SUPPLEMENTAL MATERIAL

A variant near *DHCR24* associates with white-matter microstructure and peripheral lipid metabolism in adolescents

Eeva Sliz, Jean Shin, Catriona Syme, Yash Patel, Nadine Parker, Louis Richer, Daniel Gaudet, Steffany Bennett, Tomas Paus, Zdenka Pausova

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Supplemental Methods

Genotyping

The SYS adolescents and parents were genotyped in two waves. First, the initial batch of recruited adolescents (n=592) were genotyped with the Illumina Human610-Quad BeadChip (Illumina; *n*=582,892 single nucleotide polymorphisms [SNPs]) at the Centre National de Génotypage (Paris, France). Second, the remaining adolescents and all parents were genotyped with the HumanOmniExpress BeadChip (Illumina; *n*=729,295 SNPs) at the Genome Analysis Centre of Helmholtz Zentrum Mümchen (Munich, Germany). For both chips, SNPs with call rate <95%, minor allele frequency <0.01, or not in Hardy-Weinberg equilibrium (*P* <1.0e-06) were excluded. After this quality control (QC), 542,345 SNPs on the first chip and 644,283 SNPs on the second chip were available for the further analyses. To equate the set of SNPs genotyped on each chip and increase the SNP density, we performed genotype imputations. Haplotype phasing was performed with SHAPEIT v2.790 (1), using the subset of 313,653 post-QC SNPs that were present on both genotyping platforms and the 1000 Genome CEU reference panel (Phase 1, Release 3). Imputation was conducted on the phased data with IMPUTE2 (2). Markers with low imputation quality (information score <0.5) or minor allele frequency <0.01 were removed. After this quality control of imputation, a total of 8,511,049 SNPs was analyzed.

MRI of the brain and abdomen

White-matter properties were assessed as T1-weighted signal intensity (T1W-SI) obtained as follows. T1W magnetic resonance imaging (MRI) of the brain was conducted using a Gyroscan NT 1.0-T scanner (Philips Healthcare) and a 3D radio frequency (RF)-spoiled gradient echo sequence consisting of 160 slices, 1-mm isotropic resolution, TR=25 ms, TE=4.2 ms, and flip angle=30^{o}. An in-house image-processing pipeline was used to derive T1W-signal intensity (T1W-SI) values of white-matter voxels (3). Mean T1W-SI of white- matter voxels (cerebral lobes only) normalized by mean T1W-SI of the whole brain was the main variable studied here (3).

The quantity of visceral fat was determined by abdominal MRI using a semi-automated method (4,5). MRI of visceral fat was measured from T1W images of the abdomen acquired on a Gyroscan NT 1.0-T scanner (Philips Healthcare) in adolescents, and an Avanto 1.5-T scanner (Siemens) in adults. A 10-mm thick axial slice at the level of the umbilicus was selected to quantify visceral and subcutaneous fat, in cm^3, with a semi-automatic method described previously (4,5).

Lipidomics and metabolomics

Quantification of the novel inflammatory marker, circulating phospholipid PC16:0/2:0, was performed from fasting blood serum samples using liquid chromatography-electrospray ionization-mass spectrometry (LC-ESI-MS); the method is described in more detail elsewhere (6,7). Shortly, a total of 69 GPC species were characterized within 450 to 680 m/z range, as it was expected to contain lysophosphocholines (LPCs) and platelet-activating factors (PAFs) that function as important modulators of oxidative stress and inflammation (6–10).

Metabolomic profiling of a total of 228 circulating metabolic traits including a comprehensive set of lipoprotein subfractions and their lipids, fatty acids, and non-lipid metabolites were quantified from fasting serum samples by a commercially available nuclear magnetic resonance (NMR) based metabolomics platform (Nightingale Health Ltd, Helsinki, Finland) (11,12). The experimentation has been described previously (11,13).

Figure S1. Associations of rs588709 with white matter T1W-SI, visceral fat and PC16:0/2:0 in SYS adolescents.

Linear models were fitted to study the associations between the GWAS-lead variant and the individual components of the PC1 used as the study phenotype in the GWAS. Here, adjusted (age, sex, common family environment, and height for visceral fat) and transformed phenotypes served as outcomes and the rs588709 encoded as 0, 1, and 2 representing the number of GWAS effect alleles (G) served as an explanatory variable.

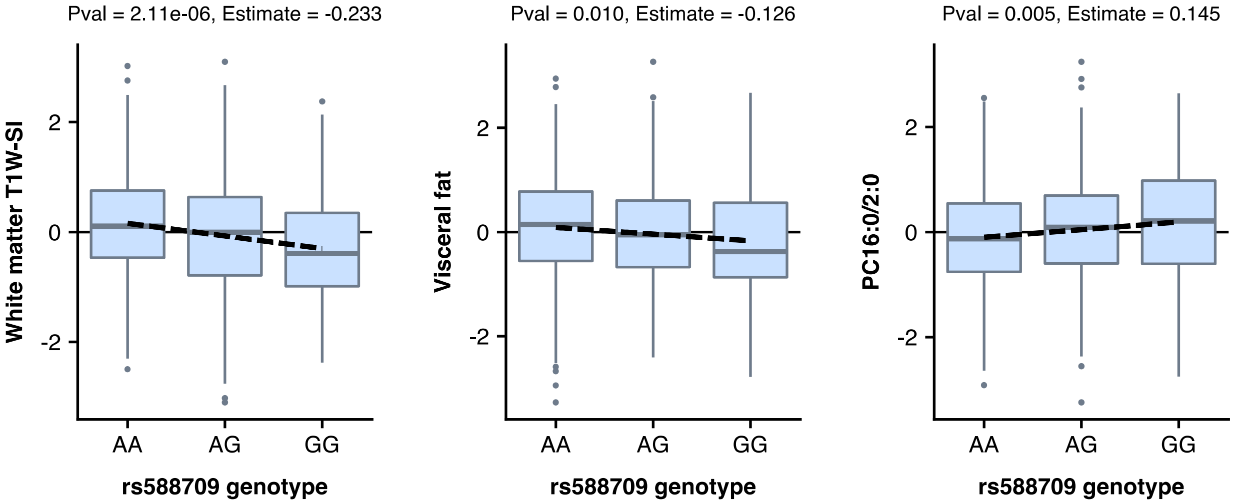
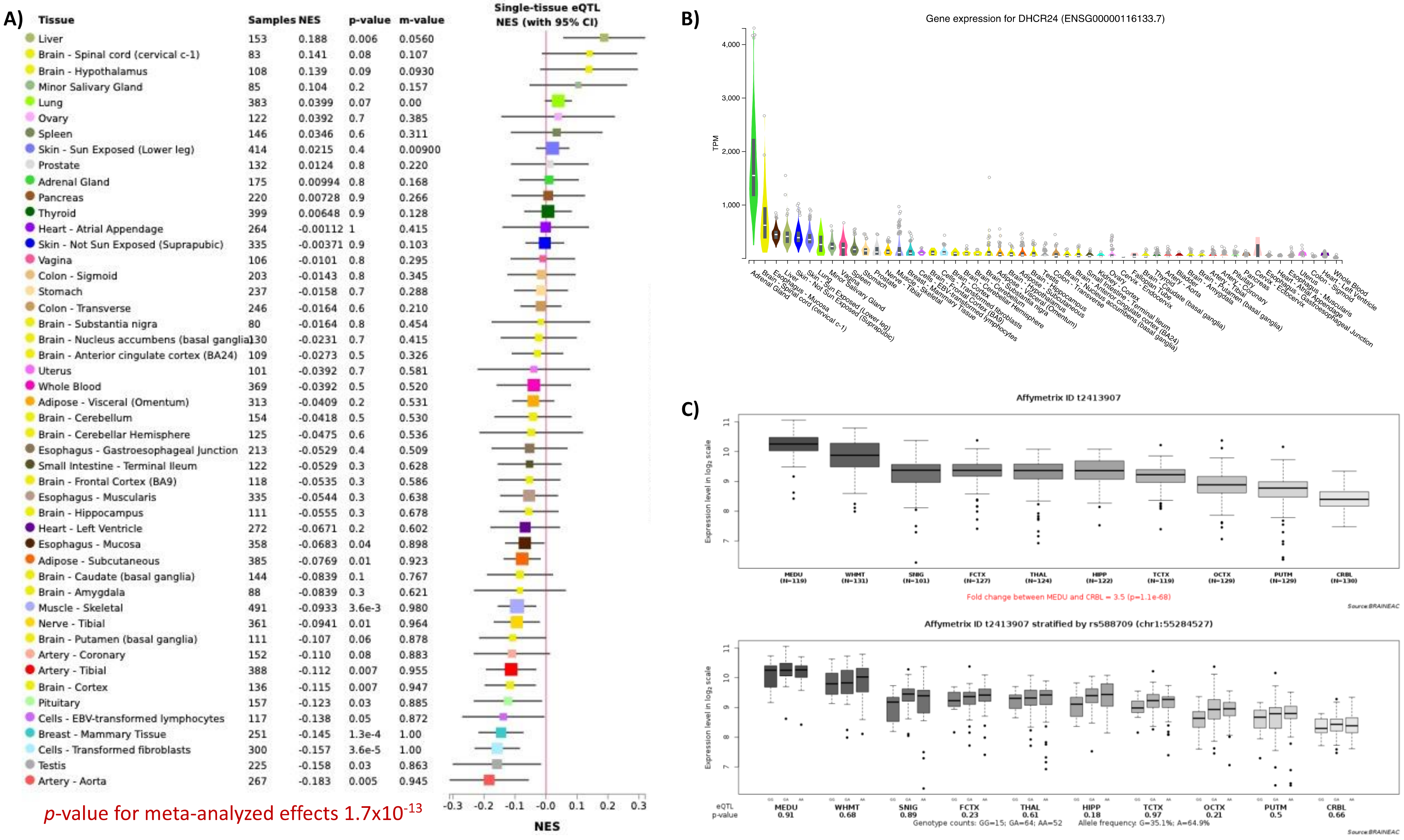


Figure S2. *DHCR24* expression summarized.

A) The effect of the GWAS-lead variant rs588709 on *DHCR24* gene expression was studied in GTEx portal (accessed on April 15th, 2019) (17). 'Samples' indicate the number of RNA-seq samples with genotype. Normalized effect size (NES) is the slope of the linear regression of the normalized data versus the three genotype categories using single-tissue expression quantitative trait locus (eQTL) analysis, representing eQTL effect size. The 'p-value' originates from a t-test that compares observed NES from single-tissue eQTL analysis to a null NES of 0. The 'm-value' indicates the posterior probability that an eQTL effect exists in each tissue tested in the cross-tissue meta-analysis. The effect estimates are for the G allele that was the effect allele in the present GWAS. **B)** The tissue expression of *DHCR24* in GTEx. Expression values are shown in Transcripts Per Million (TPM; y-axis) calculated from a model with isoforms collapsed to a single gene. The tissues are ordered according to the gene expression median (x-axis). **C)** Expression level of *DHCR24* in Braineac database (upper) and *DHCR24* expression stratified according to rs588709 genotype (lower) (braineac.org; accessed on April 15th, 2019). MEDU, medulla; WHMT, intralobular white matter; SNIG, substantia nigra; FCTX, frontal cortex; THAL, thalamus; HIPP, hippocampus; TCTX, temporal cortex; OCTX, occipital cortex; PUTM, putamen; CRBL, cerebellar cortex.



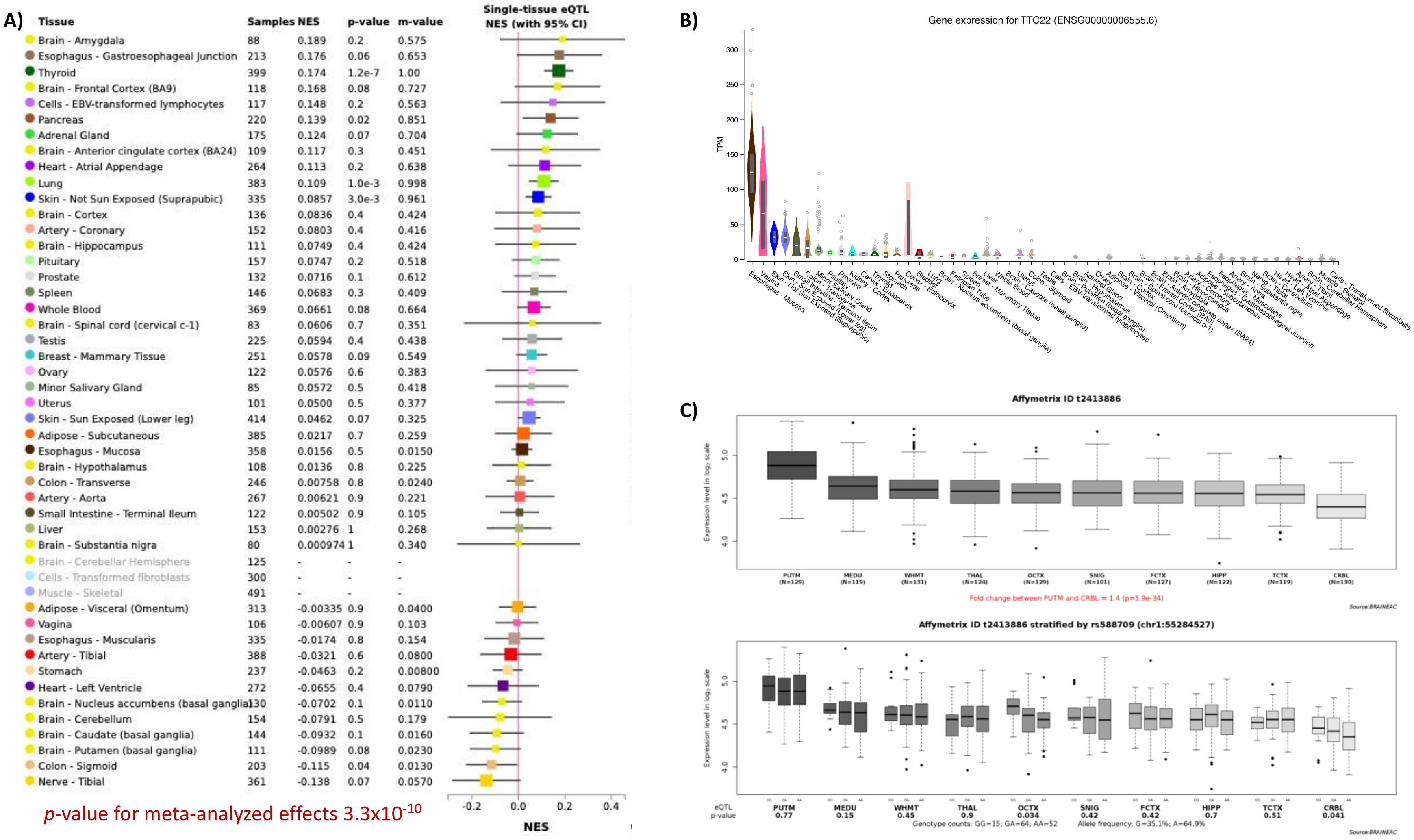
A)

Tissue	Samples	NES	p-value	m-value
Liver	153	0.188	0.006	0.0560
Brain - Spinal cord (cervical c-1)	83	0.141	0.08	0.107
Brain - Hypothalamus	108	0.139	0.09	0.0930
Minor Salivary Gland	85	0.104	0.2	0.157
Lung	383	0.0399	0.07	0.00
Ovary	122	0.0392	0.7	0.385
Spleen	146	0.0346	0.6	0.311
Skin - Sun Exposed (Lower leg)	414	0.0215	0.4	0.00900
Prostate	132	0.0124	0.8	0.220
Adrenal Gland	175	0.00994	0.8	0.168
Pancreas	220	0.00728	0.9	0.266
Thyroid	399	0.00648	0.9	0.128
Heart - Atrial Appendage	264	-0.00112	1	0.415
Skin - Not Sun Exposed (Suprapubic)	335	-0.00371	0.9	0.103
Vagina	106	-0.0101	0.8	0.295
Colon - Sigmoid	203	-0.0143	0.8	0.345
Stomach	237	-0.0158	0.7	0.288
Colon - Transverse	246	-0.0164	0.6	0.210
Brain - Substantia nigra	80	-0.0164	0.8	0.454
Brain - Nucleus accumbens (basal ganglia)	130	-0.0231	0.7	0.415
Brain - Anterior cingulate cortex (BA24)	109	-0.0273	0.5	0.326
Uterus	101	-0.0392	0.7	0.581
Whole Blood	369	-0.0392	0.5	0.520
Adipose - Visceral (Omentum)	313	-0.0409	0.2	0.531
Brain - Cerebellum	154	-0.0418	0.5	0.530
Brain - Cerebellar Hemisphere	125	-0.0475	0.6	0.536
Esophagus - Gastroesophageal Junction	213	-0.0529	0.4	0.509
Small Intestine - Terminal Ileum	122	-0.0529	0.3	0.628
Brain - Frontal Cortex (BA9)	118	-0.0535	0.3	0.586
Esophagus - Muscularis	335	-0.0544	0.3	0.638
Brain - Hippocampus	111	-0.0555	0.3	0.678
Heart - Left Ventricle	272	-0.0671	0.2	0.602
Esophagus - Mucosa	358	-0.0683	0.04	0.898
Adipose - Subcutaneous	385	-0.0769	0.01	0.923
Brain - Caudate (basal ganglia)	144	-0.0839	0.1	0.767
Brain - Amygdala	88	-0.0839	0.3	0.621
Muscle - Skeletal	491	-0.0933	3.6e-3	0.980
Nerve - Tibial	361	-0.0941	0.01	0.964
Brain - Putamen (basal ganglia)	111	-0.107	0.06	0.878
Artery - Coronary	152	-0.110	0.08	0.883
Artery - Tibial	388	-0.112	0.007	0.955
Brain - Cortex	136	-0.115	0.007	0.947
Pituitary	157	-0.123	0.03	0.885
Cells - EBV-transformed lymphocytes	117	-0.138	0.05	0.872
Breast - Mammary Tissue	251	-0.145	1.3e-4	1.00
Cells - Transformed fibroblasts	300	-0.157	3.6e-5	1.00
Testis	225	-0.158	0.03	0.863
Artery - Aorta	267	-0.183	0.005	0.945

p-value for meta-analyzed effects 1.7×10^{-13}

Figure S3. *TTC22* expression summarized.

A) The effect of the GWAS-lead variant rs588709 on *TTC22* gene expression was studied in GTEx portal (accessed on April 15th, 2019) (17). 'Samples' indicate the number of RNA-seq samples with genotype. Normalized effect size (NES) is the slope of the linear regression of the normalized data versus the three genotype categories using single-tissue expression quantitative trait locus (eQTL) analysis, representing eQTL effect size. The 'p-value' originates from a t-test that compares observed NES from single-tissue eQTL analysis to a null NES of 0. The 'm-value' indicates the posterior probability that an eQTL effect exists in each tissue tested in the cross-tissue meta-analysis. The effect estimates are for the G allele that was the effect allele in the present GWAS. **B)** The tissue expression of *TTC22* in GTEx. Expression values are shown in Transcripts Per Million (TPM; y-axis) calculated from a model with isoforms collapsed to a single gene. The tissues are ordered according to the gene expression median (x-axis). **C)** Expression level of *TTC22* in Braineac database (upper) and *TTC22* expression stratified according to rs588709 genotype (lower) (braineac.org; accessed on April 15th, 2019). MEDU, medulla; WHMT, intralobular white matter; SNIG, substantia nigra; FCTX, frontal cortex; THAL, thalamus; HIPP, hippocampus; TCTX, temporal cortex; OCTX, occipital cortex; PUTM, putamen; CRBL, cerebellar cortex.



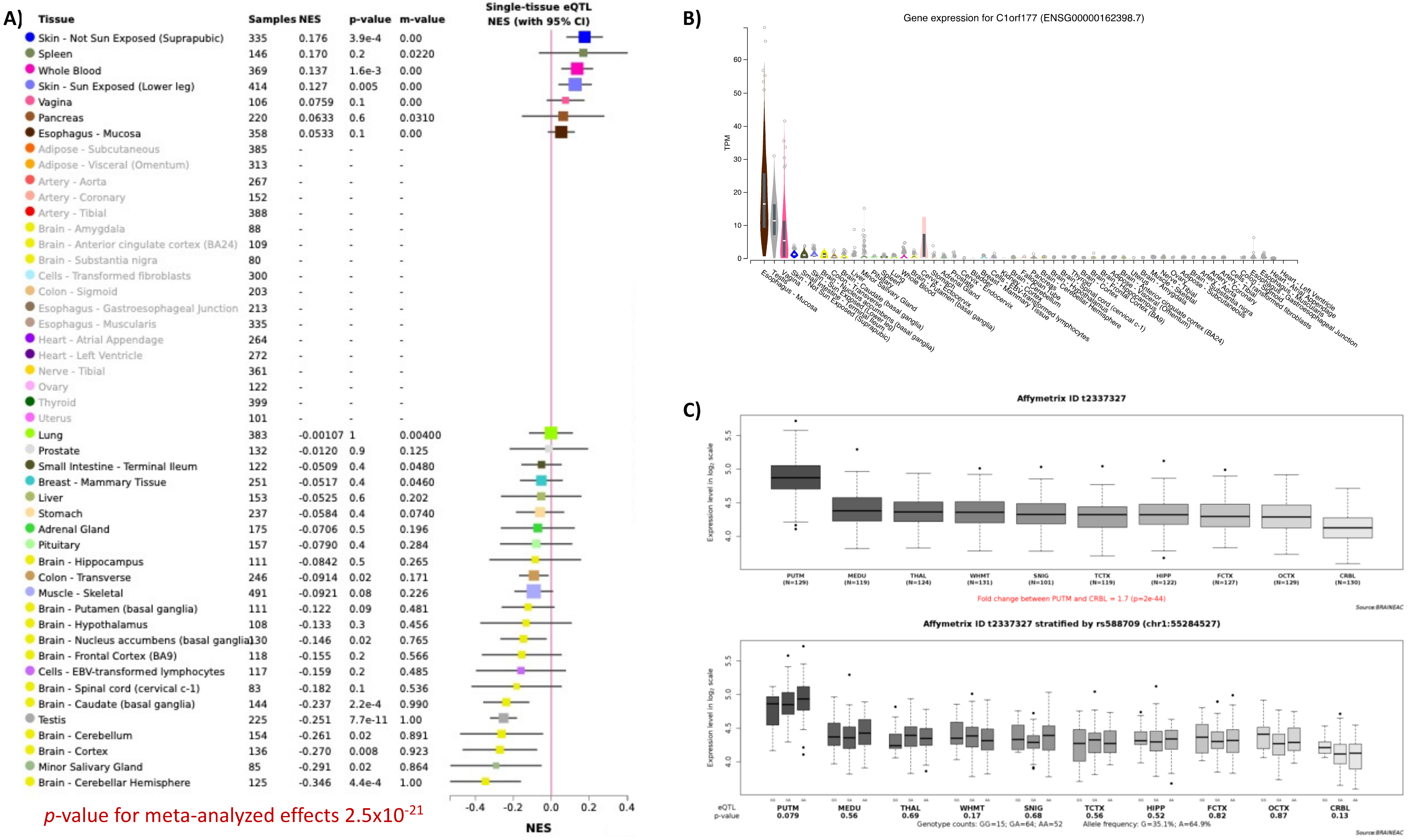
A)

Tissue	Samples	NES	p-value	m-value
Brain - Amygdala	88	0.189	0.2	0.575
Esophagus - Gastroesophageal Junction	213	0.176	0.06	0.653
Thyroid	399	0.174	1.2e-7	1.00
Brain - Frontal Cortex (BA9)	118	0.168	0.08	0.727
Cells - EBV-transformed lymphocytes	117	0.148	0.2	0.563
Pancreas	220	0.139	0.02	0.851
Adrenal Gland	175	0.124	0.07	0.704
Brain - Anterior cingulate cortex (BA24)	109	0.117	0.3	0.451
Heart - Atrial Appendage	264	0.113	0.2	0.638
Lung	383	0.109	1.0e-3	0.998
Skin - Not Sun Exposed (Suprapubic)	335	0.0857	3.0e-3	0.961
Brain - Cortex	136	0.0836	0.4	0.424
Artery - Coronary	152	0.0803	0.4	0.416
Brain - Hippocampus	111	0.0749	0.4	0.424
Pituitary	157	0.0747	0.2	0.518
Prostate	132	0.0716	0.1	0.612
Spleen	146	0.0683	0.3	0.409
Whole Blood	369	0.0661	0.08	0.664
Brain - Spinal cord (cervical c-1)	83	0.0606	0.7	0.351
Testis	225	0.0594	0.4	0.438
Breast - Mammary Tissue	251	0.0578	0.09	0.549
Ovary	122	0.0576	0.6	0.383
Minor Salivary Gland	85	0.0572	0.5	0.418
Uterus	101	0.0500	0.5	0.377
Skin - Sun Exposed (Lower leg)	414	0.0462	0.07	0.325
Adipose - Subcutaneous	385	0.0217	0.7	0.259
Esophagus - Mucosa	358	0.0156	0.5	0.0150
Brain - Hypothalamus	108	0.0136	0.8	0.225
Colon - Transverse	246	0.00758	0.8	0.0240
Artery - Aorta	267	0.00621	0.9	0.221
Small Intestine - Terminal Ileum	122	0.00502	0.9	0.105
Liver	153	0.00276	1	0.268
Brain - Substantia nigra	80	0.000974	1	0.340
Brain - Cerebellar Hemisphere	125	-	-	-
Cells - Transformed fibroblasts	300	-	-	-
Muscle - Skeletal	491	-	-	-
Adipose - Visceral (Omentum)	313	-0.00335	0.9	0.0400
Vagina	106	-0.00607	0.9	0.103
Esophagus - Muscularis	335	-0.0174	0.8	0.154
Artery - Tibial	388	-0.0321	0.6	0.0800
Stomach	237	-0.0463	0.2	0.00800
Heart - Left Ventricle	272	-0.0655	0.4	0.0790
Brain - Nucleus accumbens (basal ganglia)	130	-0.0702	0.1	0.0110
Brain - Cerebellum	154	-0.0791	0.5	0.179
Brain - Caudate (basal ganglia)	144	-0.0932	0.1	0.0160
Brain - Putamen (basal ganglia)	111	-0.0989	0.08	0.0230
Colon - Sigmoid	203	-0.115	0.04	0.0130
Nerve - Tibial	361	-0.138	0.07	0.0570

p-value for meta-analyzed effects 3.3×10^{-10}

Figure S4. *LEXM/C1orf177* expression summarized.

A) The effect of the GWAS-lead variant rs588709 on *LEXM/C1orf177* gene expression was studied in GTEx portal (accessed on April 15th, 2019) (17). 'Samples' indicate the number of RNA-seq samples with genotype. Normalized effect size (NES) is the slope of the linear regression of the normalized data versus the three genotype categories using single-tissue expression quantitative trait locus (eQTL) analysis, representing eQTL effect size. The 'p-value' originates from a t-test that compares observed NES from single-tissue eQTL analysis to a null NES of 0. The 'm-value' indicates the posterior probability that an eQTL effect exists in each tissue tested in the cross-tissue meta-analysis. The effect estimates are for the G allele that was the effect allele in the present GWAS. **B)** The tissue expression of *LEXM/C1orf177* in GTEx. Expression values are shown in Transcripts Per Million (TPM; y-axis) calculated from a model with isoforms collapsed to a single gene. The tissues are ordered according to the gene expression median (x-axis). **C)** Expression level of *LEXM/C1orf177* in Braineac database (upper) and *LEXM/C1orf177* expression stratified according to rs588709 genotype (lower) (braineac.org; accessed on April 15th, 2019). MEDU, medulla; WHMT, intralobular white matter; SNIG, substantia nigra; FCTX, frontal cortex; THAL, thalamus; HIPP, hippocampus; TCTX, temporal cortex; OCTX, occipital cortex; PUTM, putamen; CRBL, cerebellar cortex.



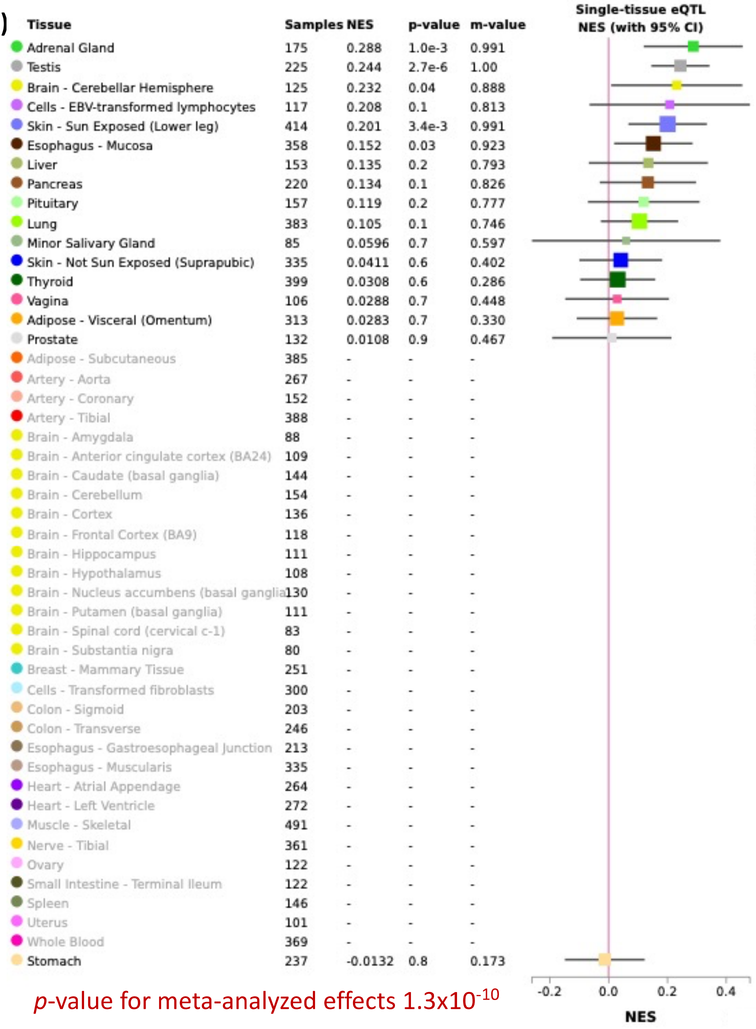
Tissue	Samples	NES	p-value	m-value
Skin - Not Sun Exposed (Suprapubic)	335	0.176	3.9e-4	0.00
Spleen	146	0.170	0.2	0.0220
Whole Blood	369	0.137	1.6e-3	0.00
Skin - Sun Exposed (Lower leg)	414	0.127	0.005	0.00
Vagina	106	0.0759	0.1	0.00
Pancreas	220	0.0633	0.6	0.0310
Esophagus - Mucosa	358	0.0533	0.1	0.00
Adipose - Subcutaneous	385	-	-	-
Adipose - Visceral (Omentum)	313	-	-	-
Artery - Aorta	267	-	-	-
Artery - Coronary	152	-	-	-
Artery - Tibial	388	-	-	-
Brain - Amygdala	88	-	-	-
Brain - Anterior cingulate cortex (BA24)	109	-	-	-
Brain - Substantia nigra	80	-	-	-
Cells - Transformed fibroblasts	300	-	-	-
Colon - Sigmoid	203	-	-	-
Esophagus - Gastroesophageal Junction	213	-	-	-
Esophagus - Muscularis	335	-	-	-
Heart - Atrial Appendage	264	-	-	-
Heart - Left Ventricle	272	-	-	-
Nerve - Tibial	361	-	-	-
Ovary	122	-	-	-
Thyroid	399	-	-	-
Uterus	101	-	-	-
Lung	383	-0.00107	1	0.00400
Prostate	132	-0.0120	0.9	0.125
Small Intestine - Terminal Ileum	122	-0.0509	0.4	0.0480
Breast - Mammary Tissue	251	-0.0517	0.4	0.0460
Liver	153	-0.0525	0.6	0.202
Stomach	237	-0.0584	0.4	0.0740
Adrenal Gland	175	-0.0706	0.5	0.196
Pituitary	157	-0.0790	0.4	0.284
Brain - Hippocampus	111	-0.0842	0.5	0.265
Colon - Transverse	246	-0.0914	0.02	0.171
Muscle - Skeletal	491	-0.0921	0.08	0.226
Brain - Putamen (basal ganglia)	111	-0.122	0.09	0.481
Brain - Hypothalamus	108	-0.133	0.3	0.456
Brain - Nucleus accumbens (basal ganglia)	130	-0.146	0.02	0.765
Brain - Frontal Cortex (BA9)	118	-0.155	0.2	0.566
Cells - EBV-transformed lymphocytes	117	-0.159	0.2	0.485
Brain - Spinal cord (cervical c-1)	83	-0.182	0.1	0.536
Brain - Caudate (basal ganglia)	144	-0.237	2.2e-4	0.990
Testis	225	-0.251	7.7e-11	1.00
Brain - Cerebellum	154	-0.261	0.02	0.891
Brain - Cortex	136	-0.270	0.008	0.923
Minor Salivary Gland	85	-0.291	0.02	0.864
Brain - Cerebellar Hemisphere	125	-0.346	4.4e-4	1.00

p-value for meta-analyzed effects 2.5×10^{-21}

Figure S5. RP11-67L3.4 expression summarized.

A) The effect of the GWAS-lead variant rs588709 on RP11-67L3.4 gene expression was studied in GTEx portal (accessed on April 15th, 2019) (17). 'Samples' indicate the number of RNA-seq samples with genotype. Normalized effect size (NES) is the slope of the linear regression of the normalized data versus the three genotype categories using single-tissue expression quantitative trait locus (eQTL) analysis, representing eQTL effect size. The 'p-value' originates from a t-test that compares observed NES from single-tissue eQTL analysis to a null NES of 0. The 'm-value' indicates the posterior probability that an eQTL effect exists in each tissue tested in the cross-tissue meta-analysis. The effect estimates are for the G allele that was the effect allele in the present GWAS. **B)** The tissue expression of RP11-67L3.4 in GTEx. Expression values are shown in Transcripts Per Million (TPM; y-axis) calculated from a model with isoforms collapsed to a single gene. The tissues are ordered according to the gene expression median (x-axis). **C)** RP11-67L3.4 was not found in Braineac database (braineac.org; accessed on April 15th, 2019).

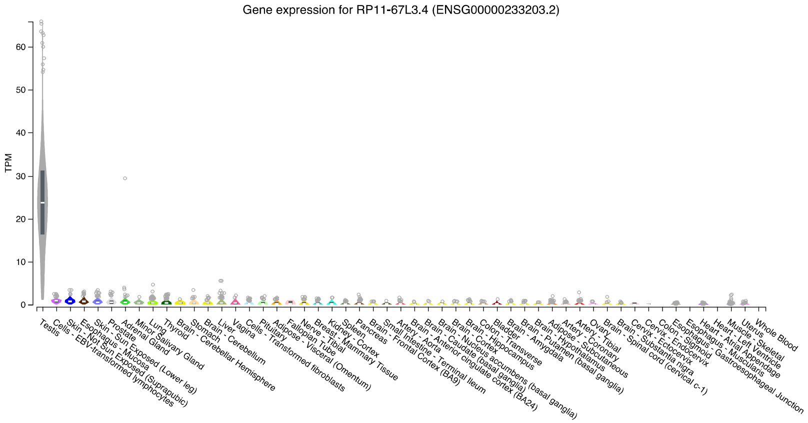
A)



Tissue	Samples	NES	p-value	m-value
Adrenal Gland	175	0.288	1.0e-3	0.991
Testis	225	0.244	2.7e-6	1.00
Brain - Cerebellar Hemisphere	125	0.232	0.04	0.888
Cells - EBV-transformed lymphocytes	117	0.208	0.1	0.813
Skin - Sun Exposed (Lower leg)	414	0.201	3.4e-3	0.991
Esophagus - Mucosa	358	0.152	0.03	0.923
Liver	153	0.135	0.2	0.793
Pancreas	220	0.134	0.1	0.826
Pituitary	157	0.119	0.2	0.777
Lung	383	0.105	0.1	0.746
Minor Salivary Gland	85	0.0596	0.7	0.597
Skin - Not Sun Exposed (Suprapubic)	335	0.0411	0.6	0.402
Thyroid	399	0.0308	0.6	0.286
Vagina	106	0.0288	0.7	0.448
Adipose - Visceral (Omentum)	313	0.0283	0.7	0.330
Prostate	132	0.0108	0.9	0.467
Adipose - Subcutaneous	385	-	-	-
Artery - Aorta	267	-	-	-
Artery - Coronary	152	-	-	-
Artery - Tibial	388	-	-	-
Brain - Amygdala	88	-	-	-
Brain - Anterior cingulate cortex (BA24)	109	-	-	-
Brain - Caudate (basal ganglia)	144	-	-	-
Brain - Cerebellum	154	-	-	-
Brain - Cortex	136	-	-	-
Brain - Frontal Cortex (BA9)	118	-	-	-
Brain - Hippocampus	111	-	-	-
Brain - Hypothalamus	108	-	-	-
Brain - Nucleus accumbens (basal ganglia)	130	-	-	-
Brain - Putamen (basal ganglia)	111	-	-	-
Brain - Spinal cord (cervical c-1)	83	-	-	-
Brain - Substantia nigra	80	-	-	-
Breast - Mammary Tissue	251	-	-	-
Cells - Transformed fibroblasts	300	-	-	-
Colon - Sigmoid	203	-	-	-
Colon - Transverse	246	-	-	-
Esophagus - Gastroesophageal Junction	213	-	-	-
Esophagus - Muscularis	335	-	-	-
Heart - Atrial Appendage	264	-	-	-
Heart - Left Ventricle	272	-	-	-
Muscle - Skeletal	491	-	-	-
Nerve - Tibial	361	-	-	-
Ovary	122	-	-	-
Small Intestine - Terminal Ileum	122	-	-	-
Spleen	146	-	-	-
Uterus	101	-	-	-
Whole Blood	369	-	-	-
Stomach	237	-0.0132	0.8	0.173

p-value for meta-analyzed effects 1.3×10^{-10}

B)



C)

Figure S6. Expression of A) *DHCR24*, B) *TTC22*, and C) *LEXM/C1orf177* in the brain during lifespan.

Cerebrocortical mRNA expression of the three genes was acquired from five post-mortem human databases (Allen Human Brain Atlas, ABHA; BrainCloud; BRAINEAC; BrainSpan; and GTEx) with a total of 572 donors. Within each database, mRNA expression was scaled by region and all scaled values were pooled by cortical lobe. Donor age (x-axis) was regressed on lobar expression (y-axis) adjusting for sex as a fixed effect and donor ID as a random effect. Colours indicate the database from which the expression data was obtained.

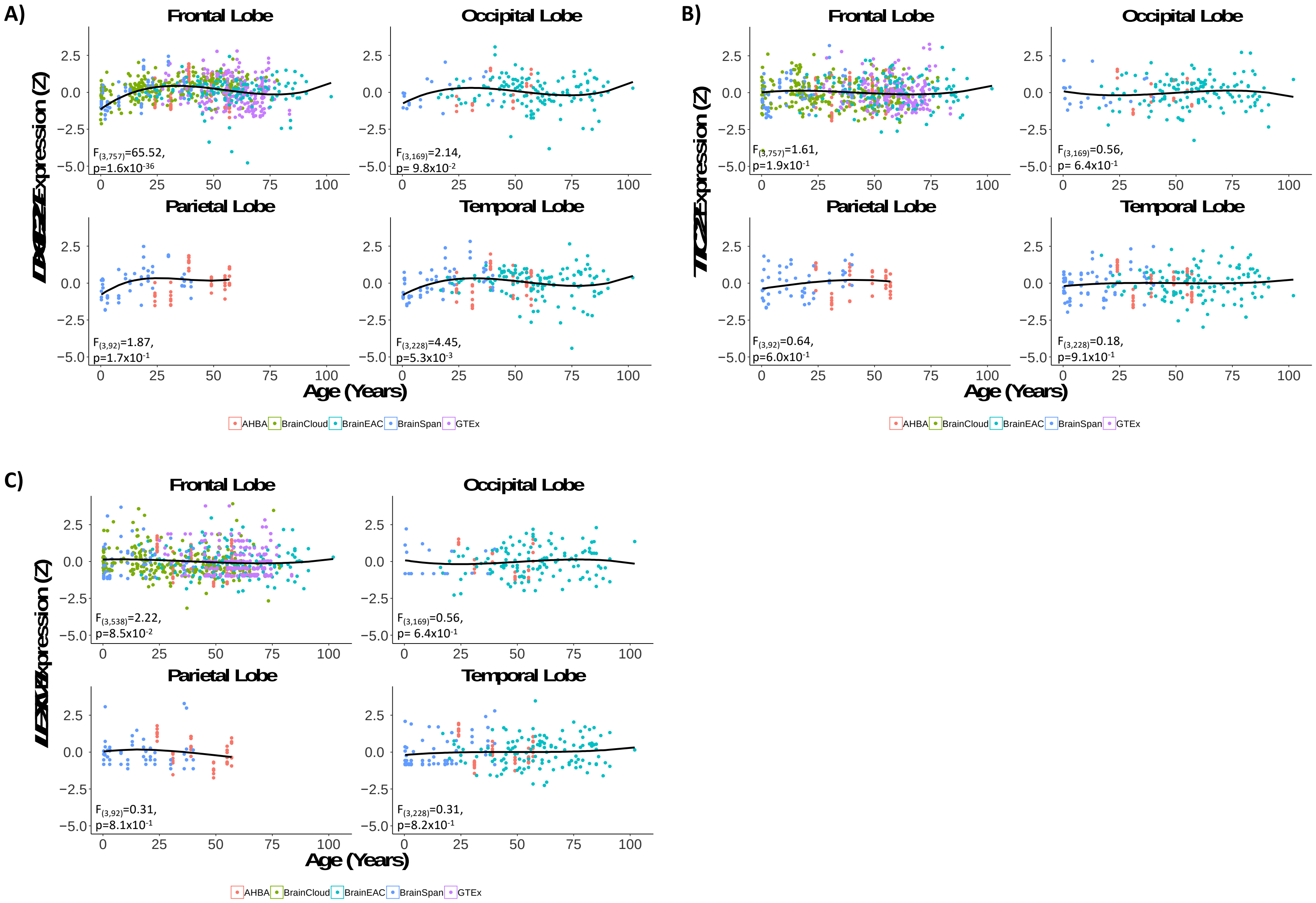


Figure S7. A) Cell Type and B) Gene Ontology (GO) enrichment analysis with top 1% of genes co-expressed with *DHCR24, TTC22, and LEXM.*

Cerebrocortical expression of *DHCR24*, *TTC22*, and *LEXM/C1orf177* mRNA was acquired from five post-mortem human databases (Allen Human Brain Atlas, ABHA; BrainCloud; BRAINEAC; BrainSpan; and GTEx) with a total of 572 donors. To study the co-expression of the three genes with all other 16,036 genes measured in each of the five databases, linear mixed models were fitted to adjust for age, sex, and repeated measures as random effect. The top 1% of positively co-expressed genes were then tested for enrichment with neural cell specific markers derived from PsychENCODE (adult) (14) and single-cell RNAseq data by Lake et al. (15). The same sets of co-expressed genes were used in GO analysis conducted using ToppGene (16). Red line represents Bonferroni-adjusted p-value threshold.

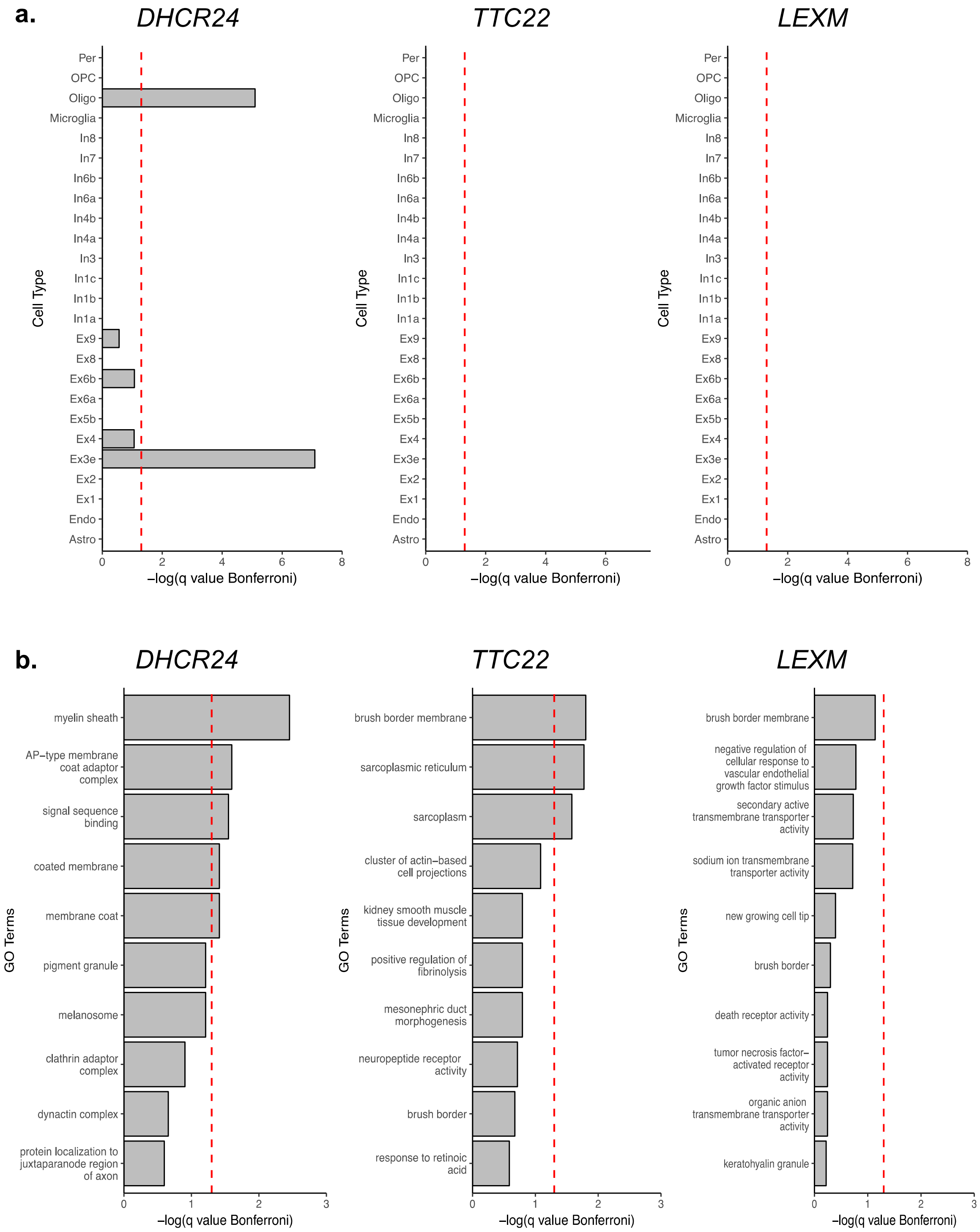


Figure S8. Genomic locations of rs588709 and the six CpG sites where DNA methylation associates with rs588709 in adolescence.

The variant rs588709 was found to be associated with the first principal component of visceral fat, circulating level of PC16:0/2:0 and T1W-SI of white-matter in the present study. Based on mQTLdb (mqtldb.org), the rs588709 genotype was found to be associated with DNA methylation at five CpG sites in childhoold (labelled with 'C') and six CpG sites in adolescence (labelled with 'A'); the GWAS effect allele G associated with higher level of methylation at all the CpG sites (Table S1). Genomic locations correspond to the GRCh37/hg19 assembly.

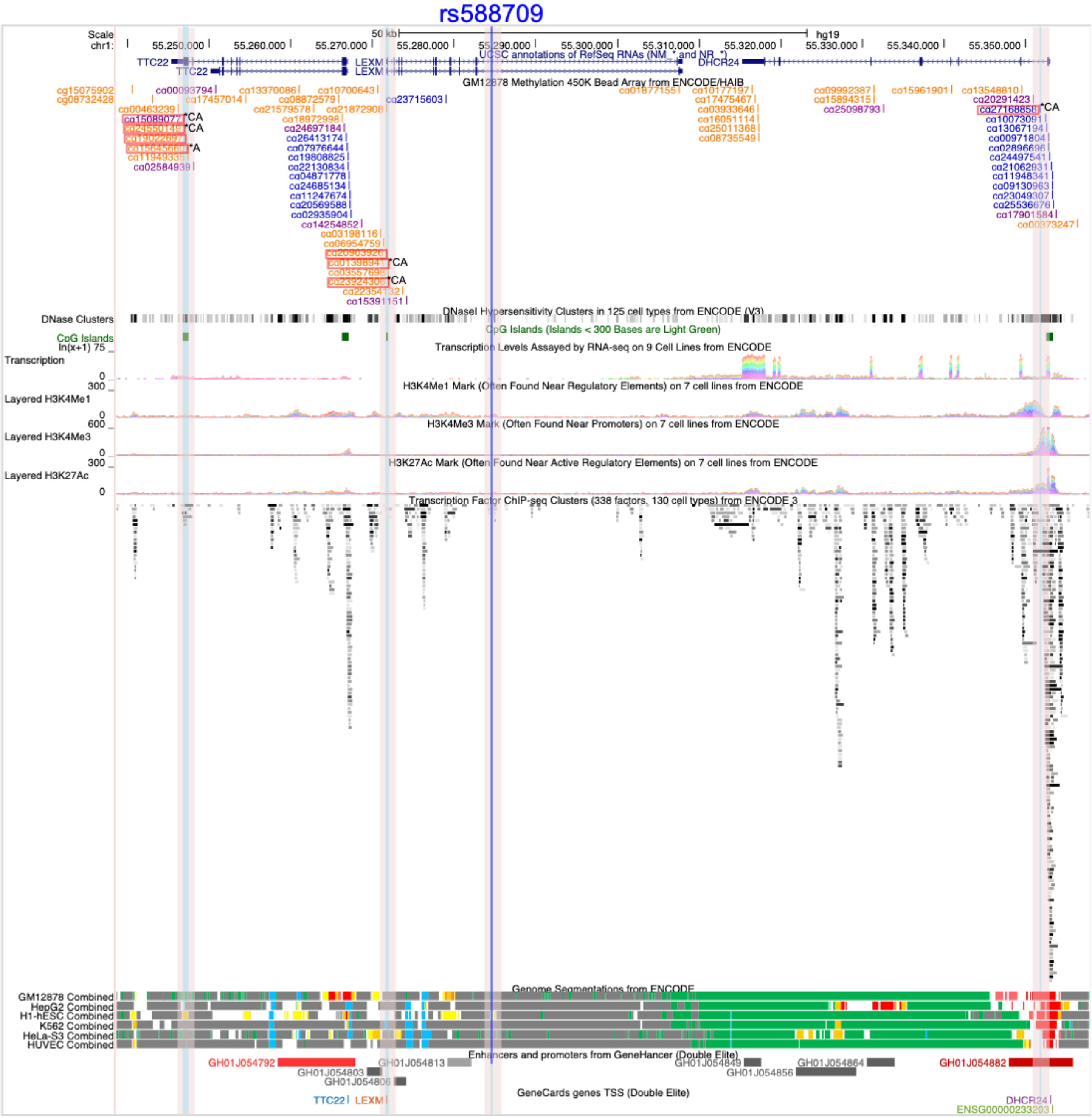


Figure S9. Associations of *DHCR24* rs588709 with 228 metabolic measures in SYS adolescents.

The metabolomic associations of rs588709 genotype were evaluated in linear models, in which metabolite concentrations served as outcome and the genotype as an explanatory variable, encoded as 0, 1, and 2 representing the number of GWAS effect alleles (G). Prior to the linear modelling, each metabolic trait was adjusted for age, sex, and common family environment by using lmekin from coxme R package, and inverse rank-transformed to normality. Effect estimates and corresponding 95% confidence intervals are in standard deviation (SD)-units. Filled circles indicate associations with p-value<0.002. Metabolite abbreviations as in Table S3.

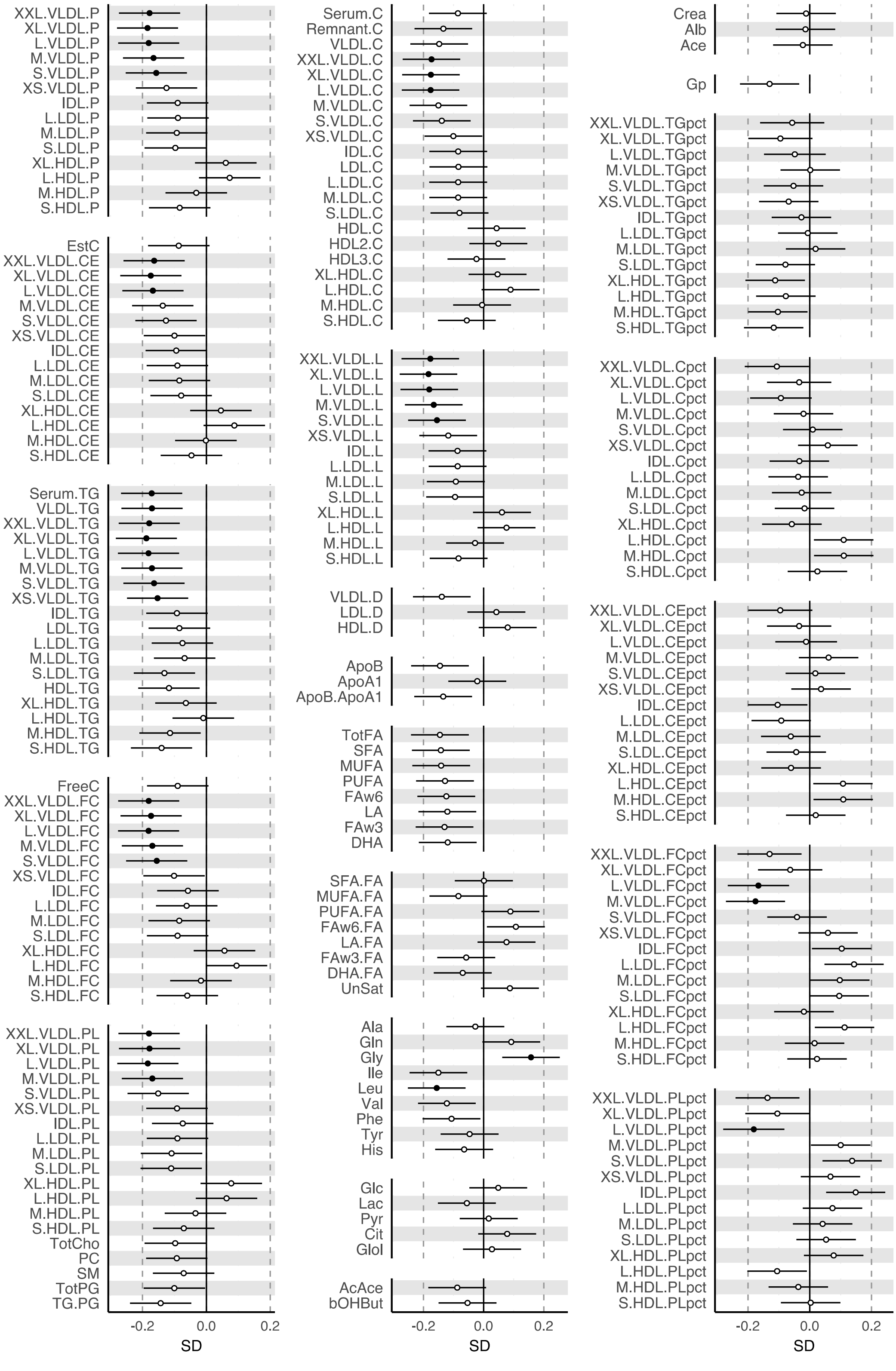


Figure S10. Comparisons of the metabolic effects of *DHCR24*, *TM6SF2*, and *HMGCR* variants.

Metabolomic association profile of *DHCR24* rs588709-G (yellow) in SYS adolescents was compared with metabolomic association profiles of *TM6SF2* rs58542926-T (turqoise) and *HMGCR* rs12916-T (gray) obtained from a published metabolomic GWAS (18). The NMR metabolomics platform used in the study by Kettunen *et al.* is an older quantification version of the platform used in the present study. The 111 metabolic measures available in both studies were compared. To overcome the differences in the effect sizes of the absolute effects, the effect estimates and corresponding 95% confidence intervals were scaled to a common factor that was the lowering effect on apolipoprotein B (ApoB) concentration. Metabolite abbreviations as in Table S3.

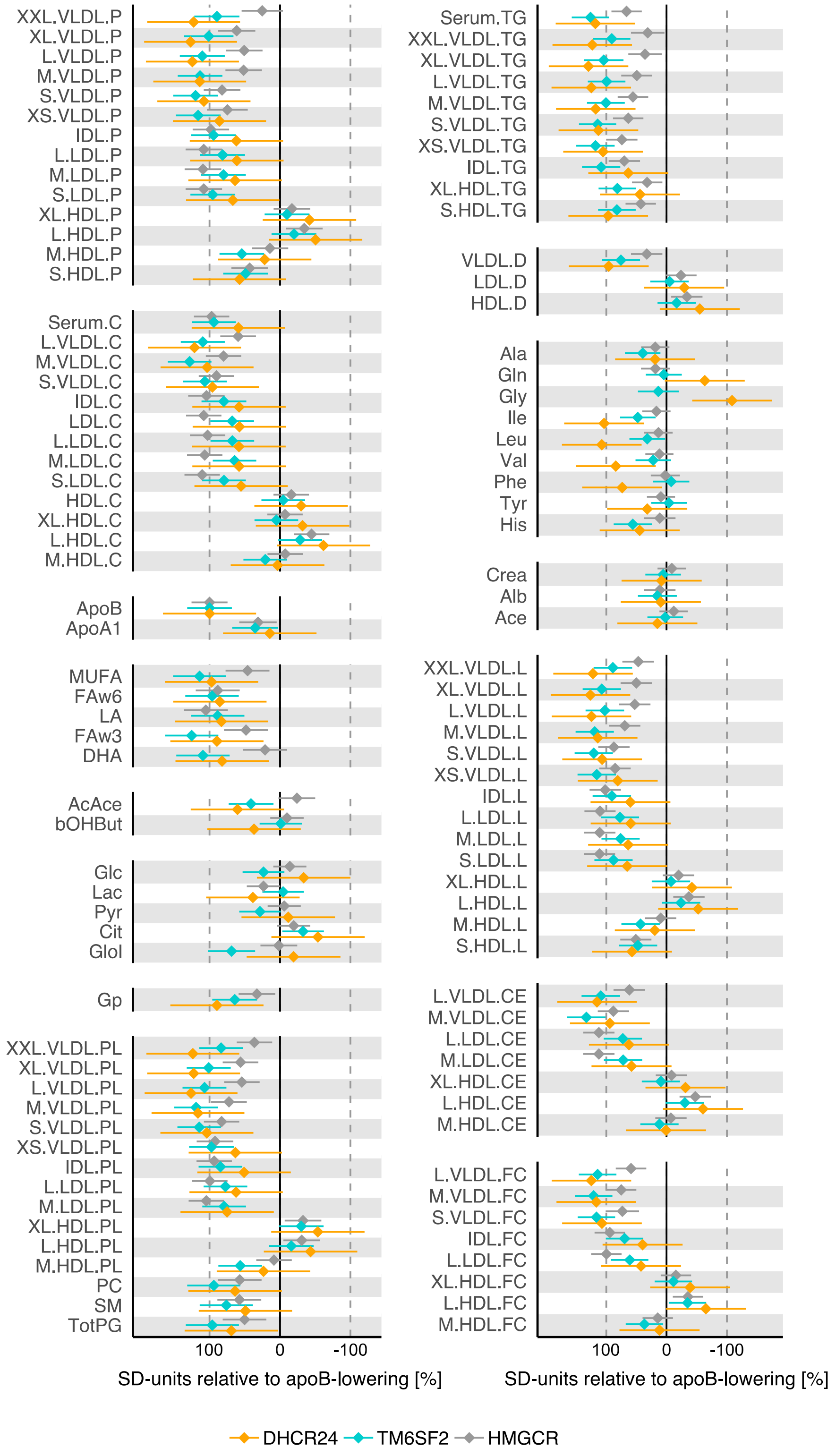


Table S1. DNA methylation in blood associating with rs588709 in mQTLdb.

Timepoint	SNP	SNP Chr	SNP Pos	A1	A2	MAF	CpG	CpG Chr	CpG Pos	beta	t-stat	Effect Size	p-value	Trans
Pregnancy	rs588709	1	55284527	G	A	0.352	cg23924306	1	55271927	0.30622	6.85474	0.01439	1.48E-11	N
Pregnancy	rs588709	1	55284527	G	A	0.352	cg01398941	1	55271902	0.27853	5.81536	0.00653	8.90E-09	N
Pregnancy	rs588709	1	55284527	G	A	0.352	cg15645660	1	55247356	0.25334	5.42319	0.01216	7.87E-08	N
Pregnancy	rs588709	1	55284527	G	A	0.352	cg19022697	1	55247140	0.26495	5.60981	0.02961	2.83E-08	N
Birth	rs588709	1	55284527	G	A	0.345	cg23924306	1	55271927	0.30239	6.773	0.02311	2.51E-11	N
Birth	rs588709	1	55284527	G	A	0.345	cg20903926	1	55271677	0.27255	5.98808	0.08344	3.26E-09	N
Childhood	rs588709	1	55284527	G	A	0.34	cg15089077	1	55246867	0.28751	6.36037	0.01114	3.32E-10	N
Childhood	rs588709	1	55284527	G	A	0.34	cg24550149	1	55246954	0.26061	5.97309	0.02648	3.45E-09	N
Childhood	rs588709	1	55284527	G	A	0.34	cg27168858	1	55351659	0.28628	6.87681	0.04399	1.20E-11	N
Childhood	rs588709	1	55284527	G	A	0.34	cg23924306	1	55271927	0.28162	6.678	0.01203	4.43E-11	N
Childhood	rs588709	1	55284527	G	A	0.34	cg01398941	1	55271902	0.29735	6.81195	0.00821	1.85E-11	N
Adolescence	rs588709	1	55284527	G	A	0.34	cg24550149	1	55246954	0.26757	5.85618	0.02491	6.81E-09	N
Adolescence	rs588709	1	55284527	G	A	0.34	cg15645660	1	55247356	0.25295	5.55413	0.02714	3.75E-08	N
Adolescence	rs588709	1	55284527	G	A	0.34	cg01398941	1	55271902	0.30548	6.98018	0.0059	6.01E-12	N
Adolescence	rs588709	1	55284527	G	A	0.34	cg15089077	1	55246867	0.26822	5.89339	0.01469	5.49E-09	N
Adolescence	rs588709	1	55284527	G	A	0.34	cg27168858	1	55351659	0.24063	5.46697	0.01988	6.05E-08	N
Adolescence	rs588709	1	55284527	G	A	0.34	cg23924306	1	55271927	0.29716	7.01128	0.00838	4.87E-12	N
Middle Age	rs588709	1	55284527	G	A	0.359	cg23924306	1	55271927	0.26017	5.70002	0.01218	1.73E-08	N

Table S2. Regulatory motifs altered by rs588709 as reported in HaploReg.

Position Weight Matrix ID (Library from Kheradpour and Kellis, 2013)	Strand	Ref (A)	Alt (G)	Match on: Ref: TCAAGCAATCTGCCTGTCTCAGCCTCCCA**A**CGTGCTGGGATTACAGGTGTGAGCCACTG Alt: TCAAGCAATCTGCCTGTCTCAGCCTCCCA**G**CGTGCTGGGATTACAGGTGTGAGCCACTG
Ik-1_2	-	12.1	10.7	YYYCCYARM
NRSF_disc10	+	13.3	1.3	AAGGWGCTS
SETDB1_disc1	-	5	8.8	RRACTACMWYTYCCRKVRDKCHNYG
SP1_known3	-	0.3	10.6	CCCYSCMSMMKKST
Znf143_disc3	+	7	12	GSVBBSBGGGVVNBGBRGB

Table S3. Metabolite mean concentrations and associations with rs588709 in SYS adolescents

	Summary of metabolic measures in SYS adolescents				**Association with rs588709 (in standard deviation units)**				
Metabolic measure (abbreviation)	**mean**	**sd**	**unit**	**n**	**beta**	**CI95L**	**CI95U**	**p**	**Rate of corroboration**
Lipoprotein subclass particle concentrations									
XXL VLDL (XXL.VLDL.P)	7.6E-11	8.65E-11	mol/l	931	-0.178	-0.274	-0.082	0.00028	0.640
XL VLDL (XL.VLDL.P)	3.8E-10	4.85E-10	mol/l	931	-0.184	-0.280	-0.089	0.00017	0.696
L VLDL (L.VLDL.P)	2.9E-09	2.77E-09	mol/l	931	-0.181	-0.276	-0.085	0.00023	0.662
M VLDL (M.VLDL.P)	1.3E-08	6.78E-09	mol/l	931	-0.165	-0.261	-0.070	0.00074	0.468
S VLDL (S.VLDL.P)	2.2E-08	7.81E-09	mol/l	931	-0.157	-0.253	-0.061	0.0014	0.349
XS VLDL (XS.VLDL.P)	2.9E-08	7.06E-09	mol/l	931	-0.125	-0.221	-0.029	0.011	0
IDL (IDL.P)	7.9E-08	2.00E-08	mol/l	931	-0.090	-0.186	0.006	0.068	0
L LDL (L.LDL.P)	1.3E-07	3.55E-08	mol/l	931	-0.089	-0.185	0.007	0.070	0
M LDL (M.LDL.P)	1.0E-07	3.04E-08	mol/l	931	-0.093	-0.189	0.004	0.059	0
S LDL (S.LDL.P)	1.2E-07	3.38E-08	mol/l	931	-0.097	-0.194	-0.001	0.048	0
XL HDL (XL.HDL.P)	3.7E-07	1.70E-07	mol/l	931	0.061	-0.036	0.157	0.217	0
L HDL (L.HDL.P)	1.0E-06	4.14E-07	mol/l	931	0.073	-0.023	0.169	0.137	0
M HDL (M.HDL.P)	1.8E-06	3.37E-07	mol/l	931	-0.032	-0.128	0.065	0.519	0
S HDL (S.HDL.P)	4.6E-06	4.57E-07	mol/l	931	-0.083	-0.180	0.013	0.089	0
Cholesterol in									
Serum total (Serum.C)	3.420	0.714	mmol/l	931	-0.086	-0.182	0.011	0.081	0
Remnants (Remnant.C)	0.975	0.294	mmol/l	931	-0.134	-0.230	-0.038	0.0064	0.002
VLDL total (VLDL.C)	0.472	0.186	mmol/l	931	-0.148	-0.244	-0.052	0.0026	0.193
XXL VLDL (XXL.VLDL.C)	0.0024	0.0032	mmol/l	931	-0.173	-0.269	-0.078	0.00041	0.586
XL VLDL (XL.VLDL.C)	0.0070	0.0094	mmol/l	931	-0.175	-0.271	-0.080	0.00035	0.615
L VLDL (L.VLDL.C)	0.036	0.037	mmol/l	931	-0.176	-0.272	-0.081	0.00032	0.618
M VLDL (M.VLDL.C)	0.104	0.060	mmol/l	931	-0.150	-0.246	-0.054	0.0022	0.250
S VLDL (S.VLDL.C)	0.141	0.055	mmol/l	931	-0.139	-0.235	-0.043	0.0046	0.054
XS VLDL (XS.VLDL.C)	0.180	0.046	mmol/l	931	-0.101	-0.197	-0.004	0.041	0
IDL (IDL.C)	0.503	0.140	mmol/l	931	-0.084	-0.181	0.012	0.086	0
LDL total (LDL.C)	1.158	0.373	mmol/l	931	-0.084	-0.180	0.013	0.089	0
L LDL (L.LDL.C)	0.609	0.188	mmol/l	931	-0.085	-0.181	0.012	0.085	0
M LDL (M.LDL.C)	0.340	0.117	mmol/l	931	-0.084	-0.181	0.012	0.086	0
S LDL (S.LDL.C)	0.208	0.070	mmol/l	931	-0.080	-0.176	0.016	0.103	0
HDL total (HDL.C)	1.287	0.261	mmol/l	931	0.043	-0.053	0.140	0.377	0
HDL$_2$ (HDL2.C)	0.820	0.242	mmol/l	931	0.049	-0.047	0.145	0.319	0
HDL$_3$ (HDL3.C)	0.467	0.025	mmol/l	931	-0.024	-0.120	0.073	0.630	0
XL HDL (XL.HDL.C)	0.176	0.080	mmol/l	931	0.046	-0.050	0.143	0.346	0
L HDL (L.HDL.C)	0.311	0.140	mmol/l	931	0.090	-0.007	0.186	0.068	0
M HDL (M.HDL.C)	0.388	0.076	mmol/l	931	-0.005	-0.101	0.091	0.918	0
S HDL (S.HDL.C)	0.409	0.050	mmol/l	931	-0.056	-0.152	0.040	0.256	0

Triglycerides in									
Serum total (Serum.TG)	0.927	0.395	mmol/l	931	-0.171	-0.267	-0.076	0.00048	0.538
VLDL total (VLDL.TG)	0.631	0.340	mmol/l	931	-0.170	-0.266	-0.075	0.00051	0.516
XXL VLDL (XXL.VLDL.TG)	0.012	0.013	mmol/l	931	-0.179	-0.275	-0.083	0.00026	0.655
XL VLDL (XL.VLDL.TG)	0.024	0.030	mmol/l	931	-0.188	-0.284	-0.092	0.00013	0.739
L VLDL (L.VLDL.TG)	0.101	0.095	mmol/l	931	-0.181	-0.277	-0.085	0.00022	0.674
M VLDL (M.VLDL.TG)	0.228	0.124	mmol/l	931	-0.170	-0.266	-0.075	0.00051	0.531
S VLDL (S.VLDL.TG)	0.181	0.070	mmol/l	931	-0.164	-0.260	-0.068	0.00083	0.450
XS VLDL (XS.VLDL.TG)	0.079	0.023	mmol/l	931	-0.153	-0.249	-0.057	0.0018	0.279
IDL (IDL.TG)	0.077	0.021	mmol/l	931	-0.092	-0.188	0.004	0.061	0
LDL total (LDL.TG)	0.110	0.036	mmol/l	931	-0.085	-0.181	0.012	0.086	0
L LDL (L.LDL.TG)	0.062	0.020	mmol/l	931	-0.075	-0.171	0.021	0.128	0
M LDL (M.LDL.TG)	0.029	0.010	mmol/l	931	-0.068	-0.164	0.028	0.166	0
S LDL (S.LDL.TG)	0.019	0.0069	mmol/l	931	-0.131	-0.227	-0.035	0.0076	0
HDL total (HDL.TG)	0.110	0.031	mmol/l	931	-0.117	-0.213	-0.021	0.017	0
XL HDL (XL.HDL.TG)	0.0099	0.0058	mmol/l	931	-0.064	-0.160	0.032	0.193	0
L HDL (L.HDL.TG)	0.022	0.011	mmol/l	931	-0.010	-0.106	0.087	0.843	0
M HDL (M.HDL.TG)	0.036	0.012	mmol/l	931	-0.114	-0.210	-0.018	0.021	0
S HDL (S.HDL.TG)	0.042	0.011	mmol/l	931	-0.140	-0.236	-0.044	0.0042	0.073
Phospholipids in									
XXL VLDL (XXL.VLDL.PL)	0.0016	0.0022	mmol/l	931	-0.180	-0.275	-0.084	0.00025	0.658
XL VLDL (XL.VLDL.PL)	0.0052	0.0076	mmol/l	931	-0.178	-0.274	-0.082	0.00028	0.639
L VLDL (L.VLDL.PL)	0.028	0.029	mmol/l	931	-0.183	-0.279	-0.088	0.00019	0.685
M VLDL (M.VLDL.PL)	0.083	0.043	mmol/l	931	-0.169	-0.265	-0.073	0.00057	0.511
S VLDL (S.VLDL.PL)	0.101	0.033	mmol/l	931	-0.151	-0.247	-0.055	0.0021	0.248
XS VLDL (XS.VLDL.PL)	0.107	0.028	mmol/l	931	-0.092	-0.188	0.004	0.061	0
IDL (IDL.PL)	0.224	0.053	mmol/l	931	-0.074	-0.170	0.022	0.132	0
L LDL (L.LDL.PL)	0.248	0.054	mmol/l	931	-0.090	-0.187	0.006	0.066	0
M LDL (M.LDL.PL)	0.153	0.032	mmol/l	931	-0.109	-0.205	-0.013	0.026	0
S LDL (S.LDL.PL)	0.114	0.021	mmol/l	931	-0.110	-0.206	-0.014	0.025	0
XL HDL (XL.HDL.PL)	0.189	0.092	mmol/l	931	0.078	-0.018	0.174	0.113	0
L HDL (L.HDL.PL)	0.307	0.117	mmol/l	931	0.063	-0.033	0.159	0.199	0
M HDL (M.HDL.PL)	0.358	0.066	mmol/l	931	-0.034	-0.130	0.062	0.490	0
S HDL (S.HDL.PL)	0.566	0.061	mmol/l	931	-0.071	-0.167	0.026	0.150	0
Total cholines (TotCho)	1.858	0.319	mmol/l	931	-0.097	-0.194	-0.001	0.047	0
Phosphatidylcholine (PC)	1.531	0.297	mmol/l	931	-0.093	-0.189	0.004	0.059	0
Sphingomyelins (SM)	0.330	0.062	mmol/l	931	-0.071	-0.168	0.025	0.147	0
Phosphoglycerides (TotPG)	1.480	0.307	mmol/l	931	-0.100	-0.196	-0.004	0.041	0
Triglycerides to phosphoglycerides ratio (TG.PG)	0.526	0.212	ratio	931	-0.143	-0.239	-0.047	0.0035	0.093

Average particle diameter of									
VLDL (VLDL.D)	36.5	1.249	nm	931	-0.139	-0.235	-0.043	0.0046	0.050
LDL (LDL.D)	23.6	0.105	nm	931	0.042	-0.054	0.139	0.389	0
HDL (HDL.D)	9.9	0.229	nm	931	0.080	-0.016	0.176	0.104	0
Apolipoproteins									
Apolipoprotein B (ApoB)	0.681	0.146	g/l	931	-0.145	-0.241	-0.049	0.0031	0.149
Apolipoprotein A-I (ApoA1)	1.363	0.162	g/l	931	-0.021	-0.117	0.075	0.668	0
ApoB to ApoA1 ratio (ApoB.ApoA1)	0.503	0.108	ratio	931	-0.134	-0.230	-0.038	0.0062	0.003
Fatty acids									
Total fatty acids (TotFA)	8.741	1.892	mmol/l	928	-0.145	-0.241	-0.049	0.0031	0.154
Saturated fatty acids (SFA)	3.150	0.695	mmol/l	928	-0.142	-0.238	-0.046	0.0038	0.099
Monounsaturated fatty acids (MUFA)	2.286	0.655	mmol/l	928	-0.141	-0.237	-0.045	0.0041	0.072
Polyunsaturated fatty acids (PUFA)	3.305	0.635	mmol/l	928	-0.128	-0.225	-0.032	0.0090	0
Omega-6 fatty acids (FAw6)	3.033	0.557	mmol/l	928	-0.124	-0.220	-0.028	0.012	0
Linoleic acid (LA)	2.549	0.495	mmol/l	928	-0.121	-0.217	-0.024	0.014	0
Omega-3 fatty acids (FAw3)	0.273	0.088	mmol/l	928	-0.130	-0.226	-0.034	0.0082	0
Docosahexaenoic acid (DHA)	0.074	0.031	mmol/l	928	-0.119	-0.216	-0.023	0.015	0
Fatty acid ratios									
SFA to total FA ratio (SFA.FA)	36.0	1.972	%	928	0.001	-0.096	0.097	0.988	0
MUFA to total FA ratio (MUFA.FA)	25.9	2.662	%	928	-0.084	-0.180	0.013	0.089	0
PUFA to total FA ratio (PUFA.FA)	38.0	2.881	%	928	0.089	-0.007	0.185	0.070	0
FAw6 to total FA ratio (FAw6.FA)	34.9	2.770	%	928	0.107	0.011	0.204	0.029	0
LA to total FA ratio (LA.FA)	29.4	2.773	%	928	0.076	-0.020	0.172	0.122	0
FAw3 to total FA ratio (FAw3.FA)	3.076	0.532	%	928	-0.058	-0.154	0.039	0.241	0
DHA to total FA ratio (DHA.FA)	0.833	0.243	%	928	-0.069	-0.166	0.027	0.158	0
Degree of unsaturation (UnSat)	1.210	0.061		928	0.087	-0.009	0.184	0.076	0
Amino acids									
Alanine (Ala)	0.378	0.054	mmol/l	931	-0.028	-0.124	0.069	0.575	0
Glutamine (Gln)	0.492	0.064	mmol/l	931	0.092	-0.004	0.188	0.062	0
Glycine (Gly)	0.273	0.049	mmol/l	931	0.158	0.062	0.253	0.0013	0.346
Isoleucine (Ile)	0.049	0.011	mmol/l	931	-0.150	-0.246	-0.054	0.0022	0.255
Leucine (Leu)	0.069	0.013	mmol/l	931	-0.156	-0.252	-0.060	0.0015	0.325
Valine (Val)	0.147	0.027	mmol/l	931	-0.122	-0.218	-0.026	0.013	0
Phenylalanine (Phe)	0.065	0.0081	mmol/l	931	-0.107	-0.203	-0.011	0.030	0
Tyrosine (Tyr)	0.050	0.010	mmol/l	931	-0.047	-0.143	0.050	0.342	0
Histidine (His)	0.067	0.016	mmol/l	931	-0.065	-0.161	0.032	0.188	0
Glycolysis and gluconeogenesis									
Glucose (Glc)	3.590	0.336	mmol/l	931	0.049	-0.048	0.145	0.322	0
Lactate (Lac)	1.593	0.393	mmol/l	931	-0.056	-0.152	0.041	0.256	0
Pyruvate (Pyr)	0.073	0.024	mmol/l	931	0.017	-0.079	0.113	0.731	0
Citrate (Cit)	0.116	0.036	mmol/l	931	0.078	-0.018	0.175	0.111	0

Glycerol (Glol)	0.078	0.032	mmol/l	927	0.028	-0.069	0.124	0.572	0
Ketone bodies									
Acetoacetate (AcAce)	0.040	0.033	mmol/l	931	-0.088	-0.184	0.008	0.074	0
β-hydroxybutyrate (bOHBut)	0.120	0.069	mmol/l	931	-0.054	-0.150	0.043	0.276	0
Miscellaneous									
Creatinine (Crea)	0.050	0.0087	mmol/l	931	-0.012	-0.108	0.084	0.808	0
Albumin (Alb)	0.089	0.0054	cu	931	-0.014	-0.110	0.083	0.778	0
Acetate (Ace)	0.038	0.0067	mmol/l	931	-0.022	-0.119	0.074	0.652	0
Inflammation									
Glycoprotein acetyls (Gp)	1.183	0.188	mmol/l	931	-0.130	-0.226	-0.034	0.0081	0
Cholesteryl esters in									
Serum total (EstC)	2.414	0.513	mmol/l	931	-0.086	-0.183	0.010	0.079	0
XXL VLDL (XXL.VLDL.CE)	0.0014	0.0018	mmol/l	931	-0.164	-0.259	-0.068	0.00085	0.444
XL VLDL (XL.VLDL.CE)	0.0042	0.0052	mmol/l	931	-0.174	-0.270	-0.078	0.00039	0.587
L VLDL (L.VLDL.CE)	0.022	0.019	mmol/l	931	-0.167	-0.263	-0.072	0.00064	0.493
M VLDL (M.VLDL.CE)	0.062	0.033	mmol/l	931	-0.136	-0.232	-0.040	0.0054	0.018
S VLDL (S.VLDL.CE)	0.086	0.036	mmol/l	931	-0.126	-0.222	-0.030	0.010	0
XS VLDL (XS.VLDL.CE)	0.123	0.032	mmol/l	931	-0.100	-0.196	-0.004	0.042	0
IDL (IDL.CE)	0.360	0.101	mmol/l	931	-0.094	-0.190	0.002	0.055	0
L LDL (L.LDL.CE)	0.425	0.143	mmol/l	931	-0.091	-0.187	0.006	0.065	0
M LDL (M.LDL.CE)	0.230	0.095	mmol/l	931	-0.084	-0.181	0.012	0.086	0
S LDL (S.LDL.CE)	0.142	0.057	mmol/l	931	-0.079	-0.175	0.017	0.109	0
XL HDL (XL.HDL.CE)	0.129	0.057	mmol/l	931	0.046	-0.051	0.142	0.355	0
L HDL (L.HDL.CE)	0.245	0.107	mmol/l	931	0.088	-0.009	0.184	0.075	0
M HDL (M.HDL.CE)	0.321	0.059	mmol/l	931	-0.001	-0.098	0.095	0.977	0
S HDL (S.HDL.CE)	0.306	0.044	mmol/l	931	-0.047	-0.143	0.050	0.343	0
Free cholesterol in									
Serum total (FreeC)	1.006	0.204	mmol/l	931	-0.090	-0.186	0.007	0.068	0
XXL VLDL (XXL.VLDL.FC)	0.00096	0.0014	mmol/l	931	-0.181	-0.276	-0.085	0.00023	0.674
XL VLDL (XL.VLDL.FC)	0.0028	0.0042	mmol/l	931	-0.173	-0.269	-0.077	0.00042	0.583
L VLDL (L.VLDL.FC)	0.014	0.018	mmol/l	931	-0.181	-0.277	-0.085	0.00022	0.678
M VLDL (M.VLDL.FC)	0.043	0.028	mmol/l	931	-0.169	-0.265	-0.073	0.00057	0.511
S VLDL (S.VLDL.FC)	0.055	0.021	mmol/l	931	-0.155	-0.251	-0.060	0.0015	0.317
XS VLDL (XS.VLDL.FC)	0.058	0.015	mmol/l	931	-0.101	-0.197	-0.005	0.039	0
IDL (IDL.FC)	0.144	0.040	mmol/l	931	-0.058	-0.154	0.039	0.241	0
L LDL (L.LDL.FC)	0.184	0.046	mmol/l	931	-0.062	-0.158	0.035	0.211	0
M LDL (M.LDL.FC)	0.110	0.022	mmol/l	931	-0.085	-0.181	0.011	0.084	0
S LDL (S.LDL.FC)	0.067	0.014	mmol/l	931	-0.090	-0.186	0.006	0.067	0
XL HDL (XL.HDL.FC)	0.047	0.023	mmol/l	931	0.057	-0.040	0.153	0.249	0
L HDL (L.HDL.FC)	0.066	0.033	mmol/l	931	0.095	-0.002	0.191	0.054	0
M HDL (M.HDL.FC)	0.068	0.017	mmol/l	931	-0.017	-0.113	0.079	0.730	0
S HDL (S.HDL.FC)	0.103	0.012	mmol/l	931	-0.060	-0.156	0.037	0.224	0

Total lipids in									
XXL VLDL (XXL.VLDL.L)	0.016	0.018	mmol/l	931	-0.177	-0.273	-0.081	0.00030	0.636
XL VLDL (XL.VLDL.L)	0.036	0.047	mmol/l	931	-0.183	-0.279	-0.088	0.00019	0.687
L VLDL (L.VLDL.L)	0.165	0.160	mmol/l	931	-0.181	-0.276	-0.085	0.00023	0.671
M VLDL (M.VLDL.L)	0.415	0.226	mmol/l	931	-0.166	-0.262	-0.070	0.00072	0.472
S VLDL (S.VLDL.L)	0.422	0.151	mmol/l	931	-0.155	-0.251	-0.059	0.0016	0.322
XS VLDL (XS.VLDL.L)	0.366	0.090	mmol/l	931	-0.118	-0.214	-0.022	0.017	0
IDL (IDL.L)	0.804	0.206	mmol/l	931	-0.087	-0.183	0.009	0.077	0
L LDL (L.LDL.L)	0.919	0.255	mmol/l	931	-0.086	-0.183	0.010	0.079	0
M LDL (M.LDL.L)	0.522	0.154	mmol/l	931	-0.092	-0.189	0.004	0.060	0
S LDL (S.LDL.L)	0.341	0.095	mmol/l	931	-0.095	-0.191	0.001	0.054	0
XL HDL (XL.HDL.L)	0.375	0.173	mmol/l	931	0.061	-0.035	0.157	0.214	0
L HDL (L.HDL.L)	0.639	0.264	mmol/l	931	0.076	-0.020	0.172	0.122	0
M HDL (M.HDL.L)	0.782	0.145	mmol/l	931	-0.028	-0.125	0.068	0.564	0
S HDL (S.HDL.L)	1.017	0.101	mmol/l	931	-0.083	-0.179	0.013	0.091	0
Total cholesterol to total lipids ratio in									
XXL VLDL (XXL.VLDL.Cpct)	10.8	6.696	%	816	-0.106	-0.210	-0.003	0.045	0
XL VLDL (XL.VLDL.Cpct)	14.4	8.800	%	806	-0.034	-0.138	0.070	0.520	0
L VLDL (L.VLDL.Cpct)	18.4	7.841	%	870	-0.093	-0.193	0.007	0.067	0
M VLDL (M.VLDL.Cpct)	24.7	3.726	%	929	-0.020	-0.116	0.076	0.684	0
S VLDL (S.VLDL.Cpct)	33.1	4.509	%	930	0.010	-0.087	0.106	0.843	0
XS VLDL (XS.VLDL.Cpct)	49.2	2.986	%	931	0.058	-0.038	0.155	0.234	0
IDL (IDL.Cpct)	62.2	2.291	%	931	-0.034	-0.130	0.063	0.494	0
L LDL (L.LDL.Cpct)	65.6	3.551	%	931	-0.038	-0.134	0.059	0.445	0
M LDL (M.LDL.Cpct)	64.1	4.905	%	931	-0.026	-0.122	0.070	0.598	0
S LDL (S.LDL.Cpct)	60.0	5.276	%	930	-0.017	-0.113	0.080	0.734	0
XL HDL (XL.HDL.Cpct)	46.8	7.445	%	925	-0.058	-0.154	0.039	0.240	0
L HDL (L.HDL.Cpct)	47.3	6.017	%	927	0.110	0.014	0.206	0.026	0
M HDL (M.HDL.Cpct)	49.6	2.607	%	931	0.110	0.014	0.206	0.025	0
S HDL (S.HDL.Cpct)	40.2	2.905	%	931	0.025	-0.072	0.121	0.616	0
Triglycerides to total lipids ratio in									
XXL VLDL (XXL.VLDL.TGpct)	61.7	31.6	%	816	-0.057	-0.161	0.047	0.286	0
XL VLDL (XL.VLDL.TGpct)	52.1	29.5	%	806	-0.095	-0.199	0.009	0.074	0
L VLDL (L.VLDL.TGpct)	53.5	21.6	%	870	-0.048	-0.148	0.052	0.344	0
M VLDL (M.VLDL.TGpct)	55.1	3.944	%	929	0.002	-0.095	0.098	0.973	0
S VLDL (S.VLDL.TGpct)	42.7	4.337	%	930	-0.052	-0.149	0.044	0.286	0
XS VLDL (XS.VLDL.TGpct)	21.6	3.992	%	931	-0.068	-0.164	0.028	0.167	0
IDL (IDL.TGpct)	9.8	2.095	%	931	-0.027	-0.123	0.069	0.583	0
L LDL (L.LDL.TGpct)	6.9	1.620	%	931	-0.006	-0.102	0.090	0.901	0
M LDL (M.LDL.TGpct)	5.6	1.546	%	931	0.019	-0.077	0.115	0.699	0
S LDL (S.LDL.TGpct)	5.6	1.571	%	930	-0.079	-0.175	0.017	0.109	0
XL HDL (XL.HDL.TGpct)	2.9	1.998	%	925	-0.112	-0.208	-0.016	0.023	0
L HDL (L.HDL.TGpct)	3.4	1.477	%	927	-0.077	-0.174	0.019	0.116	0

M HDL (M.HDL.TGpct)	4.6	1.397	%	931	-0.103	-0.199	-0.007	0.036	0
S HDL (S.HDL.TGpct)	4.1	0.967	%	931	-0.117	-0.213	-0.021	0.018	0
Phospholipids to total lipids ratio in									
XXL VLDL (XXL.VLDL.PLpct)	7.3	4.239	%	816	-0.137	-0.240	-0.033	0.0099	0
XL VLDL (XL.VLDL.PLpct)	9.8	6.137	%	806	-0.105	-0.209	-0.001	0.049	0
L VLDL (L.VLDL.PLpct)	14.4	5.862	%	870	-0.181	-0.280	-0.082	0.00037	0.591
M VLDL (M.VLDL.PLpct)	20.2	0.701	%	929	0.100	0.004	0.196	0.042	0
S VLDL (S.VLDL.PLpct)	24.2	1.381	%	930	0.137	0.041	0.233	0.0052	0.020
XS VLDL (XS.VLDL.PLpct)	29.1	1.823	%	931	0.067	-0.029	0.163	0.172	0
IDL (IDL.PLpct)	28.0	0.849	%	931	0.149	0.053	0.245	0.0024	0.234
L LDL (L.LDL.PLpct)	27.5	2.063	%	931	0.074	-0.023	0.170	0.134	0
M LDL (M.LDL.PLpct)	30.1	3.671	%	931	0.042	-0.055	0.138	0.396	0
S LDL (S.LDL.PLpct)	34.3	4.183	%	930	0.053	-0.043	0.149	0.281	0
XL HDL (XL.HDL.PLpct)	49.1	8.033	%	925	0.078	-0.019	0.174	0.115	0
L HDL (L.HDL.PLpct)	48.3	5.677	%	927	-0.106	-0.202	-0.009	0.032	0
M HDL (M.HDL.PLpct)	45.7	1.837	%	931	-0.037	-0.133	0.060	0.454	0
S HDL (S.HDL.PLpct)	55.7	2.612	%	931	0.003	-0.093	0.099	0.952	0
Cholesterol esters to total lipids ratio in									
XXL VLDL (XXL.VLDL.CEpct)	6.7	4.478	%	816	-0.095	-0.199	0.008	0.072	0
XL VLDL (XL.VLDL.CEpct)	9.4	6.081	%	806	-0.034	-0.138	0.070	0.519	0
L VLDL (L.VLDL.CEpct)	12.2	5.490	%	870	-0.012	-0.112	0.088	0.820	0
M VLDL (M.VLDL.CEpct)	15.0	3.309	%	929	0.061	-0.035	0.157	0.215	0
S VLDL (S.VLDL.CEpct)	20.2	4.237	%	930	0.018	-0.078	0.115	0.710	0
XS VLDL (XS.VLDL.CEpct)	33.5	2.638	%	931	0.037	-0.060	0.133	0.457	0
IDL (IDL.CEpct)	44.4	2.052	%	931	-0.104	-0.200	-0.008	0.035	0
L LDL (L.LDL.CEpct)	45.4	3.673	%	931	-0.092	-0.188	0.004	0.061	0
M LDL (M.LDL.CEpct)	42.5	6.666	%	931	-0.061	-0.158	0.035	0.213	0
S LDL (S.LDL.CEpct)	40.1	6.563	%	930	-0.044	-0.140	0.053	0.375	0
XL HDL (XL.HDL.CEpct)	34.6	6.330	%	925	-0.060	-0.157	0.036	0.220	0
L HDL (L.HDL.CEpct)	37.6	4.408	%	927	0.108	0.011	0.204	0.029	0
M HDL (M.HDL.CEpct)	41.0	2.262	%	931	0.108	0.012	0.205	0.027	0
S HDL (S.HDL.CEpct)	30.1	3.188	%	931	0.019	-0.077	0.116	0.692	0
Free cholesterol to total lipids ratio in									
XXL VLDL (XXL.VLDL.FCpct)	4.1	2.763	%	816	-0.130	-0.234	-0.026	0.014	0
XL VLDL (XL.VLDL.FCpct)	5.0	3.409	%	806	-0.063	-0.167	0.041	0.234	0
L VLDL (L.VLDL.FCpct)	6.2	3.503	%	870	-0.166	-0.266	-0.067	0.0011	0.397
M VLDL (M.VLDL.FCpct)	9.7	1.584	%	929	-0.176	-0.271	-0.080	0.00034	0.593
S VLDL (S.VLDL.FCpct)	12.9	0.739	%	930	-0.041	-0.138	0.055	0.403	0
XS VLDL (XS.VLDL.FCpct)	15.7	1.061	%	931	0.059	-0.037	0.155	0.229	0
IDL (IDL.FCpct)	17.8	1.245	%	931	0.104	0.007	0.200	0.035	0
L **LDL** (L.LDL.FCpct)	20.2	1.305	%	931	0.144	0.048	0.240	0.0034	0.127
M LDL (M.LDL.FCpct)	21.7	2.497	%	931	0.097	0.001	0.194	0.048	0
S LDL (S.LDL.FCpct)	20.0	1.960	%	930	0.096	-0.0005	0.192	0.051	0

XL HDL (XL.HDL.FCpct)	12.2	1.843	%	925	-0.019	-0.115	0.078	0.703	0
L HDL (L.HDL.FCpct)	9.7	1.838	%	927	0.113	0.016	0.209	0.022	0
M HDL (M.HDL.FCpct)	8.6	0.683	%	931	0.016	-0.081	0.112	0.753	0
S HDL (S.HDL.FCpct)	10.1	0.475	%	931	0.024	-0.073	0.120	0.632	0

cu. standardized concentration unit

Table S4. Nominally significant metabolomic associations of the interaction between *DHCR24* rs588709 genotype, visceral fat and circulating concentration of PC16:0/2:0, and the associations of the corresponding metabolic measures with white matter microstructure.

	Test statistics of the interaction term from a model trait~rs588709*VF*PC16:0/2:0			Test statistics from a model WMT1WSI~trait			
trait	Beta	SE	P	Beta	SE	P	N
bOHBut	-0.129	0.048	0.0079	-0.012	0.035	0.74	846
DHA to FA ratio	0.124	0.049	0.013	0.167	0.034	6.81E-07	843
DHA	0.105	0.049	0.031	0.232	0.033	7.79E-12	843
FAw3 to FA ratio	0.097	0.049	0.048	0.176	0.034	2.94E-07	843
Lac	-0.096	0.049	0.048	0.008	0.035	0.80	846

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