

SUPPLEMENTARY INFORMATION

Genome-wide association study of caffeine metabolites provides new insights to caffeine metabolism and dietary caffeine-consumption behavior

SUPPLEMENTARY MATERIAL AND METHODS

Study samples

Prospective Study of the Vasculature in Uppsala Seniors (PIVUS) (1): All 70-year-old individuals living in Uppsala, Sweden were eligible for PIVUS, and 2,025 randomly selected individuals were invited within 2 months of their 70th birthday from April 2001 to June 2004. Of these, 1,016 participated in the study and provided an overnight fasting blood sample at the baseline examination. Plasma metabolite data for up to 914 individuals passed the quality control (QC) process and were included in the current study.

Study of Health in Pomerania (SHIP) (2): SHIP-TREND is a second cohort of a population-based research project in West Pomerania, a rural region in north-east Germany. Initially, 8826 subjects were selected from population registries and 4420 choose to participate in the baseline examination between 2009 and 2012. For a subsample of 1000 subjects without self-reported diabetes, plasma as well as urine metabolomics data based on mass spectrometry were acquired. For this purpose fasting (>8h) plasma samples were drawn prior to noon and spot urine samples were collected in the same time frame. After application of exclusion criteria (i.e. pertaining to trait definitions and covariate data; see main text) up to 957 participants were available for the present analyses.

Swiss Kidney Project on Genes in Hypertension (SKIPOGH) (3, 4): SKIPOGH is a family and population-based cross-sectional study nested within the larger family-based international European Project on Genes in Hypertension (EPOGH) study (5). SKIPOGH included 1,128 participants from 273 nuclear families recruited in the cantons of Bern and Geneva and the city of Lausanne between 2009 and 2013. Participants attended study centers in the morning where blood samples were collected after an overnight fast. Participants were also asked

to collect a 24-hour urine sample, with separate day and night collections, for the measurement of urinary volume and electrolytes. Up to 833 of these participants had genotyped data approved for analysis at the time the current study was initiated.

TwinGene (6). The TwinGene project, conducted between 2004 and 2008, is a population-based Swedish study of twins born between 1911 and 1958 (7). In total, 12,591 individuals participated by donating blood to the study, and by answering questionnaires about life style and health. The subset of TwinGene with metabolomics includes 2,141 members with metabolites and is a case-cohort design enriched with incident coronary heart disease, stroke, diabetes, and dementia events(8). After application of exclusion criteria (i.e. pertaining to trait definitions and covariate data; see main text) up to 1609 participants were available for the present analyses.

TwinsUK: The TwinsUK cohort began in 1992 and is an adult twin British registry recruited from the general population in the United Kingdom (9). Participants are similar to age-matched singleton members of the general population in disease-related and lifestyle characteristics (10). The 4555 participants included in the current study had the required metabolite, GWAS and covariate data. Blood samples were collected after at least 6 hours of fasting predominantly overnight.

Uppsala Longitudinal Study of Adult Men (ULSAM) (11): ULSAM began in 1970, when all men 50 years of age and born between 1920 and 1924 in Uppsala, Sweden were invited to participate (2,322 participated of 2,841 invited). Subjects underwent a clinical exam and routine medical history and lifestyle assessment at the ages of 60, 70, 77, 82 and 88 years. After application of exclusion criteria (i.e. pertaining to trait definitions and covariate data; see main text) up to 1039 participants were available for the present analyses.

Table S1. Metabolites Examined in the Current Study

Common names	IUPAC Name	Abbreviation	Relevance to current study
caffeine 1,3,7-trimethylxanthine	1,3,7-trimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione	137X	target exposure
paraxanthine 1,7-dimethylxanthine	1,7-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione	17X	primary caffeine metabolite (major)
theophylline 1,3-dimethylxanthine	1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione	13X	primary caffeine metabolite
theobromine 3,7-dimethylxanthine	3,7-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione	37X	primary caffeine metabolites
1,3,7-trimethyluric acid	1,3,7-trimethyl-2,3,6,7,8,9-hexahydro-1H-purine-2,6,8-trione	137U	primary caffeine metabolite (minor)
1,7-dimethyluric acid	1,7-dimethyl-2,3,6,7,8,9-hexahydro-1H-purine-2,6,8-trione	17U	17X metabolite
1,3-dimethyluric acid	1,3-dimethyl-2,3,6,7,8,9-hexahydro-1H-purine-2,6,8-trione	13U	13X metabolite
3,7-dimethyluric acid	3,7-dimethyl-2,3,6,7,8,9-hexahydro-1H-purine-2,6,8-trione	37U	37X metabolite
trigonelline	1-methylpyridin-1-ium-3-carboxylate	Trig	a potential but non-specific coffee-derived biomarker of coffee consumption.
quinine	(R)-[(1S,2S,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol	QN	a potential but non-specific coffee-derived biomarker of coffee consumption.

Table S2. Description of Studies Participating in GWAS of Plasma Caffeine Metabolites

Study	Sample size (N) per Plasma Metabolite						Participant Characteristics (based on max N)			Biospecimen Collection			Metabolite Assays and Data processing		
	137X	17X	13X	37X	137U	17X/137X	Age, years (SD)	Female, %	Current Smoking, %	Year	Time of day	Fasting status	Platform	CV%	Normalization (prior to standardization)
Prospective Study of the Vasculature in Uppsala Seniors (PIVUS)	910			902	914		70.1 (0.2)	50	10	2001-2004	8 am to 10 am	Overnight	UPLC-MS/MS (Waters)	3	rank-based inverse-normal transformation
Study of Health in Pomerania TREND (SHIP-TREND)	951	952	860	957		943	50.1 (14)	56	22	2008	7 am to 11 am	> 8 h	UPLC-ESI-MS/MS (Waters ACQUITY UPLC and Thermo Scientific LTQ XL MS; Helmholtz)		Day-median normalized and log ₁₀ transformed
Swiss Kidney Project on Genes in Hypertension (SKIPOGH)	822 ^a	833 ^a	826 ^a	824 ^a		824 ^a	47.5 (17)	52	24	2009	Morning	Overnight	UPLC-ESI-MS/MS (Waters ACQUITY UPLC and TQD)	9-23	Square-root (single metabolites) or log (metabolite ratios) transformation.
TwinGene	1600			1599	1609		68.7 (8)	40	15	2004-2008	Morning	mixed	UPLC-MS/MS (Waters)	4	rank-based inverse-normal transformation
TwinsUK	4555	4401	4401	4551		4380	53.4 (14)	93	17	1996-2010	8 am to 11 am	> 8 h	UPLC-ESI-MS/MS (Waters ACQUITY UPLC and Thermo Scientific LTQ XL MS; Metabolon)	9-19	Day-median normalized

Uppsala Longitudinal Study of Adult Men (ULSAM)	1038				1039		71.0 (0.6)	0	20	1991- 1995	unknown	Overnight	UPLC- MS/MS (Waters)	5	rank-based inverse-normal transformation
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^amax N (varied due to call rate).

Table S2 (cont'd). Description of Studies Participating in GWAS of plasma caffeine and its metabolites

Study	Genotyping						Imputation		
	Platform	SNP Exclusion Criteria			Sample exclusion criteria		Software	Reference panel	Quality filter
		MAF	Call rate	P HWE	Call rate	Other			
PIVUS	Illumina HumanOmniExpress	<1%	≤95% (MAF ≥5%) or ≤99% (MAF <5%)	≤1×10 ⁻⁶	<95%	-	Impute	1000G, ALL, March 2012	0.4
SHIP-TREND	Illumina HumanOmni 2.5-4v1	mono	≤90%	≤1×10 ⁻⁴	≤94%	Sex discrepancies, duplicates, missing phenotype data, consent withdrawn	Impute	1000G, ALL, March 2012	0.4
SKIPOGH	Metabochip	<2%	≤98%	≤1×10 ⁻⁵	<93%	Duplicates, missing phenotype data	n/a	n/a	n/a
TwinGene	Illumina HumanOmniExpress	<1%	≤97%	≤1×10 ⁻⁷	<97%	-	minimac	1000G, ALL, March 2012	0.4
TwinsUK	HumanHap300, HumanHap610Q, 1M-Duo, and 1.2MDuo	<1%	≤97% (MAF ≥5%) or ≤99% (MAF <5%)	≤1×10 ⁻⁶	<98%	Sex discrepancies, duplicates, missing phenotype data, heterozygosity across all SNPs ≥2 SD from the sample mean, evidence of non-European ancestry as assessed by PCA comparison with HapMap3	Impute	1000G, ALL, March 2012	0.4
ULSAM	Illumina HumanOmni 2.5 M	<1%	≤95% (MAF ≥5%) or ≤99% (MAF <5%)	≤1×10 ⁻⁶	<95%	-	Impute	1000G, ALL, March 2012	0.4

Table S2 (cont'd). Description of Studies Participating in GWAS of plasma caffeine and its metabolites

Study	Statistical Analysis				Ref
	Software	Model covariates	SNPs in meta-analyses	λ_{GC}	
PIVUS	SNPTEST	Age, sex, smoking status, first 2 ancestry components	137X: 8478315 37X: 8485503 137U: 8478524	0.99 1.00 1.02	(8, 12)
SHIP-TREND	Quicktest	Sex, age, smoking status, fasting time *no evidence for population stratification in SHIP, thus no adjustment for PCs	137X: 8512980 17X: 8512549 13X: 8514178 37X: 8513269 17X/137X: 8523123	0.99 1.00 1.00 1.01 1.01	(2, 13)
SKIPOGH	PLINK	Sex, age, smoking status, center	137X: 113869 17X: 113874 13X: 113874 37X: 113869 17X/137X: 113874	1.09 1.09 1.10 1.15 1.18	(14, 15)
TwinGene	SNPTEST	Age, sex, smoking status, first 4 ancestry components	137X: 8198215 37X: 8198854 137U: 8197082	1.01 1.01 1.00	(8, 12)
TwinsUK	GEMMA (V0.94.1)	Sex, age, smoking status, BMI, metabolite batch	137X: 8373143 17X: 8373133 13X: 8372834 37X: 8373040 17X/137X: 8373236	1.01 1.00 1.00 1.01 1.00	(16)
ULSAM	SNPTEST	Age, smoking status, first 2 ancestry components	137X: 8558034 137U: 8558125	0.99 0.98	(8, 12)

Table S3. Studies Contributing to Follow-up SNP-Metabolite Analysis

Metabolite	SHIP-TREND	SKIPOGH	TwinsUK
Plasma*			
17U	695		
Trig	880		
QN			3634
13X/137X	851		
37X/137X	944		
17U/17X	689		
137X/Trig	870		
137/QN			3573
Urine†			
137X	819	771	
17X	959	777	
13X	906	775	
37X	961	775	
137U	940		
17U	967		
13U	946		
37U	895		
17X/137X	814		
13X/137X	806		
37X/137X	807		
17U/17X	957		
13U/13X	898		
37U/37X	888		

*See Table S2 for plasma metabolite methods

†SHIP-TREND: Fasting, cross-sectional urine collection. UPLC-ESI-MS/MS metabolite measurement (see Table S2). Day-median and creatinine normalized.

SKIPOGH: 24 hour urine UPLC-ESI-MS/MS (Waters ACQUITY UPLC I-Class and Xevo TQ-S). Prior to standardization, metabolites were square root transformed and ratios were log-transformed.

Supplementary References

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Table S4. Candidate SNP-Metabolite Associations

Main.Tables	rsID	Chr	Position	EA	NEA	EAF	137X ^a				17X				13X				37X				137U				17X/137X			
							N	Z	P	İ ²	N	Z	P	İ ²	N	Z	P	İ ²	N	Z	P	İ ²	N	Z	P	İ ²	N	Z	P	İ ²
2	rs1260326	2	27730940	T	C	0.38	9876	2.49	0.01	0.7	6204	-0.66	0.51	0	6090	0.883	0.38	60.8	8836	1.77	0.08	28.3	3562	0.05	0.96	0	6147	-4.69	2.72E-06	66.3
2	rs1481012	4	89039082	A	G	0.90	9054	2.72	0.01	0	5371	2.82	4.87E-03	0	5261	3.65	2.6E-04	9.1	8009	0.55	0.59	0	3562	-0.39	0.70	12.8	5323	-1.77	0.08	0
2	rs7800944	7	73035857	T	C	0.71	9054	1.20	0.23	0	5371	-0.20	0.84	0	5261	0.258	0.80	51.5	8009	0.87	0.38	0	3562	-0.30	0.76	0	5323	-1.91	0.06	0
2	rs17685	7	75616105	A	G	0.28	9054	-2.95	3.20E-03	66.5	5371	-1.87	0.06	85.9	5261	-1.076	0.28	62.8	8009	-1.63	0.10	29.8	3562	0.25	0.80	0	5323	1.70	0.09	0
2	rs6265	11	27679916	T	C	0.19	9876	0.44	0.66	0	6204	0.06	0.95	0	6090	-0.213	0.83	0	8836	-0.54	0.59	0	3562	-0.58	0.56	0	6147	1.35	0.18	0
2	rs9902453	17	28349095	A	G	0.54	9054	0.11	0.91	0	5371	-1.63	0.10	0	5261	0.351	0.73	0	8009	-0.60	0.55	0	3562	0.51	0.61	54.1	5323	-0.92	0.36	36.9
1,2	rs62391270	6	14161434	T	C	0.82	9054	-3.38	7.35E-04	54.4	5371	-5.54	2.96E-08	0	5261	-3.77	1.62E-04	0	8009	-3.55	3.93E-04	0	3562	-2.79	5.25E-03	23.1	5323	-0.03	0.98	0
1,2	rs4410790	7	17284577	T	C	0.36	9054	7.36	1.81E-13	0	5371	1.90	0.06	0	5261	3.15	1.6E-03	18.2	8009	2.63	8.64E-03	63.1	3562	0.12	0.90	0	5323	-8.07	7.20E-16	36.3
1,2	rs6968554	7	17287106	A	G	0.37	9875	7.22	5.36E-13	0	6203	1.42	0.15	23.3	6089	2.78	5.4E-03	51.2	8835	2.73	6.32E-03	51.2	3562	0.08	0.93	0	6146	-8.44	3.22E-17	0
1,2	rs10275488	7	17303778	T	C	0.10	9054	5.85	4.81E-09	18.3	5371	1.83	0.07	20.1	5261	3.46	5.49E-04	0	8009	1.65	0.10	74.9	3562	0.11	0.91	0	5323	-5.98	2.29E-09	37.1
1,2	rs2892838	7	17324624	A	C	0.56	9054	-4.55	5.39E-06	0	5371	-0.44	0.66	0	5261	-1.96	0.04984	0	8009	-0.77	0.44	18.3	3562	-0.17	0.86	0	5323	6.01	1.82E-09	28.5
1,2	rs12909047	15	74782356	A	G	0.51	9054	-6.77	1.28E-11	0	5371	-3.62	2.97E-04	16.9	5261	-5.70	1.20E-08	12	8009	-2.59	9.60E-03	70.6	3562	-0.03	0.97	49	5323	5.15	2.57E-07	0
1,2	rs35107470	15	74817689	A	G	0.68	9054	8.20	2.41E-16	0	5371	3.25	1.16E-03	0	5261	5.18	2.24E-07	0	8009	2.56	0.01	57.9	3562	-0.23	0.82	0	5323	-7.58	3.45E-14	0
1,2	rs62005807	15	74890981	C	G	0.11	9054	-5.92	3.16E-09	0	5371	-1.32	0.19	0	5261	-2.98	2.92E-03	0	8009	-0.18	0.86	0	3562	-0.61	0.54	0	5323	6.65	2.90E-11	0
1,2	rs2470893	15	75019449	T	C	0.33	9054	-8.65	5.25E-18	48.5	5371	-3.62	2.97E-04	71.8	5261	-5.30	1.2E-07	59.1	8009	-2.12	0.03	20.7	3562	-0.38	0.70	0	5323	7.85	4.12E-15	0
1,2	rs2472297	15	75027880	T	C	0.27	9876	-9.34	1.00E-20	0	6204	-3.07	2.15E-03	55.6	6090	-5.27	1.4E-07	37.2	8836	-1.82	0.07	32.4	3562	-0.97	0.33	0	6147	9.58	9.45E-22	0
1,2	rs66500423	19	41195170	T	C	0.67	9054	-1.36	0.17	0	5371	3.34	8.47E-04	0	5261	1.10	0.27	65.3	8009	2.48	0.01	0	3562	0.64	0.52	12.7	5323	5.83	5.57E-09	0
1,2	rs4803373	19	41326426	C	G	0.41	9054	-1.25	0.21	0	5371	3.48	4.97E-04	0	5261	0.11	0.91	45.1	8009	2.93	3.43E-03	0	3562	0.14	0.89	0	5323	6.90	5.33E-12	0
1,2	rs78011401	19	41332171	T	C	0.31	9054	1.60	0.11	0	5371	-1.99	0.04712	0	5261	1.57	0.12	0	8009	-2.11	0.03	0	3562	0.49	0.62	37.7	5323	-5.78	7.60E-09	0
1,2	rs11668399	19	41343871	C	G	0.29	9054	-1.03	0.30	0	5371	2.98	2.85E-03	0	5261	-0.28	0.78	9.8	8009	2.94	3.24E-03	0	3562	0.36	0.72	0	5323	6.37	1.91E-10	0
1,2	rs56113850	19	41353107	T	C	0.43	9054	-0.78	0.44	0	5371	5.43	5.69E-08	0	5261	0.11	0.91	68.8	8009	4.59	4.38E-06	52	3562	1.17	0.24	33	5323	9.59	9.28E-22	66
1,2	rs56267346	19	41353338	A	G	0.82	9054	-0.91	0.36	0	5371	-3.93	8.53E-05	15.2	5261	-0.51	0.61	0	8009	-2.61	9.09E-03	26.9	3562	0.93	0.35	0	5323	-6.13	8.87E-10	90.5
1,2	rs28399442	19	41354458	A	C	0.02	9054	0.14	0.89	0	5371	2.52	0.01179	0	5261	0.26	0.79	0	8009	2.52	0.01	0	3562	0.47	0.64	0	5323	6.48	9.46E-11	92.5
1,2	rs67210567	19	41357457	T	G	0.02	9054	-1.38	0.17	24.2	5371	1.67	0.09	0	5261	-0.89	0.37	0	8009	1.86	0.06	0	3562	0.18	0.86	0	5323	5.94	2.92E-09	57.8
1,2	rs7260629	19	41357632	T	G	0.30	9054	-1.12	0.26	0	5371	3.19	1.44E-03	0	5261	-0.85	0.40	0	8009	3.77	1.66E-04	2.3	3562	1.62	0.11	0	5323	6.73	1.70E-11	0
1,2	rs28602288	19	41388740	T	C	0.65	9054	-0.68	0.50	26.5	5371	-4.31	1.62E-05	0	5261	-1.00	0.32	0	8009	-2.16	0.03	0	3562	-0.27	0.79	44.1	5323	-5.72	1.05E-08	55.6
1,2	rs79600176	19	41392490	T	C	0.98	9054	-0.30	0.76	0	5371	-2.96	3.10E-03	0	5261	-0.50	0.61	0	8009	-2.44	0.01	0	3562	-0.02	0.99	0	5323	-6.64	3.06E-11	92.3
1,2	rs184589612	19	41412192	T	C	0.99	9054	-0.76	0.45	32.7	5371	-1.76	0.08	0	5261	0.05	0.96	0	8009	-1.69	0.09	0	3562	-1.35	0.18	16.4	5323	-5.92	3.24E-09	80.2
1,2	rs72480748	19	41414481	A	G	0.31	9054	1.19	0.24	33.2	5371	-1.62	0.11	73.5	5261	0.12	0.91	70.7	8009	-1.27	0.21	0	3562	-1.85	0.06	0	5323	-6.08	1.17E-09	0
1,2	rs10425738	19	41417727	A	G	0.72	9054	0.97	0.33	0	5371	-2.24	0.02515	0	5261	0.13	0.89	0	8009	-2.02	0.04	9.6	3562	-0.49	0.62	0	5323	-5.65	1.60E-08	0
1,2	rs56881024	19	41485380	A	T	0.65	9054	0.73	0.46	0	5371	-3.09	2.01E-03	0	5261	-0.09	0.93	0	8009	-2.28	0.02	0	3562	-0.63	0.53	24.8	5323	-5.57	2.50E-08	0

Chr: chromosome; EA: effect allele; EAF: effect allele frequency; NEA: non-effect allele;

^a See Table S1 for metabolite names

Table S5. Genome-wide significant indel-metabolite associations

Chr	Position	rsID	Notes	EA	NEA	EAF	137X ^a				17X				13X				37X				137U				17X/137X				
							N	Z	P	I ²	N	Z	P	I ²	N	Z	P	I ²	N	Z	P	I ²	N	Z	P	I ²	N	Z	P	I ²	
7	17385506	rs11400459	reported in Table 1	A	AT	0.64	9054	-4.52	6.3E-06	0	5371	-0.82	0.41	0	5261	-1.81	0.07	0	8009	-1.07	0.28	23.2	3562	0.19	0.85	0	5323	6.23	4.6E-10	67.7	
7	17396746	rs10683220	reported in Table 1	G	GTTAACA	0.63	9054	-4.70	2.6E-06	0	5371	-0.74	0.46	0	5261	-1.63	0.10	0	8009	-1.06	0.29	23.5	3562	-0.07	0.94	0	5323	6.11	1.0E-09	71.7	
19	41361572	rs5828081	reported in Table 1	AT	A	0.66	9054	0.75	0.45	0	5371	-3.80	1.4E-04	0	5261	-0.004	1.00	53.2	8009	-2.85	4.3E-03	44.7	3562	-1.31	0.19	58	5323	-6.92	4.7E-12	0	
19	41363094	rs200292835	reported in Table 1	T	TTTGT	0.68	9054	1.22	0.22	0	5371	-3.04	2.4E-03	0	5261	0.49	0.63	36.1	8009	-3.44	5.9E-04	0	3562	-2.36	0.02	0	5323	-5.71	1.1E-08	0	
19	41197268	rs35255138	r ² =0.98 with rs66500423	G	GC	0.67	9054	-1.51	0.13	0	5371	3.20	1.4E-03	0	5261	1.03	0.30	58.4	8009	2.57	0.01	0	3562	0.42	0.67	0	5323	5.66	1.6E-08	0	
19	41329838	rs68060906	r ² =0.42 with rs4803373	C	CAGGG	0.55	9054	0.01	0.99	25.7	5371	-3.42	6.2E-04	0	5261	0.55	0.58	28.9	8009	-1.30	0.19	62.5	3562	-0.25	0.80	0	5323	-6.37	1.9E-10	0	
19	41344569	rs11271389	r ² =0.56 with rs11668399	CTTTC	CTTTCCTTCTTCTCTTCT	C	0.73	9054	0.86	0.39	0	5371	-2.84	4.5E-03	0	5261	0.04	0.97	69	8009	-2.97	3.0E-03	0	3562	-1.10	0.27	0	5323	-5.81	6.2E-09	0
19	41363091	rs200258898	r ² =0.52 with rs56113850	C	CTG	0.66	9054	0.59	0.56	0	5371	-3.77	1.6E-04	0	5261	0.16	0.87	74.3	8009	-3.38	7.2E-04	55	3562	-1.07	0.28	45.4	5323	-6.67	2.6E-11	0	
19	41363095	rs201662855	r ² =0.62 with rs200292835 (indel)	T	TTTG	0.71	9054	1.40	0.16	5.5	5371	-3.16	1.6E-03	0	5261	0.14	0.89	75.9	8009	-3.86	1.1E-04	0	3562	-2.20	0.03	26.3	5323	-5.69	1.2E-08	0	
19	41399598	rs201285225	r ² =1 with rs79600176	CTTACTCT	CTTGA	C	0.98	9054	-0.22	0.83	0	5371	-2.80	5.1E-03	0	5261	-0.38	0.71	0	8009	-2.57	0.01	0	3562	0.01	0.99	0	5323	-6.67	2.6E-11	92.2
19	41403872	rs202174841	r ² =0.84 with rs79600176, rs201285225 (indel)	A	AG	0.98	9054	-1.10	0.27	0	5371	-2.88	3.9E-03	0	5261	-0.75	0.45	0	8009	-2.42	0.02	0	3562	0.08	0.93	30.1	5323	-5.70	1.2E-08	68.5	

Chr: chromosome; EA: effect allele; EAF: effect allele frequency; NEA: non-effect allele;

^a See Table S1 for metabolites names

Table S6. Study-level SNP-Metabolite Associations

Study	Trait ^a	Chr	Position	rsID	EA	NEA	Beta	SE	P	N	Imputed	Info
SHIP	137X	7	17284577	rs4410790	T	C	0.11	0.04	0.02	951	yes	0.99
PIVUS	137X	7	17284577	rs4410790	T	C	0.15	0.05	1.71E-03	910	yes	0.99
TwinGene	137X	7	17284577	rs4410790	T	C	0.09	0.04	0.01	1600	yes	0.99
TwinsUK	137X	7	17284577	rs4410790	T	C	0.13	0.02	1.49E-08	4555	no	1.00
ULSAM	137X	7	17284577	rs4410790	T	C	0.08	0.05	0.10	1038	yes	0.99
PIVUS	137X	7	17287106	rs6968554	A	G	0.14	0.05	2.22E-03	910	no	1.00
SHIP	137X	7	17287106	rs6968554	A	G	0.11	0.04	0.01	951	yes	1.00
SKIPOGH	137X	7	17287106	rs6968554	A	G	0.03	0.05	0.54	821	no	NA
TwinGene	137X	7	17287106	rs6968554	A	G	0.09	0.04	0.01	1600	no	1.00
TwinsUK	137X	7	17287106	rs6968554	A	G	0.13	0.02	1.65E-08	4555	yes	1.00
ULSAM	137X	7	17287106	rs6968554	A	G	0.07	0.04	0.11	1038	no	1.00
PIVUS	137X	7	17303778	rs10275488	T	C	0.22	0.08	4.29E-03	910	no	1.00
SHIP	137X	7	17303778	rs10275488	T	C	0.15	0.07	0.03	951	yes	1.00
TwinGene	137X	7	17303778	rs10275488	T	C	0.05	0.06	0.44	1600.004	no	1.00
TwinsUK	137X	7	17303778	rs10275488	T	C	0.17	0.03	9.75E-07	4555	no	1.00
ULSAM	137X	7	17303778	rs10275488	T	C	0.10	0.07	0.19	1038	no	1.00
PIVUS	137X	7	17324624	rs2892838	A	C	-0.10	0.05	0.03	910	yes	1.00
SHIP	137X	7	17324624	rs2892838	A	C	-0.06	0.04	0.15	951	yes	1.00
TwinGene	137X	7	17324624	rs2892838	A	C	-0.06	0.04	0.08	1600	yes	0.99
TwinsUK	137X	7	17324624	rs2892838	A	C	-0.08	0.02	5.05E-04	4555	yes	0.99
ULSAM	137X	7	17324624	rs2892838	A	C	-0.03	0.04	0.51	1038.001	yes	1.00
TwinGene	137X	15	74782356	rs12909047	A	G	-0.10	0.04	0.01	1600	yes	0.90
PIVUS	137X	15	74782356	rs12909047	A	G	-0.07	0.05	0.13	910.001	yes	0.95
SHIP	137X	15	74782356	rs12909047	A	G	-0.14	0.04	1.62E-03	951	yes	0.96
TwinsUK	137X	15	74782356	rs12909047	A	G	-0.11	0.02	7.46E-07	4555	yes	0.98
ULSAM	137X	15	74782356	rs12909047	A	G	-0.09	0.04	0.04	1038	yes	0.96
TwinGene	137X	15	74817689	rs35107470	A	G	0.10	0.04	0.02	1600	yes	0.67
PIVUS	137X	15	74817689	rs35107470	A	G	0.21	0.05	7.23E-05	910	yes	0.82
SHIP	137X	15	74817689	rs35107470	A	G	0.17	0.05	9.03E-04	951	yes	0.85
TwinsUK	137X	15	74817689	rs35107470	A	G	0.15	0.02	3.87E-09	4555	yes	0.95
ULSAM	137X	15	74817689	rs35107470	A	G	0.11	0.05	0.04	1038.001	yes	0.84
TwinGene	137X	15	74890981	rs62005807	C	G	-0.16	0.08	0.04	1600	yes	0.45
PIVUS	137X	15	74890981	rs62005807	C	G	-0.24	0.08	1.70E-03	909.9995	yes	0.83
SHIP	137X	15	74890981	rs62005807	C	G	-0.07	0.08	0.37	951	yes	1.00
TwinsUK	137X	15	74890981	rs62005807	C	G	-0.17	0.04	5.97E-05	4555	yes	0.90
ULSAM	137X	15	74890981	rs62005807	C	G	-0.18	0.07	6.45E-03	1038	no	1.00
PIVUS	137X	15	75019449	rs2470893	T	C	-0.22	0.05	5.29E-06	910	no	1.00
SHIP	137X	15	75019449	rs2470893	T	C	-0.20	0.05	2.20E-05	951	yes	1.00
TwinGene	137X	15	75019449	rs2470893	T	C	-0.08	0.04	0.03	1600	no	1.00
TwinsUK	137X	15	75019449	rs2470893	T	C	-0.13	0.02	1.29E-08	4555	no	1.00
ULSAM	137X	15	75019449	rs2470893	T	C	-0.12	0.05	8.67E-03	1038	no	1.00
PIVUS	137X	15	75027880	rs2472297	T	C	-0.20	0.05	9.80E-05	910	no	1.00
SHIP	137X	15	75027880	rs2472297	T	C	-0.20	0.05	5.55E-05	951	yes	1.00
SKIPOGH	137X	15	75027880	rs2472297	T	C	-0.11	0.06	0.07	822	no	NA
TwinGene	137X	15	75027880	rs2472297	T	C	-0.12	0.04	1.42E-03	1600	no	0.99
TwinsUK	137X	15	75027880	rs2472297	T	C	-0.15	0.02	1.65E-09	4555	no	1.00
ULSAM	137X	15	75027880	rs2472297	T	C	-0.16	0.05	1.30E-03	1038	no	1.00
SHIP	13X	15	74782356	rs12909047	A	G	-0.15	0.05	1.04E-03	860	yes	0.96
TwinsUK	13X	15	74782356	rs12909047	A	G	-0.11	0.02	1.71E-06	4401	yes	0.98
TwinsUK	17X	6	14161434	rs62391270	T	C	-0.14	0.03	1.86E-06	4419	yes	0.97
SHIP	17X	6	14161434	rs62391270	T	C	-0.16	0.06	3.60E-03	952	yes	1.00
SHIP	17X/137X	7	17284577	rs4410790	T	C	-0.10	0.05	0.02	943	yes	0.99
TwinsUK	17X/137X	7	17284577	rs4410790	T	C	-0.18	0.02	4.33E-15	4380	no	1.00
SHIP	17X/137X	7	17287106	rs6968554	A	G	-0.11	0.05	0.02	943	yes	1.00
SKIPOGH	17X/137X	7	17287106	rs6968554	A	G	-0.14	0.05	3.14E-03	823	no	NA
TwinsUK	17X/137X	7	17287106	rs6968554	A	G	-0.18	0.02	9.14E-15	4380	yes	1.00
SHIP	17X/137X	7	17303778	rs10275488	T	C	-0.10	0.07	0.17	943	yes	1.00
TwinsUK	17X/137X	7	17303778	rs10275488	T	C	-0.21	0.04	2.65E-09	4380	no	1.00
SHIP	17X/137X	7	17324624	rs2892838	A	C	0.07	0.05	0.14	943	yes	1.00
TwinsUK	17X/137X	7	17324624	rs2892838	A	C	0.14	0.02	2.65E-09	4380	yes	0.99
SHIP	17X/137X	7	17385506	rs11400459	A	AT	0.05	0.05	0.30	943	yes	0.98
TwinsUK	17X/137X	7	17385506	rs11400459	A	AT	0.15	0.02	1.54E-10	4380	yes	1.00
SHIP	17X/137X	7	17396746	rs10683220	G	GTTAACA	0.04	0.05	0.38	943	yes	0.99
TwinsUK	17X/137X	7	17396746	rs10683220	G	GTTAACA	0.15	0.02	2.31E-10	4380	yes	0.99
SHIP	17X/137X	15	74782356	rs12909047	A	G	0.08	0.05	0.08	943	yes	0.96
TwinsUK	17X/137X	15	74782356	rs12909047	A	G	0.11	0.02	1.05E-06	4380	yes	0.98
SHIP	17X/137X	15	74817689	rs35107470	A	G	-0.16	0.05	1.85E-03	943	yes	0.85
TwinsUK	17X/137X	15	74817689	rs35107470	A	G	-0.18	0.03	4.61E-12	4380	yes	0.95
SHIP	17X/137X	15	74890981	rs62005807	C	G	0.16	0.08	0.04	943	yes	1.00
TwinsUK	17X/137X	15	74890981	rs62005807	C	G	0.27	0.04	1.90E-10	4380	yes	0.90
SHIP	17X/137X	15	75019449	rs2470893	T	C	0.16	0.05	1.08E-03	943	yes	1.00
TwinsUK	17X/137X	15	75019449	rs2470893	T	C	0.18	0.02	9.10E-13	4380	no	1.00
SHIP	17X/137X	15	75027880	rs2472297	T	C	0.17	0.05	8.02E-04	943	yes	1.00
SKIPOGH	17X/137X	15	75027880	rs2472297	T	C	0.29	0.06	5.77E-07	824	no	NA
TwinsUK	17X/137X	15	75027880	rs2472297	T	C	0.20	0.02	5.85E-15	4380	no	1.00
SHIP	17X/137X	19	41195170	rs66500423	T	C	0.14	0.05	2.37E-03	943	yes	1.00
TwinsUK	17X/137X	19	41195170	rs66500423	T	C	0.12	0.02	5.14E-07	4380	yes	0.99
SHIP	17X/137X	19	41326426	rs4803373	C	G	0.16	0.05	5.27E-04	943	yes	0.92
TwinsUK	17X/137X	19	41326426	rs4803373	C	G	0.14	0.02	1.97E-09	4380	yes	0.90
SHIP	17X/137X	19	41332171	rs78011401	T	C	-0.16	0.05	1.35E-03	943	yes	0.90
TwinsUK	17X/137X	19	41332171	rs78011401	T	C	-0.11	0.02	1.03E-06	4380	yes	0.98
SHIP	17X/137X	19	41343871	rs11668399	C	G	0.10	0.05	0.05	943	yes	0.88
TwinsUK	17X/137X	19	41343871	rs11668399	C	G	0.14	0.02	9.03E-10	4380	yes	0.99
SHIP	17X/137X	19	41353107	rs56113850	T	C	0.25	0.04	2.01E-08	943	yes	0.94
TwinsUK	17X/137X	19	41353107	rs56113850	T	C	0.17	0.02	1.56E-15	4380	yes	0.94
SHIP	17X/137X	19	41353338	rs56267346	A	G	-0.31	0.06	3.10E-08	943	yes	0.91
TwinsUK	17X/137X	19	41353338	rs56267346	A	G	-0.13	0.03	2.71E-05	4380	yes	0.95
SHIP	17X/137X	19	41354458	rs28399442	A	C	0.86	0.14	1.28E-09	943	yes	0.99
TwinsUK	17X/137X	19	41354458	rs28399442	A	C	0.41	0.09	1.47E-05	4380	yes	0.99
SHIP	17X/137X	19	41357457	rs67210567	T	G	0.22	0.20	0.27	943	yes	0.66
TwinsUK	17X/137X	19	41357457	rs67210567	T	G	0.50	0.08	1.61E-09	4380	yes	0.99
SHIP	17X/137X	19	41357632	rs7260629	T	G	0.14	0.05	5.05E-03	943	yes	0.88
TwinsUK	17X/137X	19	41357632	rs7260629	T	G	0.14	0.02	9.21E-10	4380	yes	0.94
SHIP	17X/137X	19	41361572	rs5828081	AT	A	-0.16	0.05	5.92E-04	943	yes	0.98
TwinsUK	17X/137X	19	41361572	rs5828081	AT	A	-0.13	0.02	1.48E-09	4380	yes	0.98
SHIP	17X/137X	19	41363094	rs200292835	T	TTTTG	-0.09	0.05	0.09	943	yes	0.80
TwinsUK	17X/137X	19	41363094	rs200292835	T	TTTTG	-0.13	0.02	3.49E-08	4380	yes	0.97
SHIP	17X/137X	19	41388740	rs28602288	T	C	-0.18	0.05	1.54E-04	943	yes	0.98
TwinsUK	17X/137X	19	41388740	rs28602288	T	C	-0.11	0.02	5.12E-06	4380	yes	0.96
SHIP	17X/137X	19	41392490	rs79600176	T	C	-0.85	0.14	1.12E-09	943	yes	1.00
TwinsUK	17X/137X	19	41392490	rs79600176	T	C	-0.41	0.09	6.55E-06	4380	yes	0.99
SHIP	17X/137X	19	41412192	rs184589612	T	C	-0.84	0.18	5.45E-06	943	yes	0.89
TwinsUK	17X/137X	19	41412192	rs184589612	T	C	-0.50	0.11	9.73E-06	4380	yes	1.

Table S7. Follow-up Candidate SNP-Metabolite Associations

[illegible]

Chr: chromosome; E: effect; EA: effect allele; EAF: effect allele frequency; NEA: non-effect allele;

^a See Table S1 for metabolite names

Table S8. Top Pathways

Database	Gene Set (short name)	Original Gene Set Size	137X ^a			17X			13X			17X/137X		
			Effective Gene Set Size	Nominal GSEA P	FDR	Effective Gene Set Size	Nominal GSEA P	FDR	Effective Gene Set Size	Nominal GSEA P	FDR	Effective Gene Set Size	Nominal GSEA P	FDR
REACTOME	Xenobiotics (xeno)	15	10	0.40	0.96	12.00	4.00E-04	0.02	12	0.46	0.85	13	1.40E-05	1.90E-03
GOTERM	drug metabolic process (drug)	15	13	0.49	1.00	13	2.10E-05	0.01	13	0.14	1.00	13	4.00E-04	1.40E-01
Panther	Nicotine degradation (nicotine)	10	9	1.00	0.96	8.00	4.00E-04	0.02	8	0.34	0.97	8	1.00E-04	0.01
Panther (biological process)	NF-kappaB cascade (NFkB)	71	58	0.57	1.00	61.00	4.00E-04	0.02	60	0.35	0.95	59	1.00E-04	0.03
Panther	5HT3-type receptor mediated signaling pathway (5HT3)	7	7	1.00	0.96	7.00	3.10E-03	0.05	6	2.20E-03	0.03	4	1.00	0.97
KEGG	N glycan biosynthesis (N-glycan)	46	45	3.00E-04	0.03	44.00	0.178	0.61	44	0.38	0.93	44	0.65	1.00
Panther (biological process)	Other polysaccharide metabolism (other poly)	142	110	8.40E-05	0.04	112.00	0.488	0.97	109	0.98	1.00	109	0.92	1.00

^a See Table S1 for metabolite names

Table S9 Top Gene-based Tests (P<0.05)

Gene.ID	Gene	Chr	Gene start (kb)	Gene end (kb)	Locus	Pathway ^a	137X ^b			17X			13X			17X/137X		
							Gene-based P	Top SNP	Top SNP P	Gene-based P	Top SNP	Top SNP P	Gene-based P	Top SNP	Top SNP P	Gene-based P	Top SNP	Top SNP P
1543	CYP1A1	15	74991882	75037877	15q24.1	nicotine,drug,CYP1A2	1.00E-06	rs2472297	1.00E-20	1.69E-02	rs2470893	0.0002969	1.44E-04	rs2470893	1.16E-07	2.00E-06	rs2472297	9.45E-22
1544	CYP1A2	15	75021183	75068941	15q24.1	nicotine,drug,CYP1A2	1.00E-06	rs2472297	1.00E-20	2.63E-02	rs2470893	0.0002969	4.62E-04	rs2470893	1.16E-07	3.00E-06	rs2472297	9.45E-22
196	AHR	7	17318275	17405775	7p15	CYP1A2	3.00E-06	rs2389763	7.17E-10	2.34E-01	rs73079637	0.01156	6.74E-03	rs10275488	0.0005489	1.00E-06	rs2389763	1.36E-13
5530	PPP3CA	4	101924586	102288628	4q24	other poly	7.59E-04	rs10516471	7.09E-06	1.91E-01	rs13121347	0.0113	9.09E-02	rs10516471	0.00612	2.14E-01	rs74351276	0.0137
10195	ALG3	3	183940116	183987313	3q27.1	N-glycan,other poly	1.10E-03	rs112813049	0.0002055	5.22E-04	rs6806162	4.25E-05	1.31E-03	rs71318361	0.0002677	3.48E-01	rs3892286	0.008539
11253	MAN1B1	9	139961378	140023639	9q34	N-glycan,other poly	3.73E-03	rs10870198	5.33E-05	1.24E-01	rs11146019	0.007926	2.85E-01	rs11146019	0.01016	4.32E-01	rs185925877	0.03007
2131	EXT1	8	118791601	119144058	8q24.11	other poly	3.99E-03	rs1824175	0.0001558	9.59E-02	rs17431672	0.000396	4.90E-02	rs17431672	0.004843	2.88E-01	rs148506839	0.008394
4122	MAN2A2	15	91427419	91485815	15q26.1	N-glycan	4.09E-03	rs11073963	0.0002156	7.19E-02	rs79742014	0.000467	5.79E-02	rs78164913	0.0002781	1.70E-01	rs79742014	0.01599
6489	ST8SIA1	12	22326324	22507648	12p12.1-p11.2	other poly	6.94E-03	rs2072542	0.0009769	8.89E-02	rs976711	0.002266	5.08E-01	rs75130288	0.02272	2.22E-01	rs75130288	0.008085
9956	HS3ST2	16	22805859	22947659	16p12	other poly	7.12E-03	rs9302402	0.0005735	3.94E-03	rs756800	0.0007964	4.42E-02	rs73543184	0.0004082	1.98E-01	rs71378487	0.009431
2590	GALNT2	1	230173535	230437876	1q41-q42	other poly	7.89E-03	rs10864696	5.67E-05	4.23E-02	rs6659554	0.0006264	9.30E-03	rs12733702	0.0002905	1.25E-01	rs74145438	0.001859
57452	GALNT16	14	69706680	69841190	14q24.1	other poly	8.90E-03	rs140734049	0.0006341	4.36E-03	rs76314768	0.0004334	5.73E-02	rs116398598	0.003224	2.63E-01	rs4271533	0.005408
8509	NDST2	10	75541668	75591589	10q22	other poly	1.03E-02	rs2675662	0.0013	1.69E-01	rs35972789	0.02259	2.04E-01	rs35972789	0.0292	2.34E-01	rs35207902	0.007145
55907	CMAS	12	22179109	22238606	12p12.1	other poly	1.09E-02	rs3809205	0.0001651	2.41E-02	rs7047340	0.003115	2.26E-02	rs10770876	0.00282	4.12E-01	rs3809204	0.025
6927	HNFI A	12	121396548	121460314	12q24.2	CYP1A2	1.47E-02	rs11065381	0.0006045	1.60E-01	rs78197988	0.008192	2.19E-01	rs78671297	0.00549	3.92E-01	rs7969196	0.01252
3036	HAS1	19	52196364	52247221	19q13.4	other poly	1.77E-02	rs75310023	4.40E-05	3.98E-01	rs10408866	0.0293	1.13E-01	rs3829652	0.00439	5.37E-02	rs4802856	0.001241
50614	GALNT9	12	132660916	132925905	12q24.33	other poly	2.19E-02	rs28437244	0.0006187	2.05E-02	rs28412188	9.63E-05	8.79E-02	rs28735021	0.006779	1.60E-01	rs61945704	0.005272
440138	ALG11	13	52566522	52623780	13q14.2	N-glycan,other poly	2.21E-02	rs61958804	0.004195	8.87E-01	rs73184327	0.1454	1.46E-01	rs56219214	0.009037	6.82E-01	rs117014324	0.0969
2683	B4GALT1	9	33090638	33187356	9p13	N-glycan,other poly	2.27E-02	rs146570729	0.0001358	2.42E-03	rs62544388	5.64E-05	3.46E-02	rs874202	0.0004913	8.09E-02	rs7380500	0.007483
8813	DPM1	20	49531404	49595060	20q13.13	N-glycan	2.31E-02	rs142825371	0.0006431	1.75E-01	rs4809815	0.0178	1.01E-01	rs6096207	0.02281	1.52E-01	rs910074	0.02171
8702	B4GALT4	3	118910588	118979752	3q13.3	other poly	2.36E-02	rs58488777	0.002003	1.07E-01	rs149996849	0.008004	1.14E-01	rs58488777	0.003747	3.64E-01	rs75951664	0.007496
3551	IKKBK	8	42108819	42210171	8p11.2	NFKB	2.09E-02	rs13270748	0.00275	2.99E-02	rs2297615	0.00489	1.51E-01	rs13270719	0.006286	1.46E-01	rs72474209	0.00186
29929	ALG6	1	63813260	63924233	1p31.3	N-glycan	3.10E-02	rs11208186	0.002939	1.47E-01	rs74693182	0.005242	8.59E-02	rs75284175	0.002418	5.34E-01	rs10789135	0.01476
9334	B4GALT5	20	48229482	48350421	20q13.1-q13.2	other poly	3.13E-02	rs803192	0.003489	2.89E-01	rs6095639	0.02753	3.10E-01	rs3888385	0.04511	5.68E-01	rs6067211	0.005355
4791	NFKB2	10	104133866	104182286	10q24	NFKB	3.16E-02	rs12360330	0.003212	4.72E-01	rs78145470	0.02818	9.39E-02	rs78145470	0.0005606	2.01E-01	rs7921001	0.02692
7903	ST8SIA4	5	100122638	100258999	5q21	other poly	3.47E-02	rs10515305	0.002357	5.92E-02	rs157181	0.02415	1.04E-01	rs62386110	0.007817	1.22E-01	rs10515305	0.006955
51363	CHST15	10	125747181	125873123	10q26	other poly	3.48E-02	rs141611516	0.0007695	1.79E-03	rs141611516	2.94E-05	2.69E-02	rs141611516	0.0004263	2.82E-01	rs187109891	0.00103
201595	STT3B	3	31554490	31697556	3p23	N-glycan	3.56E-02	rs12107675	0.002775	7.67E-03	rs12107675	0.0008816	5.97E-03	rs62236739	0.0004898	1.82E-01	rs116764639	0.001667
405	ARNT	1	150762180	150869244	1q21	CYP1A2	3.61E-02	rs191784961	0.002398	1.10E-01	rs115298177	0.003178	2.04E-01	rs10305665	0.023	1.62E-01	rs10305660	0.00768
64409	WBSR17	7	70577522	71198586	7q11.23	other poly	3.84E-02	rs4129606	0.0001379	1.24E-01	rs34628923	0.0008249	8.39E-02	rs183213541	0.00306	5.60E-03	rs7786589	0.002187
8600	TNFSF11	13	43116871	43202149	13q14	NFKB	3.99E-02	rs138818878	0.00465	2.03E-01	rs61959536	0.005046	1.07E-01	rs9533138	0.006197	1.11E-02	rs9533138	0.002634
199857	ALG14	1	95428278	95558507	1p21.3	N-glycan,other poly	4.45E-02	rs2766002	0.000132	5.00E-01	rs116423542	0.01969	2.15E-01	rs2766002	0.001347	3.62E-02	rs61772636	0.0007372
79092	CARD14	17	78123790	78203130	17q25	NFKB	4.86E-02	rs118157584	0.0006827	5.47E-03	rs68089445	0.001336	2.18E-02	rs55831872	0.001845	3.19E-01	rs4889992	0.004604
3576	CXCL8	4	74586222	74629433	4q13-q21	NFKB	5.02E-02	rs138840656	0.007181	8.69E-02	rs72650806	0.004046	3.85E-02	rs138840656	0.01109	2.58E-02	rs78386414	7.22E-05
4793	NFKB1B	19	39370339	39419534	19q13.1	NFKB	5.10E-02	rs11879029	0.001765	4.80E-02	rs17134180	0.006809	7.59E-02	rs7251489	0.003867	4.78E-03	rs11672849	7.94E-05
2799	GNS	12	65087221	65173226	12q14	other poly	6.14E-02	rs2682728	0.01025	4.19E-02	rs1245182	0.002596	1.32E-02	rs1797690	0.00119	8.89E-02	rs1797687	0.0006847
6482	ST3GAL1	8	134447090	134604183	8q24.22	other poly	6.39E-02	rs68108857	0.0005574	2.25E-02	rs74513215	0.0005742	5.24E-02	rs72718267	0.001326	7.69E-02	rs2975738	0.007499
7186	TRAF2	9	139760964	139841067	9q34	NFKB	6.75E-02	rs36097075	0.004255	1.28E-02	rs35692357	0.002579	8.09E-02	rs35692357	0.01053	5.34E-01	rs146586056	0.01938
54658	UGT1A1	2	234648918	234701945	2q37	other poly	7.09E-02	rs28900435	0.002424	9.29E-02	rs6431637	0.001441	1.53E-01	rs6431637	0.000124	3.39E-02	rs56148057	0.0009802
338596	ST8SIA6	10	173162780	17516254	10p12.33	other poly	7.09E-02	rs10159766	0.001044	2.12E-01	rs11254579	0.005046	1.33E-01	rs11254625	0.007069	2.12E-02	rs17445461	0.002729
1553	CYP2A13	19	41574355	41622100	19q13.2	xeno,nicotine	7.19E-02	rs146866989	0.001283	8.79E-02	rs149767102	0.0002461	5.01E-01	rs149767102	0.003746	9.70E-03	rs117668555	0.0002865
2328	FMO3	1	171040017	171106959	1q24.3	xeno,drug	8.09E-02	rs76012774	0.002051	8.59E-02	rs76012774	0.000188	2.31E-02	rs76012774	2.53E-05	8.03E-03	rs12404183	0.000121
10891	PPARGC1A	4	23773643	23911700	4p15.1	CYP1A2	8.19E-02	rs17885261	0.0003171	1.42E-01	rs7813533	0.001855	5.66E-02	rs75901901	0.001919	1.85E-02	rs1532196	0.004008
8767	RIPK2	8	90749974	90823292	8q21	NFKB	8.19E-02	rs11995065	0.01102	3.03E-01	rs117152341	0.01693	4.10E-01	rs11783881	0.01661	1.39E-02	rs36032938	0.00144
2327	FMO2	1	171134387	171201822	1q24.3	xeno,drug	9.09E-02	rs76012774	0.002051	2.21E-01	rs76012774	0.000188	3.81E-02	rs76012774	2.53E-05	7.19E-02	rs1795243	0.002214
316	AOX1	2	201430730	201556217	2q33	xeno	1.02E-01	rs6735028	0.002098	1.84E-01	rs34771762	0.007149	2.40E-01	rs11896227	0.009782	3.07E-02	rs7589108	0.0002403
1572	CYP2F1	19	41603552	41654281	19q13.2	nicotine	1.03E-01	rs75762823	0.007067	1.10E-01	rs149767102	0.0002461	6.03E-01	rs149767102	0.003746	4.09E-02	rs74319726	0.00101
9348	NDST3	4	118935499	119199789	4q26	other poly	1.06E-01	rs131355500	0.006294	2.78E-01	rs6842524	0.02329	3.10E-02	rs7656160	0.004027	5.19E-02	rs76090359	0.003326
5971	RELB	19	45484706	45561456	19q13.32	NFKB	1.08E-01	rs204473	0.01083	4.65E-02	rs75824242	0.0007415	1.87E-01	rs11879248	0.003129	4.00E-01	rs28809016	0.02314
79053	ALG8	11	77791987	77870699	11q14.1	N-glycan	1.08E-01	rs7125563	0.00962	5.71E-02	rs113390							

Figure S1. GWAS of plasma caffeine (137X)

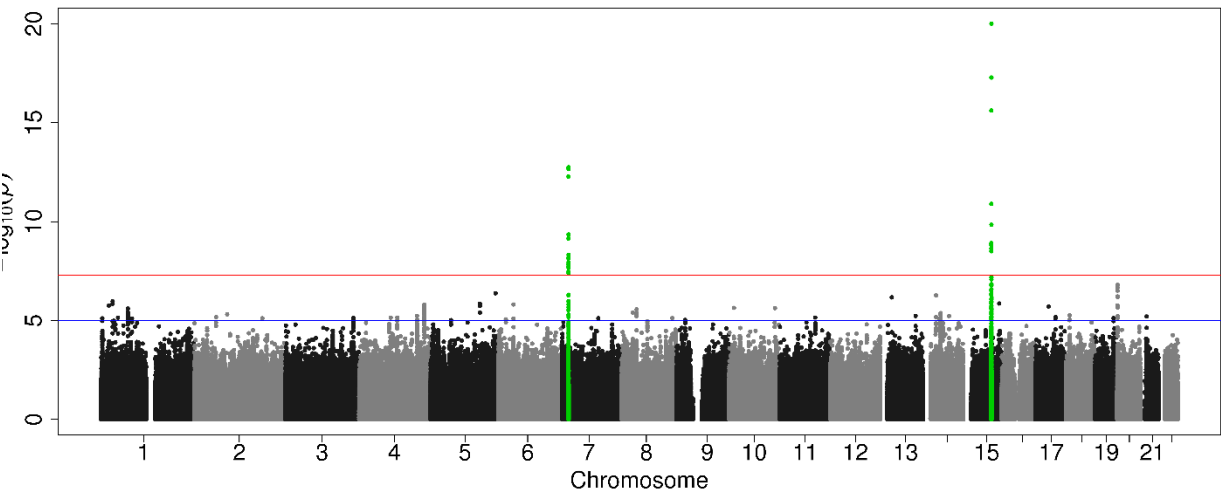


Figure S2. GWAS of plasma paraxanthine (17X)

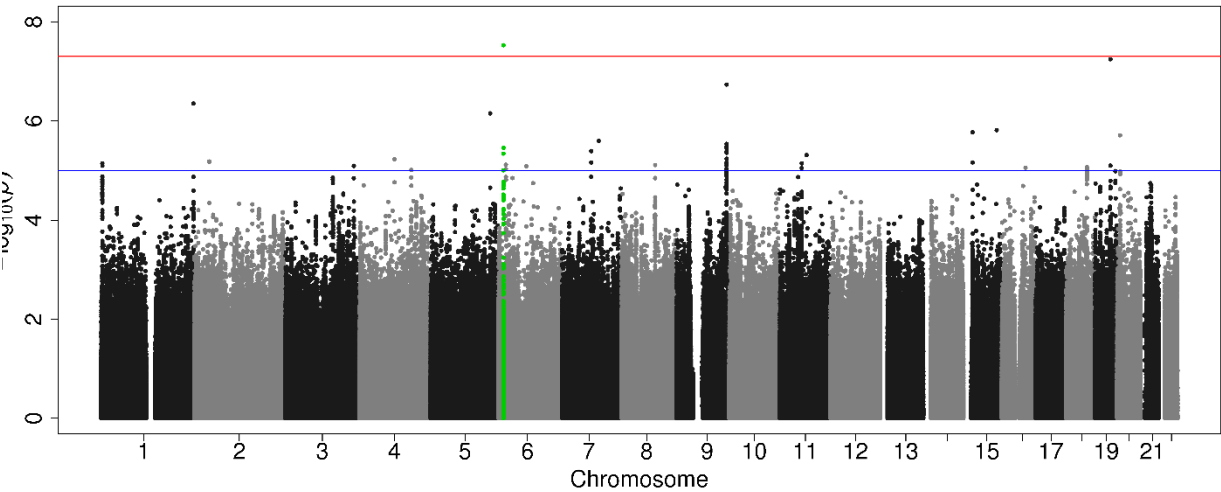


Figure S3. GWAS of plasma theophylline (13X)

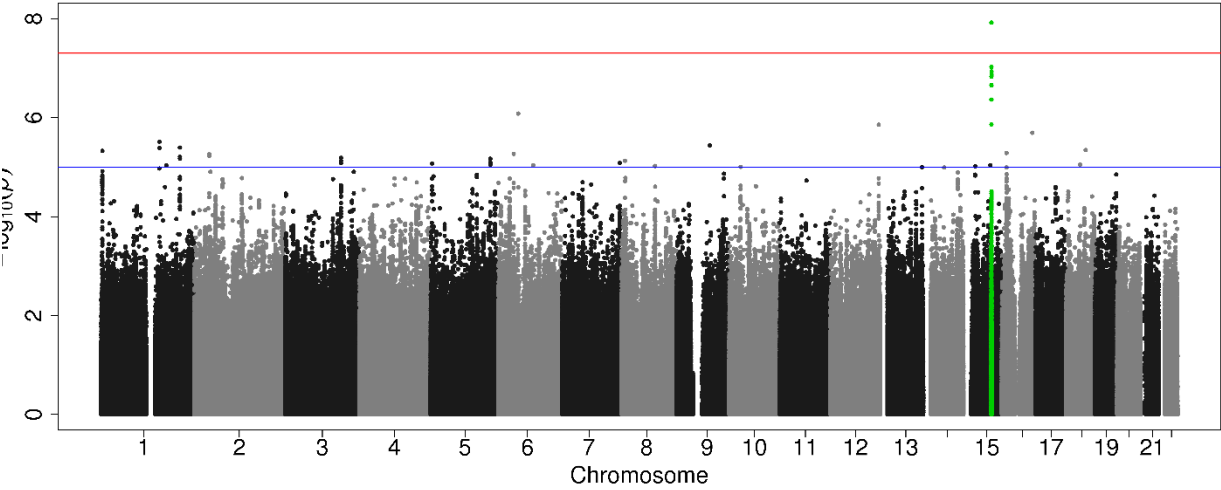


Figure S4. GWAS of plasma theobromine (37X)

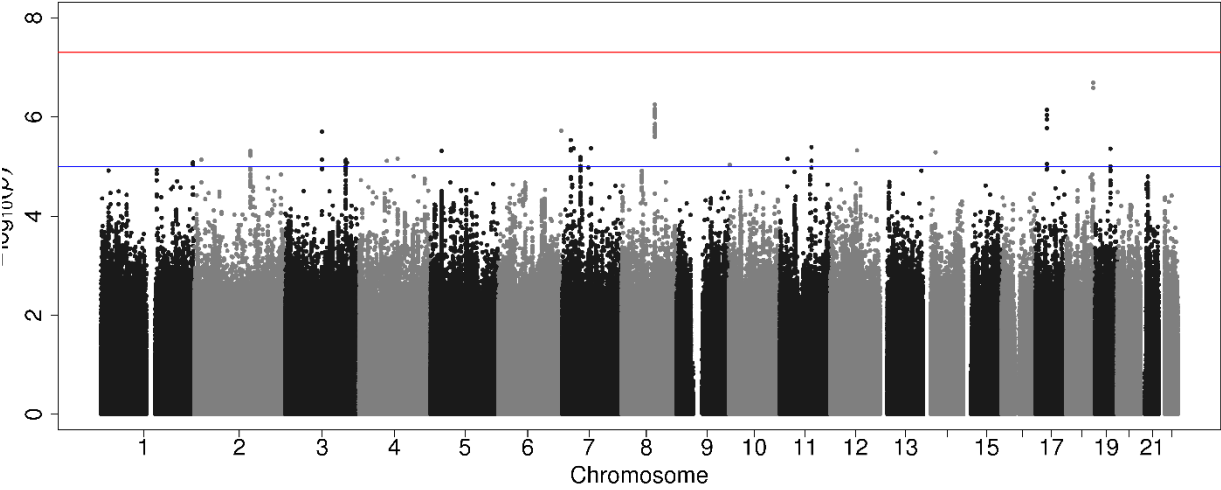


Figure S5. GWAS of plasma 1,3,7 trimethyluric acid (137U)

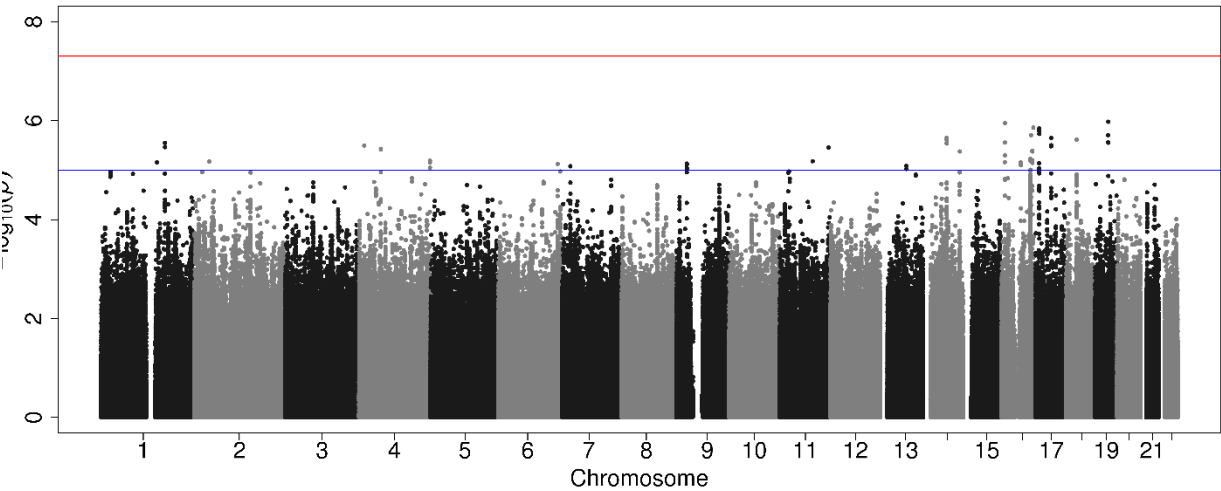


Figure S6. GWAS of paraxanthine/caffeine (17X/137X)

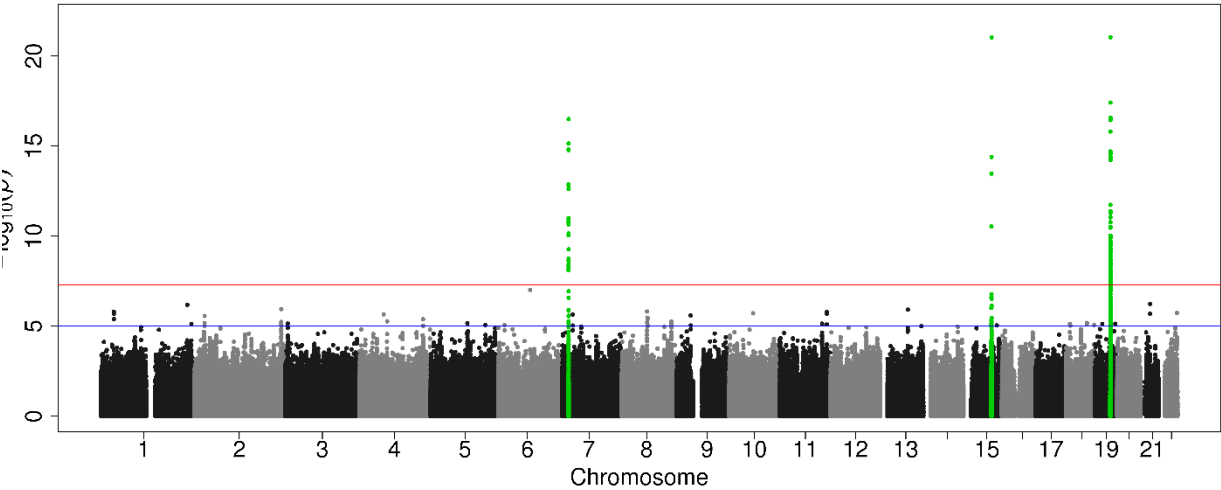
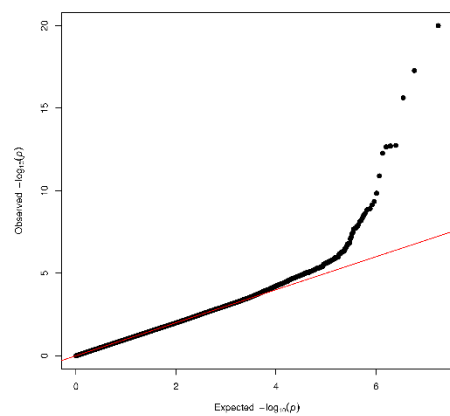
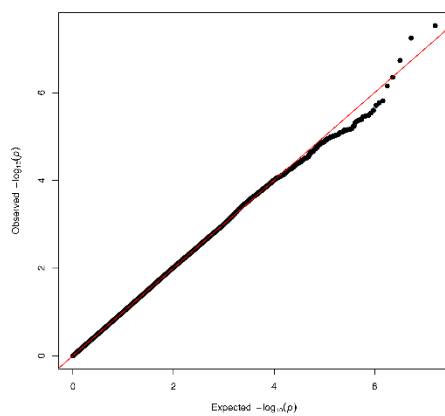


Figure S7. QQ-plots of plasma metabolite GWAS

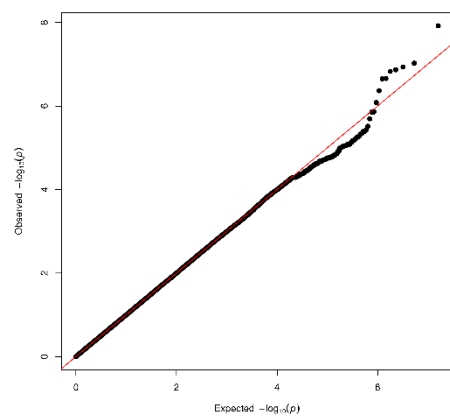
a. 137X



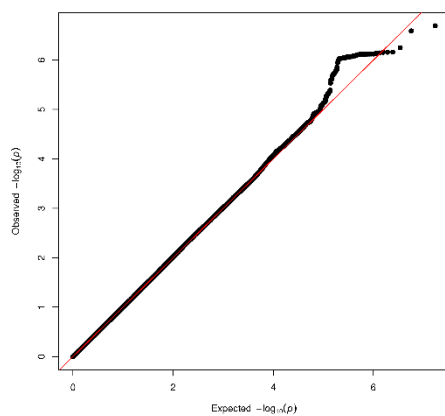
b. 17X



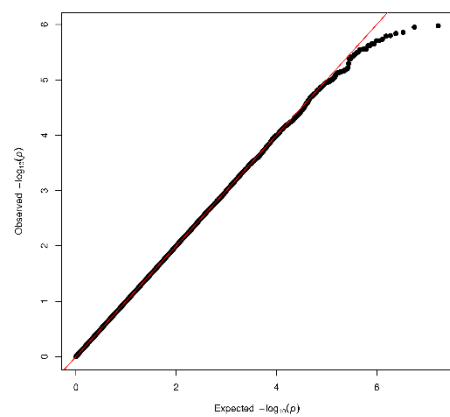
c. 13X



d. 37X



e. 137U



f. 17X/137X

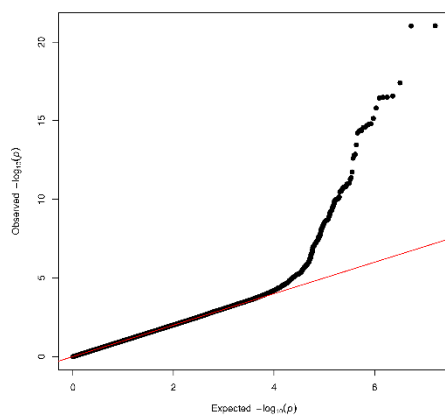
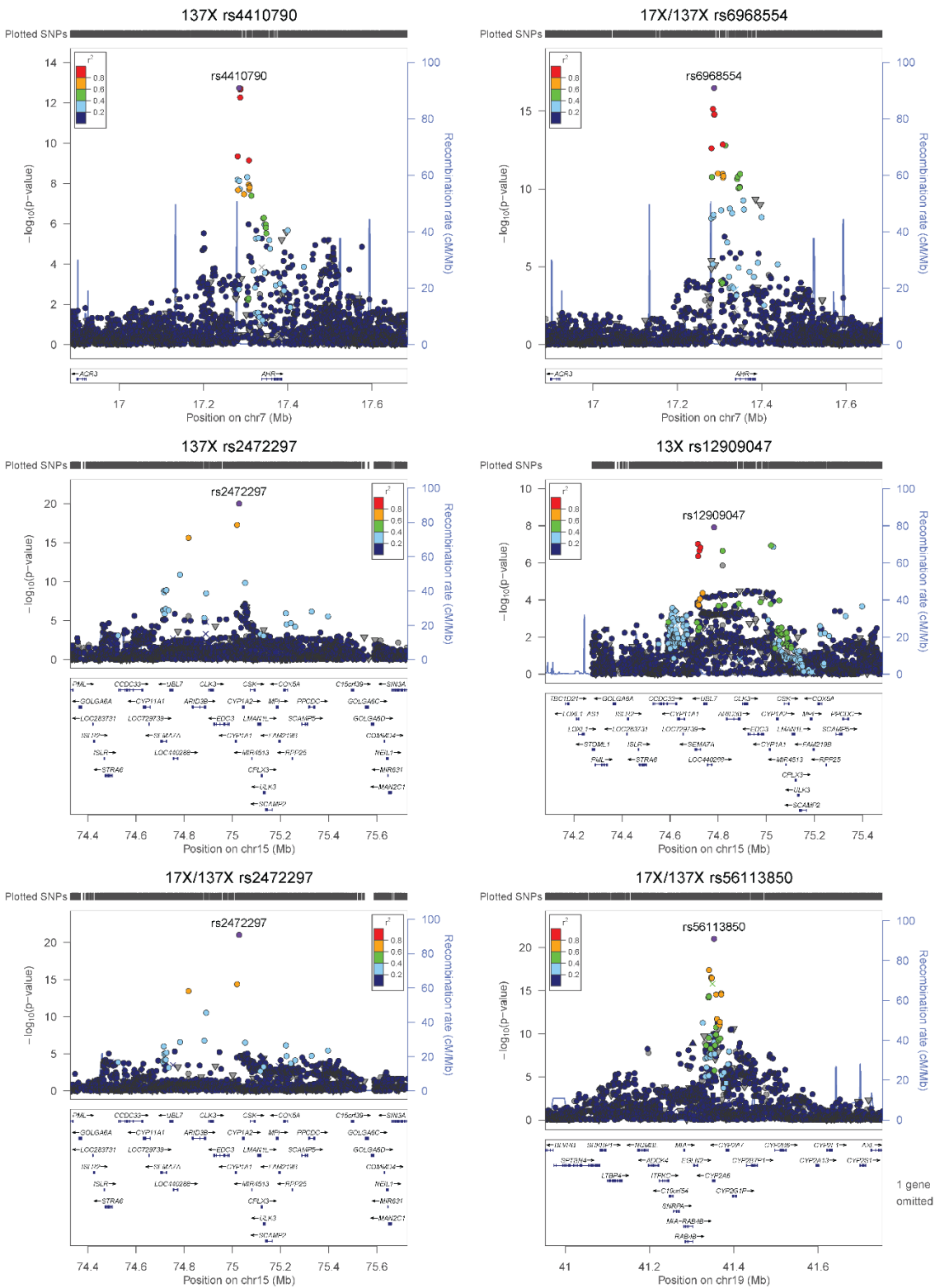


Figure S8. Regional Association Plots



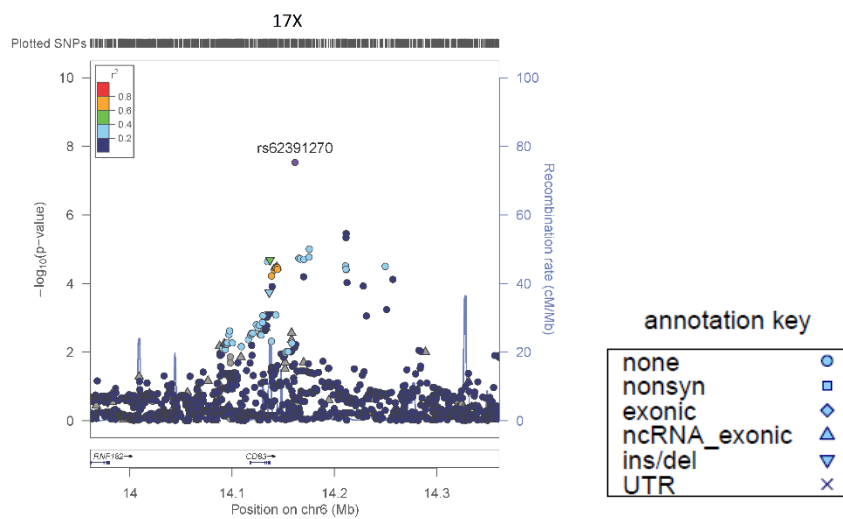


Table S9 Top Gene-based Tests (P<0.05)

Gene.ID	Gene	Chr	Gene start (kb)	Gene end (kb)	Locus	Pathway ^a	137X ^b			17X			13X			17X/137X			
							Gene-based P	Top SNP	Top SNP P	Gene-based P	Top SNP	Top SNP P	Gene-based P	Top SNP	Top SNP P	Gene-based P	Top SNP	Top SNP P	
1543	CYP1A1	15	74991882	75037877	15q24.1	nicotine,drug,CYP1A2	1.00E-06	rs2472297	1.00E-20	1.69E-02	rs2470893	0.0002969	1.44E-04	rs2470893	1.16E-07	2.00E-06	rs2472297	9.45E-22	
1544	CYP1A2	15	75021183	75068941	15q24.1	nicotine,drug,CYP1A2,caffeine	1.00E-06	rs2472297	1.00E-20	2.63E-02	rs2470893	0.0002969	4.62E-04	rs2470893	1.16E-07	3.00E-06	rs2472297	9.45E-22	
196	AHR	7	17318275	17405775	7p15	CYP1A2	3.00E-06	rs2389763	7.17E-10		2.34E-01	rs73079637	0.01156	6.74E-03	rs10275488	0.0005489	1.00E-06	rs2389763	1.36E-13
5530	PPP3CA	4	101924586	102288628	4q24	other poly	7.59E-04	rs10516471	7.09E-06	1.91E-01	rs13121347	0.0113	9.09E-02	rs10516471	0.00612	2.14E-01	rs74351276	0.0137	
10195	ALG3	3	183940116	183987313	3q27.1	N-glycan,other poly	1.10E-03	rs112813049	0.0002055	5.22E-04	rs6806162	4.25E-05	1.31E-03	rs71318361	0.0002677	3.48E-01	rs3892286	0.008539	
11253	MAN1B1	9	139961378	140023639	9q34	N-glycan,other poly	3.73E-03	rs10870198	5.33E-05	1.24E-01	rs11146019	0.007926	2.85E-01	rs11146019	0.01016	4.32E-01	rs185925877	0.03007	
2131	EXT1	8	118791601	119144058	8q24.11	other poly	3.99E-03	rs1824175	0.0001558	9.59E-02	rs17431672	0.000396	4.90E-02	rs17431672	0.004843	2.88E-01	rs148506839	0.008394	
4122	MAN2A2	15	91427419	91485815	15q26.1	N-glycan	4.09E-03	rs11073963	0.0002156	7.19E-02	rs79742014	0.000467	5.79E-02	rs78164913	0.0002781	1.70E-01	rs79742014	0.01599	
6489	ST8SIA1	12	22326324	22507648	12p12.1-p11.2	other poly	6.94E-03	rs2072542	0.0009769	8.89E-02	rs976711	0.002266	5.08E-01	rs75130288	0.02272	2.22E-01	rs75130288	0.008085	
9956	HS3ST2	16	22805859	22947659	16p12	other poly	7.12E-03	rs9302402	0.0005735	3.94E-03	rs756800	0.0007964	4.42E-02	rs73543184	0.0004082	1.98E-01	rs71378487	0.009431	
2590	GALNT2	1	230173535	230437876	1q41-q42	other poly	7.89E-03	rs10864696	5.67E-05	4.23E-02	rs6659554	0.0006264	9.30E-03	rs12733702	0.0002905	1.25E-01	rs74145438	0.001859	
57452	GALNT16	14	69706680	69841190	14q24.1	other poly	8.90E-03	rs140734049	0.0006341	4.36E-03	rs76314768	0.0004334	5.73E-02	rs116398598	0.003224	2.63E-01	rs4271533	0.005408	
8509	NDST2	10	75591668	75591589	10q22	other poly	1.03E-02	rs2675662	0.0013	1.69E-01	rs35972789	0.02259	2.04E-01	rs35972789	0.0292	2.34E-01	rs35207902	0.007145	
55907	CMAS	12	22179109	22238606	12p12.1	other poly	1.09E-02	rs3809205	0.0001651	2.41E-02	rs10743430	0.003115	2.26E-02	rs10770876	0.00282	4.12E-01	rs3809204	0.025	
6927	HNFI A	12	121396548	121460314	12q24.2	CYP1A2	1.47E-02	rs11065381	0.0006045	1.60E-01	rs78197988	0.008192	2.19E-01	rs78671297	0.00549	3.92E-01	rs7969196	0.01252	
3036	HAS1	19	52196364	52247221	19q13.4	other poly	1.77E-02	rs75310023	4.40E-05	3.98E-01	rs10408866	0.0293	1.13E-01	rs3829652	0.00439	5.37E-02	rs4802856	0.001241	
50614	GALNT9	12	132660916	132925905	12q24.33	other poly	2.19E-02	rs28437244	0.0006187	2.05E-02	rs28421288	9.63E-05	8.79E-02	rs28735021	0.006779	1.60E-01	rs61945704	0.005272	
440138	ALG11	13	52566522	52623780	13q14.2	N-glycan,other poly	2.21E-02	rs61958804	0.004195	8.87E-01	rs73184327	0.1454	1.46E-01	rs56219214	0.009037	6.82E-01	rs117014324	0.0969	
2683	B4GALT1	9	33090638	33187356	9p13	N-glycan,other poly	2.27E-02	rs146570729	0.0001358	2.42E-03	rs62544388	5.64E-05	3.46E-02	rs874202	0.0004913	8.09E-02	rs7380500	0.007483	
8813	DPM1	20	49531404	49595060	20q13.13	N-glycan	2.31E-02	rs142825371	0.0006431	1.75E-01	rs4809815	0.0178	1.01E-01	rs6096207	0.02281	1.52E-01	rs910074	0.02171	
8702	B4GALT4	3	118910588	118979752	3q13.3	other poly	2.36E-02	rs58488777	0.002003	1.07E-01	rs149996849	0.008004	1.14E-01	rs58488777	0.003747	3.64E-01	rs75951664	0.007496	
3551	IKBK B	8	42108819	42210171	8p11.2	NFKB	2.99E-03	rs13270748	0.00275	2.99E-02	rs2272615	0.00489	1.51E-01	rs13270719	0.006286	1.46E-01	rs72474209	0.0186	
29929	ALG6	1	63813260	63924233	1p31.3	N-glycan	3.10E-02	rs11208186	0.002939	1.47E-01	rs74693182	0.005242	8.59E-02	rs75284175	0.002418	5.34E-01	rs10789135	0.01476	
9334	B4GALT5	20	48229482	48350421	20q13.1-q13.2	other poly	3.13E-02	rs803192	0.003489	2.89E-01	rs6095639	0.02753	3.10E-01	rs3888385	0.04511	5.68E-01	rs6067211	0.005355	
4791	NFKB2	10	104133866	104182286	10q24	NFKB	3.16E-02	rs12360330	0.003212	4.72E-01	rs78145470	0.02818	9.39E-02	rs78145470	0.0005606	2.01E-01	rs7921010	0.02692	
7903	ST8SIA4	5	100122638	100258989	5q21	other poly	3.47E-02	rs10515305	0.002357	5.92E-02	rs157181	0.02415	1.04E-01	rs62386110	0.007817	1.22E-01	rs10515305	0.006955	
51363	CHST15	10	125747181	125873123	10q26	other poly	3.48E-02	rs141611516	0.0007695	1.79E-03	rs141611516	2.94E-05	2.69E-02	rs141611516	0.0004263	2.82E-01	rs187109891	0.00103	
201595	STT3B	3	31554490	31697556	3p23	N-glycan	3.56E-02	rs12107675	0.002775	7.67E-03	rs12107675	0.0008816	5.97E-03	rs62236739	0.0004898	1.82E-01	rs116764639	0.001667	
405	ARNT	1	150762180	150869244	1q21	CYP1A2	3.61E-02	rs191784961	0.002398	1.10E-01	rs115298177	0.003178	2.04E-01	rs10305665	0.023	1.62E-01	rs10305660	0.00768	
64409	WBSCR17	7	70577522	71198586	7q11.23	other poly	3.84E-02	rs1429606	0.0001379	1.24E-01	rs34628923	0.0008249	8.39E-02	rs183213541	0.00306	5.60E-03	rs7786589	0.002187	
8600	TNFSF11	13	43116871	43202149	13q14	NFKB	3.99E-02	rs138818878	0.000465	2.03E-01	rs61959536	0.005046	1.07E-01	rs9533138	0.006197	1.11E-02	rs95331384	0.002634	
199857	ALG14	1	95428278	95558507	1p21.3	N-glycan,other poly	4.45E-02	rs2766002	0.000132	5.00E-01	rs116423542	0.01969	2.15E-01	rs2766002	0.001347	3.62E-02	rs61772636	0.0007372	
79092	CARD14	17	78123790	78203130	17q25	NFKB	4.86E-02	rs118157584	0.0006827	5.47E-03	rs68089445	0.001336	2.18E-02	rs55831872	0.001845	3.19E-01	rs4889992	0.004604	
3576	CXCL8	4	74586222	74629433	4q13-q21	NFKB	5.02E-02	rs138840656	0.007181	8.69E-02	rs72650806	0.004046	3.85E-02	rs138840656	0.01109	2.58E-02	rs78386414	7.22E-05	
4793	NFKB1B	19	39370339	39419534	19q13.1	NFKB	5.10E-02	rs11879029	0.001765	4.80E-02	rs1134180	0.006809	7.59E-02	rs11672849	0.003867	4.78E-03	rs11672849	7.94E-05	
2799	GNS	12	65087221	65173226	12q14	other poly	6.14E-02	rs2682728	0.01025	4.19E-02	rs1245182	0.002596	1.32E-02	rs1797690	0.00119	8.89E-02	rs1797687	0.0006847	
6482	ST3GAL1	8	134447090	134604183	8q24.22	other poly	6.39E-02	rs68108857	0.0005574	2.25E-02	rs74513215	0.0005742	5.24E-02	rs72718267	0.001326	7.69E-02	rs2975738	0.007499	
7186	TRAF2	9	139760964	139841067	9q34	NFKB	6.75E-02	rs36097075	0.004255	1.28E-02	rs35692357	0.002379	8.09E-02	rs35692357	0.01053	5.34E-01	rs146586056	0.01938	
54658	UGT1A1	2	234648918	234701945	2q37	other poly	7.09E-02	rs28900435	0.002424	9.29E-02	rs6431637	0.001441	1.53E-01	rs6431637	0.000124	3.39E-02	rs56148057	0.0009802	
338596	ST8SIA6	10	17342675	17516254	10p12.33	other poly	7.09E-02	rs10159766	0.001044	2.12E-01	rs711254579	0.007891	1.33E-01	rs11254625	0.007069	2.12E-02	rs71445461	0.002729	
1553	CYP2A13	19	41574355	41622100	19q13.2	xeno,nicotine	7.19E-02	rs146866981	0.001283	8.79E-02	rs149767102	0.0002461	5.01E-01	rs149767102	0.003746	9.70E-03	rs117668555	0.0002865	
2328	FMO3	1	171040017	171106959	1q24.3	xeno,drug	8.09E-02	rs76012774	0.000188	8.59E-02	rs76012774	0.000188	2.31E-02	rs76012774	2.53E-05	8.03E-03	rs12404183	0.000121	
10891	PPARGC1A	4	23773643	23911700	4p15.1	CYP1A2	8.19E-02	rs17885261	0.0003171	1.42E-01	rs1873533	0.001855	5.66E-02	rs75901901	0.001919	1.85E-02	rs1532196	0.004008	
8767	RIPK2	8	90749974	90823292	8q21	NFKB	8.19E-02	rs11995065	0.01102	3.03E-01	rs117152341	0.01693	4.10E-01	rs11783881	0.01661	1.39E-02	rs36032938	0.00144	
2327	FMO2	1	171134387	171201822	1q24.3	xeno,drug	9.09E-02	rs76012774	0.002051	2.21E-01	rs76012774	0.000188	3.81E-02	rs76012774	2.53E-05	7.19E-02	rs1795243	0.002214	
316	AOX1	2	201430730	201556217	2q33	xeno	1.02E-01	rs6735028	0.002098	1.84E-01	rs34771762	0.007149	2.40E-01	rs11896227	0.009782	3.07E-02	rs7589108	0.0002403	
1572	CYP2F1	19	41600352	41654281	19q13.2	nicotine	1.03E-01	rs75762823	0.007067	1.10E-01	rs149767102	0.0002461	6.03E-01	rs149767102	0.003746	4.09E-02	rs74319726	0.00101	
9348	NDST3	4	118935499	119199789	4q26	other poly	1.06E-01	rs131355500	0.006294	2.78E-01	rs6842524	0.02329	3.10E-02	rs7656160	0.004027	5.19E-02	rs76090359	0.003326	
5971	RELB	19	45484706	45561456	19q13.32	NFKB	1.08E-01	rs204473	0.01083	4.65E-02	rs78824242	0.0007415	1.87E-01	rs11879248	0.003129	4.00E-01	rs28809016	0.02314	
79053	ALG8	11	77791987	77870699	11q14.1	N-glycan	1.08E-01	rs1215563	0.00962	5.71E-02									