17	1.48E-07
	C47H85O13P/C43H82O8PN	PI(38:3)/PE(38:2)	D/S	1.93	0.15	5.03E-07
	C47H85O13P/C49H87O13P	PI(38:3)/PI(40:4)	S/D	4.59	0.18	3.54E-08
	C43H80O8PN/C45H79O13P	PE(38:3)/PI(36:4)	S/D	0.28	0.19	2.14E-08
	C43H80O8PN/C43H80O7PN	PE(38:3)/ePE(38:4)	S/D	0.70	0.15	4.49E-07
rs102275	C44H80O8PN/C47H85O13P	PC(36:4)/PI(38:3)	D/S	-2.10	0.16	2.95E-07
	C44H82O8PN/C46H82O8PN	PC(36:3)/PC(38:5)	S/D	0.42	0.16	2.08E-07
	C47H83O13P/C47H85O13P	PI(38:4)/PI(38:3)	D/S	1.94	0.23	4.31E-10
	C46H84O8PN/C46H86O8PN	PC(38:4)/PC(38:3)	D/S	-0.87	0.17	1.50E-07
	C43H76O8PN/C47H85O13P	PE(38:5)/PI(38:3)	D/S	-1.10	0.16	1.76E-07
	C46H82O8PN/C46H86O8PN	PC(38:4)/PC(38:3)	D/S	-0.51	0.17	1.31E-07
	C46H82O8PN/C47H85O13P	PC(38:5)/PI(38:3)	D/S	-0.50	0.18	5.14E-08
	C47H85O13P/C47H81O13P	PI(38:3)/PI(38:5)	S/D	0.46	0.18	2.65E-08
	C47H85O13P/C44H78O8PN	PI(38:3)/PC(36:5)	S/D	1.28	0.17	1.75E-07
	C47H85O13P/C45H79O13P	PI(38:3)/PI(36:4)	S/D	0.55	0.19	1.02E-08
	C47H85O13P/C49H85O13P	PI(38:3)/PI(40:5)	S/D	0.88	0.20	4.46E-09
	C47H85O13P/C43H82O8PN	PI(38:3)/ePE(38:4)	S/D	1.95	0.16	2.41E-07

	C47H85O13P/C49H87O13P	PI(38:3)/PI(40:5)	S/D	4.42	0.17	7.63E-08
	C43H80O8PN/C47H81O13P	PE(38:3)/PI(38:5)	S/D	0.26	0.16	3.85E-07
	C43H80O8PN/C45H79O13P	PE(38:3)/PI(38:5)	S/D	0.29	0.21	2.26E-09
	C43H80O8PN/C43H80O7PN	PE(38:3)/ePE(38:4)	S/D	0.69	0.16	4.40E-07
rs174537	C44H80O8PN/C47H85O13P	PC(36:4)/PI(38:3)	D/S	-2.11	0.16	3.78E-07
	C44H82O8PN/C46H82O8PN	PC(36:3)/PC(38:5)	S/D	0.43	0.17	1.27E-07
	C47H83O13P/C47H85O13P	PI(38:4)/PI(38:3)	D/S	-1.88	0.21	3.08E-09
	C43H76O8PN/C47H85O13P	PE(38:5)/PI(38:3)	D/S	-1.10	0.16	2.80E-07
	C46H82O8PN/C47H85O13P	PC(38:5)/PI(38:3)	D/S	-0.50	0.17	1.06E-07
	C47H85O13P/C47H81O13P	PI(38:3)/PI(38:5)	S/D	0.43	0.16	2.97E-07
	C47H85O13P/C44H78O8PN	PI(38:3)/PC(36:5)	S/D	1.28	0.16	2.42E-07
	C47H85O13P/C45H79O13P	PI(38:3)/PI(36:4)	S/D	0.54	0.18	3.11E-08
	C47H85O13P/C49H85O13P	PI(38:3)/PI(40:5)	S/D	0.86	0.19	1.81E-08
	C47H85O13P/C43H80O7PN	PI(38:3)/ePE(38:4)	S/D	1.51	0.17	1.48E-07
	C47H85O13P/C43H82O8PN	PI(38:3)/PE(38:2)	D/S	1.93	0.15	5.03E-07
	C47H85O13P/C49H87O13P	PI(38:3)/PI(40:4)	S/D	4.59	0.18	3.53E-08
	C43H80O8PN/C45H79O13P	PE(38:3)/PI(36:4)	S/D	0.28	0.19	2.14E-08
	C43H80O8PN/C43H80O7PN	PE(38:3)/ePE(38:4)	S/D	0.70	0.15	4.49E-07
rs174556	C44H82O8PN/C46H82O8PN	PC(36:3)/PC(38:5)	S/D	0.45	0.16	1.90E-07
	C47H83O13P/C47H85O13P	PI(38:4)/PI(38:3)	D/S	-1.89	0.18	3.80E-08
	C43H76O8PN/C47H85O13P	PE(38:5)/PI(38:3)	D/S	-1.15	0.15	5.79E-07
	C46H82O8PN/C47H85O13P	PC(38:5)/PI(38:3)	D/S	-0.51	0.15	4.68E-07
	C47H85O13P/C45H80O8PN	PI(38:3)/PE(40:5)	S/D	0.27	0.16	3.90E-07
	C47H85O13P/C45H79O13P	PI(38:3)/PE(40:7)	S/D	0.60	0.19	1.62E-08
	C47H85O13P/C49H85O13P	PI(38:3)/PI(40:5)	S/D	0.96	0.20	3.94E-09
	C47H85O13P/C43H80O7PN	PI(38:3)/ePE(38:4)	S/D	1.61	0.16	1.99E-07
	C47H85O13P/C49H87O13P	PI(38:3)/PI(40:4)	S/D	5.31	0.21	2.17E-09

*D/S refers to the ratios between more desatuarated (D) lipids and relatively more saturated (S) lipids.

Table S4. Six core study SNPs and their LD proxies located in transcription factor binding sites (TFBS) that were identified in the ENCODE project. *MAF refers to minor allele frequency.

SNPs	Gene Position	TFBS	MAF*
rs174537	MYRF intron	Pol2A, REST, MAZ, SRF, POU2F2	0.333
rs174576	FADS2 intron	JUND	0.392
rs102275	TMEM258 intron	NA	0.482
rs174546	FADS1 3'UTR	POLR2A	0.33
rs1535	FADS2 intron	POLR2A, ESR1	0.349
rs174556	FADS1 intron	CEBPB	0.308
rs174536	MYRF intron	CTCF	0.333
rs174535	MYRF synonymous	CTCF	0.357
rs174533	MYRF intron	NA	0.332
rs102274	TMEM258 intron	NA	0.332
r174554	FADS1 intron	FOS, MYC, STAT3, CEBPB	0.33
rs174561	FADS1 intron	POLR2A, TAF1, TCF12, PML, GATA2, MYC, UBTF, CEBPB, EF300, GATA3, RCOR1, USF2, MAZ, MAX, CCNT2, MXI1, IRF1, SP1, SREBP1, NFYA, E2F4, E2F6, TEAD4, ELK1, CHD2, NR3C1, HMGN3, NFYB, FOXP2, PAX5, CREb1, SMC3, ZKSLAN1, RFX5, TCF7L2, MAFK, JUND, GIF2F1, BRCA1, NRF1, ZBTB7A, ELF1, NF1C, SMARCB1, JUN, EGR1, TBF, SIN3A, FOXA1	0.308
rs174562	FADS2 upstream	POLR2A, CHD1	0.33
rs174566	FADS2 intron	NA	0.372
rs174568	FADS2 upstream	NA	0.329
rs99780	FADS2 intron	POLR2A, CTBF2, TAF1, CTCF, PAX5, WRNIP1	0.408
rs174574	FADS2 intron	POLR2A, WRNIP1	0.462
rs174577	FADS2 intron	POLR2A	0.41
rs174578	FADS2 intron	POLR2A, STAT1, STAT2A	0.411
rs174583	FADS2 intron	POLR2A, RCOR1, SMARCB1, GATA1, HDAC8	0.397
rs174547	FADS1 intron	POLR2A	0.33
rs174550	FADS1 intron	POLR2A	0.33
rs174580	FADS2 intron	NA	0.411
rs174581	FADS2 intron	NA	0.412
rs174584	FADS2 intron	NA	0.418
rs174545	FADS1 3'UTR variant	POLR2A	0.33

rs174538	TMEM258 5'UTR variant	POLR2A, PML, TAF1, MYC, CHD1, TBP, GATA1, MYB12, MAZ, NFIC, CHD2, HDAC1, E2F1, PAF8, REST, TAF7, RELA, ZBTB7A, YY1, GABPA, MAX< CBX3, UBTF, SIN3A, ELK4, POU2F2, TCF12, KDN5B, ELK1, MXI1, CREB1, NRF1, E2F6, TBL1XR, ELF1, SRF, BCL3, SIX5, SFI1, FOXF2, ETS1, RBBF5, ZNF143, TCF7L2, CEBPB	0.314
rs174553	FADS1 intron	NA	0.392
rs174541	Unknown	POLR2A	0.339
rs174594	FADS2 intron	NA	0.437
rs174599	FADS2 intron	NA	0.491
rs174601	FADS2 intron	STAT1	0.494
rs174530	MYRF intron	NA	0.343
rs174529	MYRF intron	CTCF	0.372
rs174549	FADS1 intron	POL-.4H8	0.308
rs174555	FADS1 intron	NA	0.308
rs174560	FADS1 intron	POL2-4H8	0.344
rs174592	FADS2 intron	NA	0.477
rs174544	FADS1 3'UTR variant	NA	0.308
rs174548	FADS1 intron	NA	0.344
rs174528	MYRF intron	CTCF	0.449
rs174559	FADS1 intron	POL2-4H8	0.293

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