Supplemental Text

Agrawal et al., Genomewide association study identifies a novel locus for cannabis dependence.

SAMPLE DESCRIPTIONS

Discovery samples:

Collaborative Study on the Genetics of Alcoholism (COGA): COGA is a multi-site study of alcohol dependent probands and their extended families (details available in(1)). Initially, a sample of unrelated alcohol dependent cases (n=847) and alcohol exposed controls aged 25 years or older (n=552) was constructed (COGA-ccGWAS(2)). In a follow-up genotyping effort, a subset of the most genetically informative families was selected for a family-based GWAS (COGA-fGWAS(3;4)). This sample consisted of 118 European-American families with 2232 individuals with genotyping data. There was overlap between the ccGWAS and fGWAS cohorts – to preserve patterns of relatedness, 183 overlapping subjects were preferentially retained in the fGWAS cohort. Institutional review boards at all participating institutions provided approval (Indiana University, State University of New York Health Science Center Brooklyn, University of Connecticut, University of Iowa, University of California/San Diego, Washington University School of Medicine and Howard University).

Study of Addictions Genes and Environment (SAGE): The primary objective of SAGE was to conduct a GWAS of alcohol dependent cases and alcohol exposed non-dependent controls. Subjects were selected from three large, complementary studies: COGA(1), Family Study of Cocaine Dependence (FSCD(5)), and Collaborative Genetic Study of Nicotine Dependence (COGEND(6)). Further details of the SAGE sample are available elsewhere(7). One hundred

and twenty nine individuals who were both in SAGE and the COGA discovery sample were excluded. For the current analyses, data on 1286 individuals of European-American descent was used for the primary meta-analysis. The Institutional Review Board at each contributing institution (i.e., Henry Ford Health Sciences Center, Howard University, Indiana University, SUNY Health Sciences Center at Brooklyn, University of California—San Diego, University of Connecticut Health Center, University of Iowa, and Washington University in St. Louis) reviewed and approved the protocols for genetic studies under which all participants were recruited.

Comorbidity and Trauma Study (CATS): This study consisted of opioid dependent individuals recruited from opioid substitution therapy clinics and genetically unrelated individuals with little or no lifetime opioid misuse from neighborhoods in geographic proximity to these clinics. Only subjects of European-Australian descent were included in current analyses. Further details are available elsewhere (8). CATS data were part of the replication cohort in Sherva et al(9) although only the top loci were studied. Institutional review board (IRB) approval was obtained from University of New South Wales (UNSW), Washington University School of Medicine (WUSM), Queensland Institute of Medical Research (QIMR), and area health service ethics committees governing participating clinics.

Australian alcohol and trauma studies (OZALC+): This sample consisted of 3451 individuals from 1831 families ascertained from four coordinated studies derived from a larger Australian twin registry: (i) the NAG (Nicotine Addiction Genetics) Study(10) which ascertained heavy smoking index cases; (ii) the OZALC-EDAC study, which ascertained index cases with a history of alcohol dependence or scoring above the 85th centile for heaviness of drinking factor score (operationalized as in(11)); (iii) the OZALC-BIGSIB study(12), which ascertained large sibships (4–14 full siblings), regardless of sibling phenotypes and (iv) the Midwest Alcohol Research Center Project 7 (13). Institutional review boards approving this study included Washignton University School of Medicine and Queensland Institute of Medical Research (QIMR).

Interview data across all discovery samples was collected using the the Semi-Structured Assessment of the Genetics of Alcohol (SSAGA)(14;15) which includes DSM-IV(16) diagnoses of cannabis dependence.

Replication sample:

Yale-Penn is a series of studies representing a cohort of 850 small nuclear families and 6951 unrelated individuals.(9) Families, primarily sibling pairs, and unrelated subjects were ascertained from treatment centers and advertisements. The sample included subjects of both European-American and African-American descent who were genotyped using the Illumina HumanOmni1-Quad v1.0. Interview data were collected using the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA)(17). Data were imputed to the March 2012 1000 Genomes reference panel using IMPUTE2. The EA and AA data were analyzed separately using logistic regression within a generalized estimating equations framework, to account for familial relatedness. Covariates included sex, age and the first 3 ancestral principal components**.**

Neuroimaging sample:

Duke Neurogenetics Study (DNS): Data were drawn from all Caucasian subjects with overlapping genetic and structural MRI data who completed the ongoing DNS by 06/01/2015 (n=438). The DNS assesses a wide range of behavioral, experiential, and biological phenotypes among young-adult (18-22 year-old) college students. Each participant provided informed written consent prior to participation in accord with the guidelines of the Duke University Medical Center Institutional Review Board and received $120 remuneration. All participants were in good general health and free of DNS exclusion criteria: (1) medical diagnosis of cancer, stroke, diabetes requiring insulin treatment, chronic kidney or liver disease or lifetime psychotic symptoms; (2) use of psychotropic, glucocorticoid or hypolipidemic medication, and (3)

conditions affecting cerebral blood flow and metabolism (e.g., hypertension). Current DSM-IV Axis I and select Axis II disorders (Antisocial Personality Disorder and Borderline Personality Disorder) were assessed with the electronic Mini International Neuropsychiatric Interview(18) and Structured Clinical Interview for the DSM-IV Axis II Personality Disorders(19). These disorders are not exclusionary as the DNS seeks to establish broad variability in multiple behavioral phenotypes related to psychopathology. Participants were excluded from the present analyses for 1) non-completion of T1 structural scans (n=1), 2) scanner-related artifacts in MRI data (n=3), 3) genetic-relatedness (e.g. cousins) of other study participants (n=2), and 4) poor imputation quality of the SNP of interest (see below; n=2). The final sample consisted of n=430 participants.

DNA was isolated from saliva derived from Oragene DNA self-collection kits (DNA Genotek) customized for 23andMe (www.23andme.com). DNA extraction and genotyping were performed through 23andMe by the National Genetics Institute (NGI), a CLIA-certified clinical laboratory and subsidiary of Laboratory Corporation of America. One of two different Illumina arrays with custom content was used to provide genome-wide SNP data, the HumanOmniExpress or HumanOmniExpress-24. Cannabis use and frequency of use were assessed using a single item from the Recreational Drug Use question.

SUPPLEMENTAL METHODS

Overall Meta-analysis Quality Control

Individual studies performed internal quality control. Prior to meta-analysis, we performed post-hoc quality control of each dataset. SNPs with minor allele frequency < 3%, missing in >4% of

the sample and those with a best-guess genotype HWE p-value of 1E-5 were excluded from each individual dataset. Adopting a conservative approach, only SNPs that passed stringent QC across all 5 samples were meta-analyzed. During meta-analysis, strand alignment was confirmed for unambiguous SNPs; ambiguous SNPs were excluded.

Genomic and Epigenomic Annotation

SNAP(20) was used to search for LD proxies (r2 ≥ 0.6, using the 1000 Genomes pilot 1 CEU data). GTEx (21) and Common Mind Consortium (22) was used to assess expression of genes corresponding to top SNPs and to search for cis-acting eQTLs (i.e., loci that explain a proportion of variability in aspects of expression of neighboring genes). Initial analyses examined all tissue types interrogated in GTEx with follow-up analyses focusing on tissue derived from brain regions. Analyses with Common Mind Consortium data relied on dorsolateral prefrontal cortex gene expression in control subjects (N=279).

RegulomeDB (23) (version 1.1) was used to examine initial evidence for regulatory elements. When there was evidence that a non-coding SNP was related to epigenetic function (i.e., scores of 1a – 3b), a combination of additional resources were used for annotation. The Washington University Epigenome Browser (24) (epigenomegateway.wustl.edu) examined histone modification H3K4me1, H3K27ac and H3K27me3 marks in brain-derived tissue to assess potential enhancer and repressor roles. Histone modification peak calling was conducted via Model-based Analysis of ChIP-seq (MACS)(25). The boundaries of the topologically associated domains harboring the genome-wide significant loci were defined using high resolution Hi-C sequencing data(26), and brain expression data for genes and pseudogenes within the domain was derived from GTEx. Motif finding analyses were performed using the FIMO tool (27) from the MEME suite, and the Transcription Factor Position Weight Matrix (TF PWM) was downloaded from JASPAR database (28).

Finally, we examined whether genotype was associated with differences in CpG methylation scores (29-31). CpG methylation status at 27,578 CpG dinucelotides corresponding to 14, 495 genes was acquired from neurologically normal Caucasian subjects via Human Methylation27 Beadchips while genotyping was conducted on the Infinium HumanHap550 beadchip(29;31). Methylation scores were residualized for sex, age, postmortem interval, tissue source and hybridization batch effects. After removal of those aged <10 years or >89 years, methylation data on the frontal cortex and cerebellum were available from 347 samples of European descent, with CT (n=34) and TT (n=313) genotype for rs1409568. Due to outlier effects, data were quantile transformed prior to linear regression. Any nominally significant differences (i.e. $p < .005$) were further examined using a Wilcoxon signed-rank test which is a more robust test of mean differences when data are non-normally distributed. All analyses were conducted in R.

Voxel-Based Morphometry to assess gray matter volume

A research-dedicated GE MR750 3 T scanner equipped with high-power high-duty-cycle 50-mT/m gradients at 200 T/m/s slew rate, and an eight-channel head coil for parallel imaging at high band-width up to 1 MHz was used to acquire data at the Duke-UNC Brain Imaging and Analysis Center. High-resolution T1-weighted images (3D Ax FSPGR BRAVO sequence: TR, 8.148 s; TE, 3.22 ms; 162 sagittal slices; flip angle, 12 º; FOV,240 mm; matrix 256 × 256; slice thickness, 1 mm with no gap) were obtained for voxel-based morphometry (VBM).

T1-weighted images were obtained using a 3D Ax FSPGR BRAVO with the following parameters: TR = 8.148 s; TE = 3.22 ms; 162 sagittal slices; flip angle, 12°; FOV, 240 mm; matrix =256×256; slice thickness = 1 mm with no gap; and total scan time = 4 min and 13 s. Regional gray matter volumes were determined using the unified segmentation(32) and DARTEL normalization(33) modules in SPM12 (http://www.fil.ion.ucl.ac.uk/spm). Using this approach, individual T1-weighted images were segmented into gray, white, and CSF images

then non-linearly registered to the existing IXI template of 550 healthy subjects averaged in standard Montreal Neurological Institute space, available with VBM8 (http://dbm.neuro.uni-jena.de/vbm/). Subsequently, gray matter images were modulated for nonlinear effects of the high-dimensional normalization to preserve the total amount of signal from each region, and smoothed with an 8mm FWHM Gaussian kernel. The voxel size of processed images was 1.5×1.5×1.5 mm. A gray matter mask for subsequent analyses was created by thresholding the final stage (6th) IXI template at 0.1.

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List of Supplemental Tables for Agrawal et al., Genomewide association study identifies a novel locus for cannabis dependence

Table S1. Characteristics of genotypic data from individual contributing studies.

Study	Genotyping Platform	Imputation software	MAF cutoff[A]	HWE cutoff	INFO cutoff[B]	NSNPs for analysis	Lambda	Covariates
CATS	Illumina Human660W-Quad	MACH	1%	1.00E-05	0.1	8,326,529	1.02	Case/control status, sex, 4 categorical age variables, principal components 1-2
COGA-cc	Illumina HumanHap1M	IMPUTE2	1%	1.00E-05	0.3	4,916,924	1.02	Age, sex, principal components 1-4
COGA-f	Illumina Human OmniExpress array 12.VI	SHAPEIT/IMPUTE2	1%	1.00E-05	0.3	6,860,478	1.03	Age, sex, principal components 1-4
OZALC	Illumina HumanCNV370-Quadv3	MACH	1%	1.00E-05	0.3	6,096,472	1.03	Sex, age
SAGE	Illumina Human1Mv1_c	Beagle	1%	1.00E-05	0.1	6,652,666	1	Sex, study site 1, study site 2, 3 categorical age variables, principal components 1-3
Yale-Penn	Illumina HumanOmni1-Quad v1.0	Impute2	3%	1.00E-05	0.8	6,876,520	1.02	Sex, Age, principal components 1-3
DNS	HumanOmniExpress or HumanOmniExpress-24	SHAPEIT/IMPUTE2	-	-	-	-	-	All analyses controlled for age and sex. Analyses with genotype also controlled for principal components 1-3. Analyses of brain volume also controlled for total intracranial volume

Legend:
[A]1% (PLINK automatically exclude these SNPs during analyses)
[B]0.1 (PLINK automatically excludes during analysis)

Table S2. Effect sizes across individual discovery samples that were combined in meta-analysis

	CATS			COGA-cc			COGA-f			OZALC+			SAGE		
SNP	**Beta**	**SE**	**p-value**	**Beta**	**SE**	**p-value**	**Beta**	**SE**	**p-value**	**Beta**	**SE**	**p-value**	**Beta**	**SE**	**p-value**
rs77300175	-0.633	0.1648	1.219E-04	-0.794	0.250	1.481E-03	0.347	0.201	8.358E-02	-0.296	0.203	1.448E-01	0.601	0.231	9.126E-03
rs7920901	-0.655	0.164	6.554E-05	-0.781	0.245	1.441E-03	0.225	0.214	2.927E-01	-0.293	0.193	1.291E-01	0.644	0.227	4.532E-03
rs7074123	-0.647	0.1641	8.035E-05	-0.810	0.247	1.044E-03	0.253	0.214	2.370E-01	-0.293	0.195	1.339E-01	0.619	0.229	6.942E-03
rs115048844	-0.652	0.1639	6.903E-05	-0.773	0.244	1.549E-03	0.225	0.214	2.927E-01	-0.292	0.192	1.274E-01	-0.646	0.227	4.519E-03
rs57602752	-0.651	0.1638	6.965E-05	-0.772	0.244	1.557E-03	0.225	0.214	2.927E-01	-0.293	0.193	1.287E-01	0.644	0.227	4.544E-03
rs1961317	-0.651	0.1645	7.628E-05	-0.794	0.246	1.251E-03	0.212	0.215	3.241E-01	-0.292	0.191	1.260E-01	0.644	0.227	4.572E-03
rs111332403	-0.638	0.1648	1.075E-04	-0.732	0.249	3.253E-03	0.230	0.214	2.830E-01	-0.281	0.159	7.722E-02	0.715	0.229	1.809E-03
rs7098706	-0.643	0.1637	8.633E-05	-0.816	0.246	8.932E-04	0.237	0.215	2.706E-01	-0.294	0.197	1.360E-01	-0.600	0.230	9.039E-03
rs150525973	-0.642	0.17	1.603E-04	-0.783	0.250	1.728E-03	0.241	0.214	2.592E-01	-0.333	0.199	9.465E-02	0.789	0.280	4.875E-03
rs149791363	-0.652	0.1663	8.892E-05	-0.785	0.250	1.681E-03	0.207	0.218	3.437E-01	-0.439	0.260	9.186E-02	1.203	0.433	5.429E-03
rs1409568	-0.591	0.1615	2.529E-04	-0.693	0.240	3.947E-03	0.361	0.199	7.027E-02	-0.297	0.207	1.510E-01	-0.564	0.224	1.167E-02
rs147702664	-0.633	0.1638	1.123E-04	-0.764	0.247	1.986E-03	0.227	0.214	2.894E-01	-0.439	0.260	9.196E-02	1.203	0.433	5.427E-03
rs118006754	-0.628	0.1644	1.315E-04	-0.791	0.250	1.571E-03	0.241	0.215	2.638E-01	-0.293	0.196	1.359E-01	0.615	0.230	7.313E-03
rs79516280	-0.638	0.1652	1.107E-04	-0.762	0.248	2.127E-03	0.357	0.201	7.567E-02	-0.294	0.212	1.662E-01	0.485	0.228	3.338E-02
rs145575521	-0.639	0.1653	1.099E-04	-0.759	0.248	2.204E-03	0.357	0.201	7.567E-02	-0.295	0.213	1.668E-01	-0.485	0.228	3.336E-02
rs75312482	-0.638	0.165	1.113E-04	-0.763	0.248	2.100E-03	0.348	0.201	8.303E-02	-0.295	0.212	1.640E-01	0.487	0.228	3.292E-02
rs79277226	-0.648	0.1662	9.741E-05	-0.765	0.249	2.094E-03	0.241	0.214	2.592E-01	-0.271	0.164	9.873E-02	-0.617	0.234	8.369E-03
rs113036365	-0.635	0.1639	1.075E-04	-0.761	0.247	2.086E-03	0.227	0.214	2.894E-01	-0.267	0.160	9.511E-02	0.617	0.234	8.411E-03
rs60120125	-0.635	0.1639	1.074E-04	-0.761	0.247	2.087E-03	0.227	0.214	2.894E-01	-0.267	0.160	9.503E-02	-0.616	0.234	8.445E-03
rs61538293	-0.638	0.1645	1.053E-04	-0.768	0.249	2.050E-03	0.200	0.203	3.250E-01	-0.288	0.176	1.020E-01	0.691	0.259	7.563E-03
rs112825709	-0.642	0.165	9.974E-05	-0.757	0.248	2.240E-03	0.302	0.209	1.481E-01	-0.295	0.213	1.666E-01	-0.485	0.228	3.342E-02
rs151284751	-0.642	0.1649	9.980E-05	-0.757	0.248	2.254E-03	0.302	0.209	1.481E-01	-0.295	0.213	1.665E-01	-0.485	0.228	3.343E-02
rs12413263	-0.625	0.1559	6.100E-05	-0.431	0.220	5.015E-02	0.106	0.195	5.885E-01	-0.269	0.143	5.899E-02	0.572	0.212	6.893E-03
rs12771281	-0.625	0.1559	6.107E-05	-0.431	0.220	4.999E-02	0.106	0.195	5.885E-01	-0.272	0.150	7.067E-02	0.631	0.233	6.716E-03
rs35728709	-0.608	0.1569	1.078E-04	-0.447	0.217	3.923E-02	0.079	0.198	6.891E-01	-0.298	0.157	5.816E-02	0.559	0.210	7.837E-03

Table S3. Results for cannabis dependence symptom counts in cannabis exposed individuals. Corressponding p-value from the meta-analysis for DSM-IV dependence is shown as a reference

					META-ANALYSIS				**STUDY-SPECIFIC EFFECT SIZES**					
SNP	Chromosome	Position	A1	A2	Effect	SE	P-value	Direction	CATS	COGAcc	COGAf	SAGE	OZALC	P_dependence
rs2287641	2	54342955	A	G	0.1138	0.0232	9.04E-07	+++++	-0.1383	-0.2143	0.04593	-0.0451	-0.155	9.58E-05
rs2287640	2	54342974	A	T	-0.1141	0.0234	1.08E-06	-----	-0.1383	-0.214	0.04593	0.0467	-0.152	1.19E-04
rs150525973	10	120659352	T	C	0.1156	0.0238	1.21E-06	+++++	-0.152	-0.2498	0.09192	0.1342	-0.071	3.30E-08
rs56696975	2	54369308	A	G	0.1049	0.0218	1.5E-06	+++++	-0.1432	-0.2273	0.03816	-0.0441	-0.114	2.19E-04
rs149791363	10	120658646	A	C	-0.131	0.0273	1.54E-06	-----	-0.1497	-0.2516	0.0897	0.1815	-0.085	3.80E-08
rs5751150	22	42153292	T	G	-0.06	0.0125	1.76E-06	-----	0.0476	-0.0701	-0.06383	-0.0714	0.058	9.57E-04
rs12623320	2	54353554	T	C	0.1002	0.021	1.93E-06	+++++	-0.1464	-0.2297	0.04271	0.0461	-0.101	1.51E-04
rs111332403	10	120666212	A	G	-0.0998	0.0211	2.17E-06	-----	-0.142	-0.2224	0.09101	0.1368	-0.056	2.20E-08
rs1883369	22	42143572	A	G	-0.0592	0.0125	2.18E-06	-----	0.0504	-0.0703	-0.06383	0.0696	0.056	9.76E-04
rs147702664	10	120658617	A	G	-0.1283	0.0271	2.26E-06	-----	-0.144	-0.2393	0.08983	0.1815	-0.085	4.10E-08
rs57514421	16	25529893	T	C	0.1507	0.0319	2.28E-06	+++++	-0.0768	-0.1097	0.18	0.124	-0.189	.
rs5758459	22	42157081	T	C	-0.059	0.0125	2.46E-06	-----	0.0506	-0.0688	-0.06383	-0.0715	0.055	1.24E-03
rs1421619	2	54366449	A	G	-0.0988	0.021	2.51E-06	-----	-0.153	-0.224	0.03816	0.0416	-0.1	1.86E-04
rs115048844	10	120651442	C	G	0.1063	0.0226	2.51E-06	+++++	-0.1484	-0.2438	0.08376	-0.1077	-0.062	1.90E-08
rs202629	22	41849975	T	C	0.056	0.0119	2.54E-06	+++++	0.0511	-0.0854	-0.07506	0.0509	0.051	2.65E-03
rs57602752	10	120649972	A	C	-0.1062	0.0226	2.54E-06	-----	-0.1483	-0.2435	0.08376	0.1073	-0.062	1.90E-08
rs2899349	22	42164660	T	C	-0.0589	0.0125	2.55E-06	-----	0.0496	-0.0688	-0.06465	-0.0717	0.055	1.24E-03
rs5751153	22	42156561	T	C	-0.0588	0.0125	2.57E-06	-----	0.0492	-0.0704	-0.06383	-0.071	0.055	1.21E-03
rs17045536	2	54370506	T	C	0.0988	0.021	2.64E-06	+++++	-0.1528	-0.228	0.03816	0.0401	-0.1	1.82E-04
rs5758461	22	42162189	C	G	0.0588	0.0125	2.66E-06	+++++	0.0495	-0.0688	-0.06465	-0.0709	0.055	1.29E-03
rs1807725	22	42147725	A	G	-0.0587	0.0125	2.67E-06	-----	0.0488	-0.0703	-0.06383	0.071	0.055	1.25E-03
rs2050033	22	42159229	T	G	0.0587	0.0125	2.67E-06	+++++	0.0494	-0.0687	-0.06383	0.0712	0.055	1.28E-03
rs118006754	10	120641184	T	G	0.1068	0.0227	2.68E-06	+++++	-0.1465	-0.2518	0.09159	0.103	-0.063	4.10E-08
rs2050031	22	42152266	A	G	-0.0587	0.0125	2.69E-06	-----	0.0488	-0.07	-0.06383	0.071	0.055	1.26E-03
rs139571	22	42214238	A	G	-0.0586	0.0125	2.72E-06	-----	0.0495	0.0715	-0.06126	0.0743	0.054	1.24E-03
rs139573	22	42214785	A	G	-0.0586	0.0125	2.74E-06	-----	0.0495	0.0707	-0.06126	0.0745	0.054	1.19E-03
rs5758432	22	42111693	T	C	-0.059	0.0126	2.76E-06	-----	0.0481	-0.0673	-0.06711	-0.0721	0.055	9.56E-04
rs139572	22	42214532	A	G	-0.0586	0.0125	2.78E-06	-----	0.0495	0.0706	-0.06126	0.0743	0.054	1.19E-03
rs2899346	22	42134895	T	C	-0.0587	0.0125	2.78E-06	-----	0.0471	-0.0701	-0.06383	-0.07	0.056	1.40E-03

rs1534932	22	42150146	T	C	0.0586	0.0125	2.81E-06	+++++	0.0488	-0.0676	-0.06383	0.0711	0.055	1.31E-03
rs12615044	2	54374555	T	G	0.0987	0.0211	2.9E-06	+++++	-0.1499	-0.2268	0.03816	0.0391	-0.101	2.31E-04
rs112524762	22	42202944	A	G	-0.0585	0.0125	2.92E-06	-----	0.0497	0.0694	-0.06279	0.0727	0.054	1.12E-03
rs12617094	2	54341098	A	G	0.098	0.021	2.96E-06	+++++	-0.1351	-0.2044	0.04139	-0.0346	-0.11	6.00E-04
rs5758436	22	42124265	T	C	0.0586	0.0125	2.97E-06	+++++	0.0477	-0.0702	-0.06383	0.0714	0.055	1.42E-03
rs13417064	2	54362726	A	G	-0.0979	0.0209	3E-06	-----	-0.1532	-0.2259	0.03542	0.0417	-0.098	1.71E-04
rs4822044	22	41979668	C	G	-0.0584	0.0125	3.01E-06	-----	0.0487	0.0646	-0.06577	0.0702	0.055	1.84E-03
rs5751149	22	42139501	A	G	-0.0585	0.0125	3.01E-06	-----	0.049	-0.0703	-0.06383	0.0696	0.055	1.26E-03
rs5758431	22	42109917	A	G	-0.0578	0.0124	3.09E-06	-----	0.0443	-0.084	-0.05549	0.0706	0.055	1.96E-03
rs4820444	22	42202606	A	G	-0.0583	0.0125	3.09E-06	-----	0.0495	0.0673	-0.06279	0.0727	0.054	1.21E-03
rs5751148	22	42139078	A	G	-0.0583	0.0125	3.16E-06	-----	0.0479	-0.0704	-0.06383	0.0695	0.055	1.29E-03
rs5758464	22	42171300	T	C	-0.0582	0.0125	3.17E-06	-----	0.0497	-0.0704	-0.06279	-0.068	0.055	1.25E-03
rs5751139	22	42099981	C	G	0.0584	0.0125	3.18E-06	+++++	0.0472	-0.0705	-0.06383	-0.0703	0.055	1.52E-03
rs1983576	22	42166486	A	G	0.0582	0.0125	3.24E-06	+++++	0.0496	-0.0688	-0.06477	-0.0703	0.054	1.30E-03
rs5758412	22	42080803	A	T	0.0583	0.0125	3.26E-06	+++++	0.0478	-0.0707	-0.06383	-0.0693	0.055	1.54E-03
rs2899348	22	42164516	C	G	-0.0582	0.0125	3.26E-06	-----	0.0496	-0.0687	-0.06465	0.0703	0.054	1.32E-03
rs4820446	22	42215684	T	C	-0.058	0.0125	3.27E-06	-----	0.0512	0.0691	-0.05578	-0.074	0.054	1.42E-03
rs5758439	22	42131762	T	C	0.0583	0.0125	3.28E-06	+++++	0.0475	-0.0702	-0.06383	0.0695	0.055	1.37E-03
rs4512	22	42206084	C	G	-0.0581	0.0125	3.3E-06	-----	0.0494	0.0687	-0.06279	0.0713	0.054	1.34E-03
rs5758430	22	42109844	T	G	0.0577	0.0124	3.31E-06	+++++	0.0443	-0.0814	-0.05549	0.0707	0.055	2.08E-03
rs1961317	10	120654022	T	C	0.1052	0.0226	3.31E-06	+++++	-0.1484	-0.2534	0.07622	0.1073	-0.061	2.10E-08
rs139560	22	42194962	A	G	0.0581	0.0125	3.32E-06	+++++	0.0495	0.0688	-0.05897	-0.0709	0.055	1.40E-03
rs5751156	22	42170025	A	G	-0.058	0.0125	3.43E-06	-----	0.0508	-0.0716	-0.05954	0.0705	0.054	1.14E-03
rs10775759	22	42088158	T	C	-0.0575	0.0124	3.47E-06	-----	0.0436	-0.0823	-0.05549	-0.0702	0.055	2.17E-03
rs2009394	16	25540005	T	C	0.1537	0.0331	3.49E-06	+++++	-0.0774	-0.1085	0.18	0.1355	-0.188	.
rs5758450	22	42141640	A	G	0.0582	0.0125	3.53E-06	+++++	0.0469	-0.0705	-0.0638	-0.0694	0.055	2.00E-03
rs57437150	2	54378968	A	G	-0.0976	0.021	3.55E-06	-----	-0.1503	-0.2231	0.03412	0.0385	-0.101	3.00E-04
rs2092274	22	42123737	A	G	-0.0576	0.0124	3.56E-06	-----	0.0443	-0.0809	-0.05549	0.0707	0.055	2.00E-03
rs4820443	22	42193913	T	C	0.0581	0.0125	3.61E-06	+++++	0.0495	0.0685	-0.05897	0.0713	0.055	1.39E-03
rs5758465	22	42175314	T	C	-0.0579	0.0125	3.64E-06	-----	0.0499	-0.0715	-0.06279	-0.0684	0.054	1.24E-03
rs132797	22	42064765	A	G	-0.0581	0.0126	3.73E-06	-----	0.049	-0.0705	-0.06383	0.0731	0.053	1.38E-03
rs13057349	22	42081697	T	C	-0.058	0.0125	3.74E-06	-----	0.0492	-0.071	-0.06383	-0.0691	0.054	1.42E-03
rs139562	22	42196684	C	G	-0.0578	0.0125	3.75E-06	-----	0.0477	0.069	-0.06279	0.0709	0.054	1.26E-03

rs132804	22	42068510	A	G	0.0574	0.0124	3.76E-06	+++++	0.0501	-0.0814	-0.05549	-0.0695	0.053	1.36E-03
rs2092275	22	42129964	T	C	-0.0579	0.0125	3.76E-06	-----	0.0454	-0.0703	-0.06383	-0.0695	0.055	1.53E-03
rs4075765	11	26209271	T	G	0.0991	0.0214	3.77E-06	+--++	-0.0807	0.0143	-0.01347	0.0702	-0.16	2.10E-03
rs132781	22	42046122	T	G	-0.0607	0.0131	3.78E-06	-----	0.061	-0.0678	-0.07255	-0.0726	0.052	3.61E-04
rs5758427	22	42099688	A	G	-0.0573	0.0124	3.83E-06	-----	0.0439	-0.0774	-0.05549	0.0706	0.055	2.30E-03
rs5751141	22	42107745	A	G	-0.0595	0.0129	3.84E-06	-----	0.048	-0.0695	-0.06711	0.0703	0.056	9.02E-04
rs5758408	22	42077737	A	C	-0.0578	0.0125	3.86E-06	-----	0.0477	-0.0704	-0.06383	0.0694	0.054	1.57E-03
rs57536238	2	54379081	T	G	-0.0972	0.0211	3.9E-06	-----	-0.1504	-0.223	0.03412	-0.0385	-0.1	3.35E-04
rs4822046	22	41987543	A	G	-0.0577	0.0125	3.93E-06	-----	0.0489	0.0623	-0.06383	0.0709	0.054	1.78E-03
rs202627	22	41847367	A	T	-0.0566	0.0123	3.94E-06	-----	0.0464	-0.0862	-0.07378	0.0499	0.054	2.71E-03
rs1421618	2	54366605	A	G	0.0969	0.021	3.95E-06	+++++	-0.153	-0.2233	0.03816	-0.0311	-0.1	1.89E-04
rs5751160	22	42175695	A	G	-0.0576	0.0125	3.98E-06	-----	0.0499	-0.0684	-0.06279	0.068	0.054	1.30E-03
rs5758405	22	42076381	A	C	0.0571	0.0124	4.01E-06	+++++	0.0444	-0.0821	-0.05549	-0.0699	0.054	2.09E-03
rs13056262	22	42081921	A	G	-0.0577	0.0125	4.01E-06	-----	0.0478	-0.0707	-0.06383	0.069	0.054	1.56E-03
rs5758406	22	42076641	A	G	-0.0571	0.0124	4.01E-06	-----	0.0445	-0.0818	-0.05549	0.0699	0.054	2.11E-03
rs112825709	10	120622014	A	C	0.1077	0.0234	4.11E-06	+++++	-0.1497	-0.2538	0.10888	-0.0706	-0.065	8.00E-08
rs2011790	22	41835452	A	G	0.055	0.0119	4.13E-06	+++++	0.0426	-0.0877	-0.08007	-0.0487	0.051	4.04E-03
rs151284751	10	120622746	A	C	0.1076	0.0234	4.2E-06	+++++	-0.1496	-0.2536	0.10888	-0.0705	-0.065	8.10E-08
rs45500192	22	42177899	A	G	0.0575	0.0125	4.28E-06	+++++	0.0486	0.0677	-0.06279	-0.0687	0.054	1.56E-03
rs5758416	22	42082791	T	C	-0.0575	0.0125	4.31E-06	-----	0.0461	-0.0692	-0.06487	-0.0692	0.054	1.88E-03
rs145575521	10	120622907	T	C	-0.1076	0.0234	4.34E-06	-----	-0.1485	-0.2537	0.11037	-0.0706	-0.065	4.40E-08
rs139561	22	42195410	T	C	0.0573	0.0125	4.36E-06	+++++	0.0495	0.0712	-0.05897	0.0651	0.055	1.41E-03
rs57220560	16	25539119	T	C	-0.1495	0.0326	4.42E-06	-----	-0.0772	-0.1088	0.18	-0.1112	-0.188	.
rs1858856	16	25539706	T	C	-0.1496	0.0326	4.45E-06	-----	-0.077	-0.1087	0.18	-0.1112	-0.188	.
rs2413653	22	42106996	T	C	-0.059	0.0129	4.46E-06	-----	0.048	-0.0695	-0.06711	-0.0703	0.055	9.44E-04
rs56771502	16	25539632	T	C	-0.1495	0.0326	4.46E-06	-----	-0.077	-0.1087	0.18	-0.1111	-0.188	.
rs17256972	16	25537531	T	C	-0.1495	0.0326	4.47E-06	-----	-0.0769	-0.1088	0.18	-0.1111	-0.188	.
rs148894219	22	41996131	T	C	-0.0574	0.0125	4.49E-06	-----	0.049	0.0598	-0.06383	-0.0699	0.054	1.87E-03
rs5758428	22	42106216	A	G	0.059	0.0129	4.52E-06	+++++	0.048	-0.0696	-0.06692	-0.0703	0.055	9.43E-04
rs202630	22	41850230	T	C	0.0546	0.0119	4.55E-06	+++++	0.0433	-0.0885	-0.07227	0.051	0.051	3.23E-03
rs139566	22	42199277	A	G	0.0573	0.0125	4.62E-06	+++++	0.0495	0.0692	-0.06279	-0.0721	0.052	9.83E-04
rs132793	22	42063681	A	G	-0.0572	0.0125	4.68E-06	-----	0.0475	-0.068	-0.06383	0.0731	0.052	1.49E-03
rs132807	22	42071584	T	C	-0.0572	0.0125	4.72E-06	-----	0.0479	-0.0703	-0.06383	-0.069	0.053	1.34E-03

rs4822045	22	41985958	A	C	-0.059	0.0129	4.78E-06	-----	0.0495	0.06	-0.06383	0.0729	0.056	1.83E-03
rs2076200	22	41985956	T	G	-0.0589	0.0129	4.81E-06	-----	0.0495	0.06	-0.06383	-0.0728	0.056	1.83E-03
rs142108391	11	26216166	A	G	0.0969	0.0212	4.83E-06	+--++	-0.0835	0.016	-0.01363	-0.067	-0.157	1.84E-03
rs13055804	22	42081620	T	C	0.0592	0.0129	4.88E-06	+++++	0.0539	-0.0707	-0.06383	0.0695	0.054	1.11E-03
rs1988153	22	42104929	A	G	-0.0583	0.0128	4.91E-06	-----	0.0446	-0.0805	-0.0589	0.0714	0.055	1.25E-03

Table S4. Meta-analysis of top loci from Yale-Penn and the current meta-analysis of 2080 cannabis dependent cases and 6435 controls (3,757 cases and 9,931 controls

				Yale-Penn EA			Yale-Penn AA			Meta-analysis		
SNP	A1	A2	p-value in current analysis	b	se	p	b	se	p	b	se	p
rs145575521	T	C	4.39E-08	-0.00033	0.14662	0.99823			NA			
rs79516280	A	G	4.34E-08	0.000601	0.14664	0.99673			NA			
rs75312482	T	C	4.66E-08	-0.00127	0.14663	0.99309			NA			
rs1409568	T	C	3.95E-08	-0.07245	0.13804	0.59968	-0.1806	0.08219	0.02799	-0.2848	0.0555	2.86E-07
rs77300175	T	C	1.30E-08	-0.00031	0.14721	0.99834			NA			
rs7098706	T	C	2.44E-08	0.078188	0.13927	0.57452	-0.0315	0.0942	0.73809	-0.2147	0.0593	0.000292
rs118006754	T	G	4.12E-08	0.004228	0.14448	0.97666			NA			
rs7074123	A	C	1.79E-08	0.008798	0.13996	0.94988	-0.16075	0.11297	0.15477	-0.2977	0.0632	2.51E-06
rs7920901	T	C	1.74E-08	0.019508	0.13484	0.88497	0.18004	0.08447	0.03304	0.2804	0.0562	5.92E-07
rs57602752	A	C	1.88E-08	-0.05114	0.13166	0.69767	-0.1987	0.07944	0.01237	-0.2866	0.0544	1.35E-07
rs115048844	C	G	1.86E-08			NA			NA			
rs1961317	T	C	2.08E-08	0.014821	0.1388	0.91496	0.18833	0.09339	0.04373	0.2933	0.0589	6.32E-07
rs147702664	A	G	4.07E-08	0.015849	0.14281	0.91163			NA			
rs149791363	A	C	3.76E-08	0.000493	0.14397	0.99727	-0.10358	0.17227	0.54767	-0.3245	0.0756	1.75E-05
rs150525973	T	C	3.27E-08	-0.0016	0.14669	0.99127			NA			
rs111332403	A	G	2.15E-08	0.002771	0.14331	0.98457			NA			

Table S5. Results from current meta-analysis for top loci from two existing large-scale GWAS of cannabis related phenotypes**.**

			DSM-IV cannabis dependence diagnosis						**DSM-IV cannabis dependence symptom counts**					
SNP	Chr:Pos	Passed QC	A1	A2	Effect	StdErr	P	Direction	A1	A2	Effect	StdErr	P	Direction
Sherva et al., Cannabis dependence (EA only)														
rs77378271	8:3073489	0	a	g	0.0612	0.1045	0.5579	-++-+	a	g	0.0087	0.0239	0.7169	-+?-+
Stringer et al., Cannabis Use														
rs73067624	1:196333461	1	t	c	-0.009	0.0731	0.902	+-+-+	t	c	0.0079	0.0167	0.6373	+-+-+
rs58691539	2:52753909	0	t	g	0.0432	0.1185	0.7155	-+?+-	t	g	0.0079	0.0305	0.7944	-+?+-
rs2033867	2:175188281	0	a	g	-0.0999	0.0896	0.2645	-+---	a	g	-0.0582	0.0208	0.00511	-+---
rs35053471	3:47124761	1	a	t	-0.0601	0.0459	0.191	-----	a	t	-0.0072	0.0114	0.5293	+-?--
rs7675351	4:141218757	1	a	c	-0.0006	0.0615	0.9916	---+-	a	c	0.0065	0.0149	0.6605	--?+-
rs12518098	5:60864467	0	c	g	0.0261	0.05	0.6017	+++--	c	g	0.0041	0.012	0.7331	++?-+
rs7107977	11:915764	0	a	g	0.0768	0.0628	0.2216	++?++	a	g	0.0299	0.0152	0.04924	-+?++
rs4471463	11:112983595	1	t	c	-0.0177	0.043	0.6806	+----	t	c	-0.012	0.0097	0.217	+----
rs2099149	12:30479358	0	t	g	0.01	0.0709	0.8878	--?++	t	g	0.0072	0.0158	0.6465	+-?-+
rs4984460	15:96424399	1	t	g	-0.0397	0.0502	0.4287	-----	t	g	-0.0009	0.0111	0.9367	+--+-

Table S6. Gene-based association for DSM-IV cannabis dependence (N=8515; Ngenes = 17, 407; p=2.87E-06; shown for p < 0.002 – full results on request)

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P
APBB2	4	40802044	41228731	827	64	8515	4.2644	1.00E-05
AMFR	16	56385364	56469450	153	10	8515	4.1159	1.93E-05
RGS20	8	54754368	54881863	34	3	8515	3.9253	4.33E-05
GABRR1	6	89877223	89951007	203	22	8515	3.5724	0.000177
DVL3	3	183863099	183901314	40	5	8515	3.5138	0.000221
ZNF22	10	45486273	45510777	30	5	8515	3.4533	0.000277
CD1C	1	158249563	158274564	9	1	8515	3.4181	0.000315
CERS3	15	100930600	101094925	403	18	8515	3.4057	0.00033
CD1E	1	158313486	158337343	29	4	8515	3.3867	0.000354
SYNGR4	19	48857559	48889634	41	6	8515	3.3852	0.000356
WDR66	12	122346463	122451839	141	10	8515	3.3729	0.000372
SMLR1	6	131138545	131168275	73	8	8515	3.3605	0.000389
LDB3	10	88416542	88505829	162	20	8515	3.3276	0.000438
C10orf25	10	45483146	45506470	21	4	8515	3.3208	0.000449
ANKRD37	4	186307840	186331529	31	5	8515	3.3128	0.000462
SLC44A3	1	95275898	95370803	195	25	8515	3.2723	0.000533
RASSF2	20	4750669	4814291	147	24	8515	3.2673	0.000543
ZMYND11	10	170405	310577	93	7	8515	3.266	0.000545
PSMD9	12	122316637	122365771	75	6	8515	3.2598	0.000557
SLC20A1	2	113393434	113431402	63	5	8515	3.2445	0.000588
CD1B	1	158287740	158311321	28	4	8515	3.2402	0.000597
TMEM143	19	48825613	48877489	82	8	8515	3.2352	0.000608
RFX6	6	117188376	117263326	193	11	8515	3.2312	0.000616
SRSF9	12	120889471	120917558	51	7	8515	3.2216	0.000637
UFSP2	4	186310691	186357139	63	7	8515	3.1969	0.000694
RWDD3	1	95689711	95722781	72	10	8515	3.1418	0.00084
KCP	7	128506919	128560773	27	6	8515	3.1286	0.000878
GATC	12	120874241	120911556	73	9	8515	3.1141	0.000923
TMEM67	8	94757072	94841462	40	4	8515	3.1109	0.000933
OSER1	20	42814579	42849702	70	10	8515	3.1104	0.000934
TRIM36	5	114450459	114526243	71	7	8515	3.0998	0.000968

RASSF3	12	64994293	65101347	191	15	8515	3.099	0.000971
TTYH3	7	2661603	2714436	34	6	8515	3.0752	0.001052
ARHGEF10	8	1762149	1916807	227	45	8515	3.0644	0.001091
IGFL3	19	46613328	46637931	14	3	8515	2.9882	0.001403
BUD31	7	98996243	99027239	20	2	8515	2.98	0.001442
SLC37A1	21	43909742	44011550	312	18	8515	2.9753	0.001464
POP5	12	121006848	121029201	52	8	8515	2.9718	0.00148
ANP32A	15	69060874	69123261	19	3	8515	2.9692	0.001493
DYNLL1	12	120897660	120946298	110	11	8515	2.9668	0.001505
TENM3	4	183055112	183734177	1036	118	8515	2.9566	0.001555
KLC2	11	66014765	66045332	32	6	8515	2.9462	0.001609
SCN10A	3	38728837	38845501	236	26	8515	2.9409	0.001636
XRCC6	22	42007250	42070052	36	2	8515	2.9409	0.001636
TRIAP1	12	120871764	120894215	43	8	8515	2.9336	0.001675
RNF10	12	120962132	121025397	152	14	8515	2.9315	0.001687
PTGDR2	11	60608398	60633444	34	7	8515	2.9271	0.001711
PLXND1	3	129264056	129335582	132	11	8515	2.9207	0.001746
MEI1	22	42085518	42205459	151	5	8515	2.9179	0.001762
ARPC1B	7	98962298	99014226	42	2	8515	2.917	0.001767
TUBE1	6	112381860	112418751	52	3	8515	2.9141	0.001783
FAM229B	6	112398674	112433993	84	3	8515	2.8897	0.001928
PDAP1	7	98982296	99016305	22	2	8515	2.8874	0.001942
ELMOD3	2	85571843	85628875	101	12	8515	2.8856	0.001953
NHP2L1	22	42059937	42095296	44	2	8515	2.8813	0.00198

Table S7. Gene association results for cannabis dependence symptom counts (N=8515; Ngenes = 17,407; p=2.87E-06; shown for p < 0.002, full results on request)

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P
MEI1	22	42085518	42205459	167	7	8515	4.561	**2.55E-06**
XRCC6	22	42007250	42070052	37	3	8515	4.4966	3.45E-06
NHP2L1	22	42059937	42095296	42	2	8515	4.3605	6.49E-06
DESI1	22	41984032	42027079	25	2	8515	4.3533	6.7E-06
CCDC134	22	42186636	42238175	92	11	8515	4.314	8.02E-06
PMM1	22	41962890	41995871	27	2	8515	4.2964	8.68E-06
CSDC2	22	41947014	41982670	40	2	8515	4.2941	8.77E-06
PHF5A	22	41845721	41874708	27	2	8515	4.2632	1.01E-05
C22orf46	22	42076547	42104140	30	2	8515	4.2596	1.02E-05
ACO2	22	41855099	41934993	54	3	8515	4.2384	1.13E-05
TOB2	22	41819492	41854234	50	2	8515	4.1446	1.7E-05
POLR3H	22	41911803	41950479	46	2	8515	4.0807	2.25E-05
RGS20	8	54754368	54881863	30	2	8515	3.9495	3.92E-05
PLAG1	8	57063463	57133859	63	5	8515	3.9385	4.1E-05
TEF	22	41753337	41805332	68	3	8515	3.8162	6.78E-05
AFMID	17	76173398	76213782	46	10	8515	3.7731	8.06E-05
LOC100996598	22	41755086	41776400	18	2	8515	3.7609	8.46E-05
TFCP2L1	2	121964163	122052778	50	8	8515	3.7158	0.000101
NXN	17	692553	893017	203	45	8515	3.7081	0.000104
TMEM120A	7	75606155	75633992	39	6	8515	3.6544	0.000129
ZC3H7B	22	41687507	41766151	65	4	8515	3.6352	0.000139
STRA8	7	134906731	134953244	50	7	8515	3.5805	0.000171
CDH13	16	82650399	83840215	4228	275	8515	3.573	0.000176
ACYP2	2	54332410	54542437	256	26	8515	3.5564	0.000188
MED20	6	41863092	41898877	36	8	8515	3.5324	0.000206
PTH2	19	49915671	49936698	1	1	8515	3.4725	0.000258
GFY	19	49919688	49942075	1	1	8515	3.4725	0.000258
LDB3	10	88416542	88505829	150	19	8515	3.4663	0.000264
AGL	1	100305633	100399579	185	20	8515	3.4283	0.000304
VCPIP1	8	67532488	67589452	11	4	8515	3.3856	0.000355

TK1	17	76160160	76193285	48	10	8515	3.343	0.000414
FHL3	1	38452439	38481199	6	3	8515	3.328	0.000437
TRIM36	5	114450459	114526243	22	4	8515	3.3107	0.000465
SDR16C5	8	57202570	57243335	60	7	8515	3.287	0.000506
GNA15	19	3126191	3173766	52	8	8515	3.2056	0.000674
POP5	12	121006848	121029201	57	9	8515	3.1878	0.000717
SRSF9	12	120889471	120917558	53	8	8515	3.1521	0.000811
CDK14	7	90215681	90849905	1348	51	8515	3.1448	0.000831
CALCRL	2	188196690	188323021	206	15	8515	3.1271	0.000883
NMBR	6	142386745	142419936	47	5	8515	3.1227	0.000896
LOC101929728	22	31053507	31075003	21	5	8515	3.0926	0.000992
PAK2	3	196456728	196569518	72	10	8515	3.0807	0.001033
TRIM66	11	8623584	8714205	143	15	8515	3.0748	0.001053
FRS3	6	41727914	41757643	36	10	8515	3.0653	0.001087
RNF10	12	120962132	121025397	166	16	8515	3.0573	0.001117
ZNF227	19	44706684	44751421	30	3	8515	3.0503	0.001143
STYXL1	7	75615610	75687321	78	9	8515	3.0483	0.001151
DYNLL1	12	120897660	120946298	116	12	8515	3.042	0.001175
RAB3GAP2	1	220311610	220455843	200	16	8515	3.0284	0.001229
CHCHD7	8	57114315	57141178	8	4	8515	3.0201	0.001264
AP2A2	11	915809	1022245	195	5	8515	2.9966	0.001365
NFE2L2	2	178085031	178139859	48	7	8515	2.9958	0.001369
SGK2	20	42177566	42224317	11	4	8515	2.9776	0.001453
RCSD1	1	167589474	167687933	144	23	8515	2.971	0.001484
GJD2	15	35034642	35056782	27	5	8515	2.9668	0.001504
LHFP	13	39907029	40187356	683	64	8515	2.9541	0.001568
GATC	12	120874241	120911556	73	10	8515	2.9457	0.001611
TRMT5	14	61428159	61457888	25	3	8515	2.9456	0.001611
CPNE4	3	131242413	131769152	1503	56	8515	2.9441	0.00162
LOC101929211	8	22450648	22472925	4	1	8515	2.9402	0.00164
SH3GL3	15	84106091	84297495	177	36	8515	2.9193	0.001754
SLC7A13	8	87216288	87252609	43	6	8515	2.9184	0.001759
BYSL	6	41878965	41910784	23	7	8515	2.9155	0.001776

NOP2	12	6656036	6687498	2	1	8515	2.9028	0.001849
SLC44A3	1	95275898	95370803	181	24	8515	2.8958	0.001891
COQ5	12	120931082	120976964	113	12	8515	2.8925	0.001911
UTP11L	1	38468384	38500497	20	5	8515	2.8833	0.001968
IPO9	1	201788288	201863422	89	11	8515	2.8807	0.001984

Supplemental Table S8. De novo motif prediction for binding sites for transcription factors that are modified by rs1409568. "n" indicates allele is associated with minimal binding; Scores ≥ 8 are meaningful

			T (or A) allele			C (or G) allele		
Motif_Name	**Motif Strand**	**SNP position in motif**	**Score1**	**Pvalue**	**Qvalue**	**Score2**	**Pvalue**	**Qvalue**
MA0132.2_PDX1	-	4	8.85	0.001	2.21E-02	NA*	NA*	NA*
MA0151.1_Arid3a	+	5	8.33	0.001	1.93E-02	5.22E-01	4.11E-03	1.32E-01
MA0158.1_HOXA5	+	6	9.44	0.000	5.98E-03	NA*	NA*	NA*
MA0651.1_HOXC11	-	6	6.64	0.001	1.30E-02	9.03E+00	2.08E-04	4.59E-03
MA0674.1_NKX6-1	-	4	9.81	0.000	6.47E-03	2.58E+00	8.30E-03	2.32E-01
MA0675.1_NKX6-2	-	4	8.88	0.000	1.03E-02	NA*	NA*	NA*
MA0722.1_VAX1	+	4	8.54	0.000	1.06E-02	NA*	NA*	NA*
MA0723.1_VAX2	+	4	8.35	0.001	1.50E-02	NA*	NA*	NA*
MA0790.1_POU4F1	+	9	14.24	0.000	9.69E-05	9.05E+00	2.03E-04	3.25E-03
MA0790.1_POU4F1	-	6	8.63	0.000	2.05E-03	4.58E+00	1.86E-03	1.49E-02
MA0791.1_POU4F3	+	9	12.76	0.000	2.22E-04	7.23E+00	4.64E-04	5.57E-03
MA0791.1_POU4F3	-	8	9.31	0.000	9.40E-04	4.97E+00	1.32E-03	7.94E-03
MA0793.1_POU6F2	-	4	10.16	0.000	3.23E-03	NA*	NA*	NA*
MA0908.1_HOXD11	-	6	7.34	0.001	1.31E-02	9.38E+00	2.19E-04	5.24E-03
MA0910.1_Hoxd8	-	10	9.05	0.000	2.14E-03	3.83E+00	2.92E-03	2.92E-02

* : NA indicates that the motif cannot be detected with assigned SNP allele.

Table S9. meQTL results for rs1409568 for genes with a TSS within 1Mb of the SNP.

				Frontal Cortex		Cerebellum	
Probe	**Gene**	**Cpg Island location**	**Distance in bp to TSS**	**β**	**p-value**	**β**	**p-value**
cg03690162	BAG3	10:121400389-121401974	429	-0.1201	0.50637	0.29785	0.09892
cg04041960	RGS10	10:121291002-121293299	457	-0.2801	0.12582	-0.2248	0.21338
cg04126427	EIF3S10	10:120829444-120830795	375	-0.1866	0.30188	0.23684	0.18981
cg04466870	SFXN4	10:120914699-120915690	24	-0.2125	0.2397	0.34218	0.05785
cg08102619	TIAL1	10:121345655-121347083	755	-0.3375	0.06138	-0.1496	0.4078
cg08551088	C10orf119	10:121621485-121623237	611	0.00332	0.98534	-0.2039	0.25908
cg10222574	RAB11FIP2	10:119795705-119797139	288	-0.1756	0.33133	0.12801	0.47892
cg10367730	PRDX3	10:120927561-120928529	150	-0.0836	0.64395	0.086	0.63439
cg14916079	NANOS1	10:120778301-120780478	532	0.04865	0.78791	0.24135	0.18149
cg15748507	PRLHR	10:120343551-120346241	129	-0.2049	0.25683	0.05574	0.75793
cg15752043	NANOS1	10:120778301-120780478	727	-0.035	0.8465	0.22663	0.20967
cg16196812	PRLHR	10:120343551-120346241	383	-0.2128	0.23885	-0.0251	0.88956
cg17198722	PRDX3	10:120927561-120928529	132	-0.1762	0.32965	0.08468	0.63958
cg17797815	RAB11FIP2	10:119795705-119797139	858	-0.2526	0.16199	0.13094	0.46891
cg18755204	FAM45A	10:120853141-120854488	112	-0.1033	0.568	0.18608	0.30317
cg18870413	BAG3	10:121400389-121401974	286	-0.0935	0.60521	0.25593	0.15645
cg19653161	RGS10	10:121291002-121293299	270	-0.3113	0.08451	0.23712	0.18929
cg21289924	EIF3S10	10:120829444-120830795	358	-0.1873	0.30015	0.00028	0.99875
cg22082243	C10orf84	10:120091284-120092010	68	-0.1409	0.43572	0.15285	0.3978
cg23182539	TIAL1	10:121345655-121347083	314	-0.5626	***0.00173***	0.18371	0.30938
cg23274030	SFXN4	10:120914699-120915690	428	-0.2579	0.15325	0.15902	0.37899
cg23303782	GRK5	10:120955944-120958030	547	-0.2356	0.19219	0.25433	0.15912
cg24257768	C10orf84	10:120091284-120092010	166	-0.2497	0.16683	0.12154	0.50146
cg24618244	INPP5F	10:121474688-121476410	154	-0.2393	0.18533	0.04653	0.79695
cg27315279	GRK5	10:120955944-120958030	354	-0.0107	0.95267	0.23178	0.19947
cg27613076	INPP5F	10:121474688-121476410	665	-0.2512	0.16431	0.3486	0.05328

Supplemental Table S10. Association between rs1409568 and comorbid alcohol, nicotine and cocaine dependence

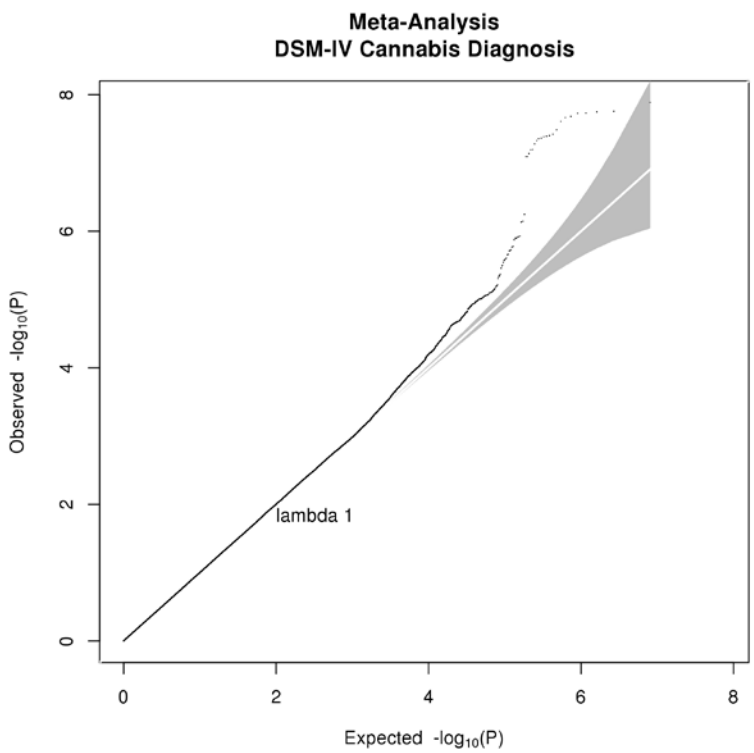
	Alcohol dependence	**Nicotine dependence**	**Cocaine dependence**	**Cannabis dependence, adjusted**
	Effect (b), SE, p-value	Effect (b), SE, p-value	Effect (b), SE, p-value	Effect (b), SE, p-value
CATS	-0.18, 0.15, p=0.23	-0.49, 0.16, p=0.003	-0.02, 0.17, p=0.89	-0.50, 0.17, p=0.002
COGA-cc	-0.24, 0.20, p=0.23	-0.32, 0.19, p=0.10	-0.42, 0.25, p=0.09	-0.73, 0.22, p=0.0008
COGA-f	-0.15, 0.20, p=0.47	0.21, 0.21, p=0.31	-0.04, 0.26, p=0.89	-0.36, 0.20, p=0.07
OZALC	-0.17, 0.12, p=0.16	0.05, 0.12, p=0.69	0.41, 1.35, p=0.76	-0.30, 0.21, p=0.15
SAGE	-0.06, 0.16, p=0.73	-0.02, 0.16, p=0.88	-0.39, 0.33, p=0.23	-0.56, 0.22, p=0.01
Meta-analysis	-0.16, 0.07, p=0.03	-0.10, 0.07, p=0.17	-0.16, 0.12, p=0.18	**-0.48, 0.09, p=5.51e-08**

Supplemental Figures

Agrawal et al., Cannabis dependence GWAS identifies a new locus on chromosome 10.

Figure S1. Quantile-quantile (QQ) plots from meta-analysis of (A) 2,080 cannabis dependent cases and 6,435 cannabis exposed controls of European descent; and (B) cannabis dependence symptom count.

(A)



(B)

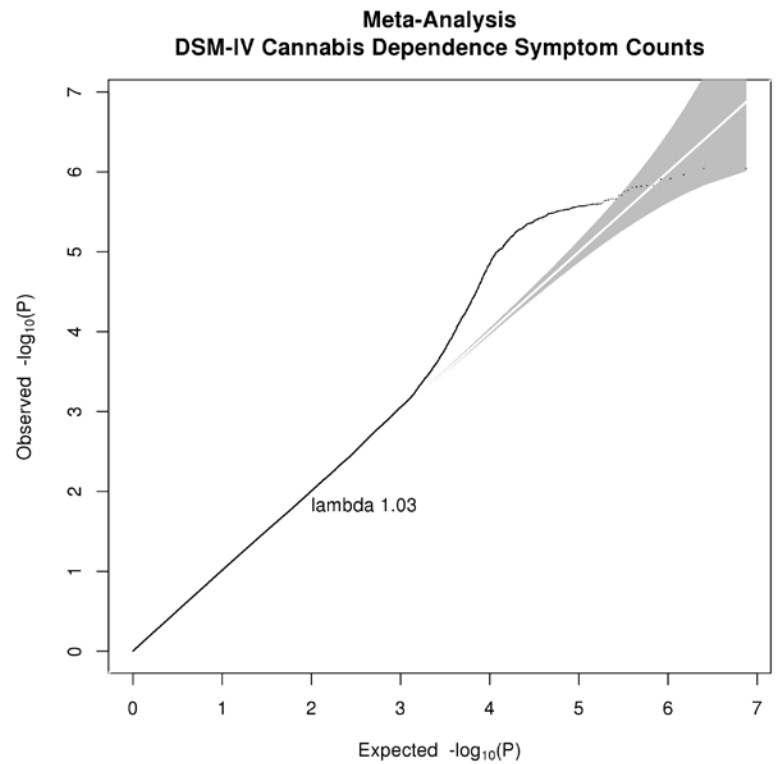
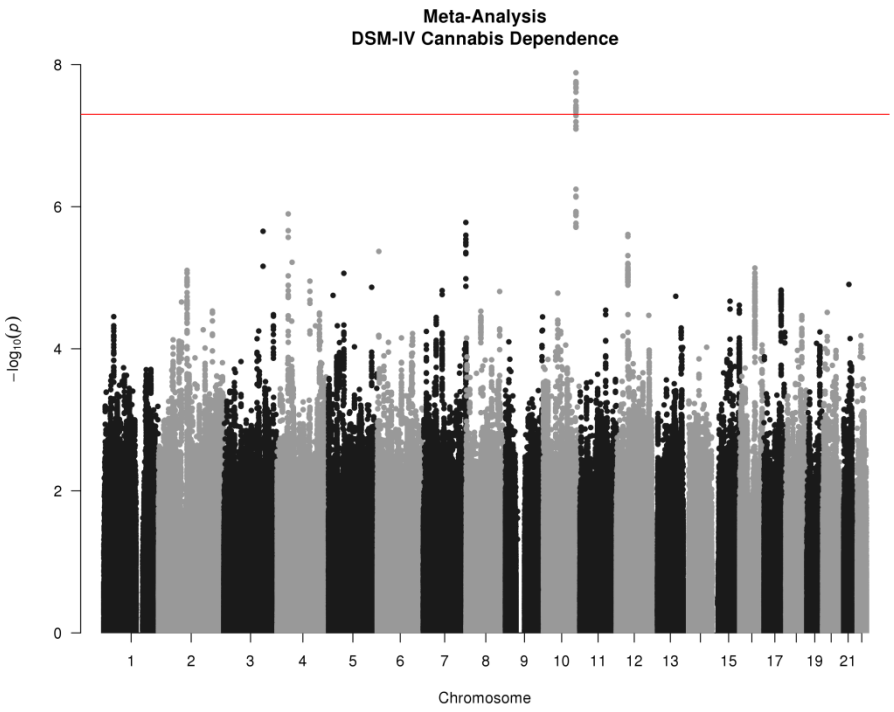


Figure S2. Manhattan plot of results from meta-analysis of (A) 2,080 cannabis dependent cases and 6,435 cannabis exposed controls of European descent; and (B) cannabis dependence symptom count.

(A)



(B)

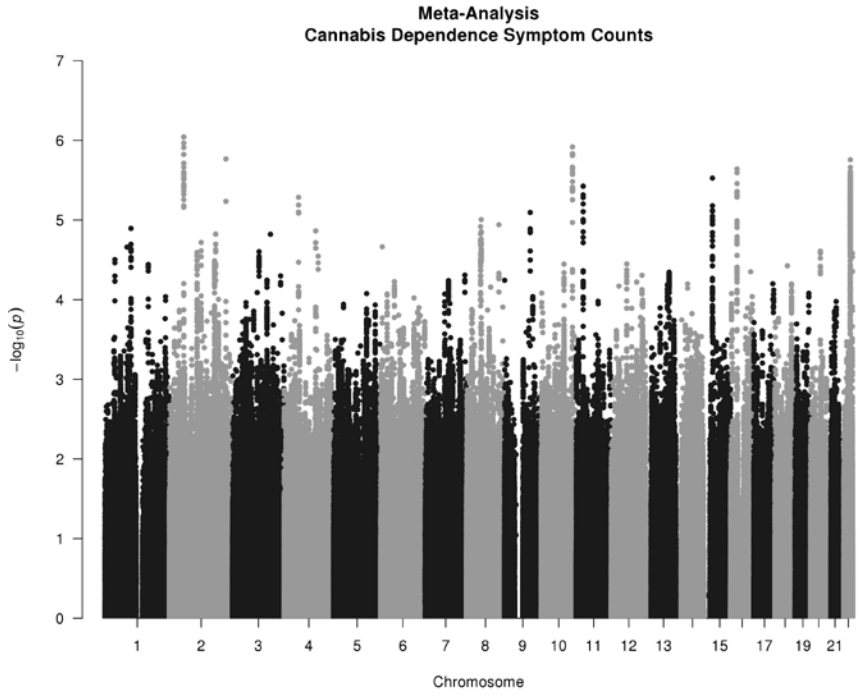


Figure S3. Regional association plot for chromosome 22 SNPs that were nominally associated with cannabis dependence symptom counts, including SNPs in MEI1, which was significant in gene-based analyses

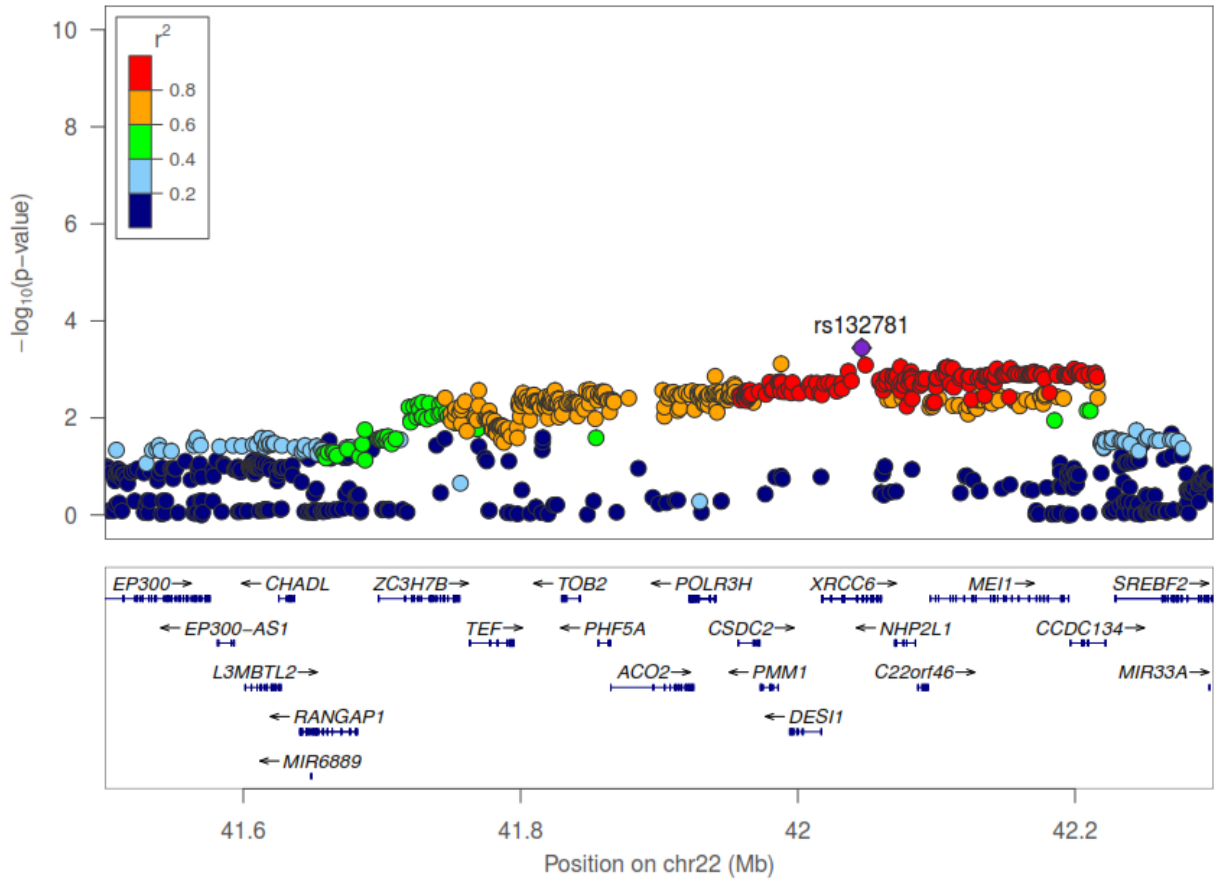


Figure S4. Evidence for brain expression of (A) coding genes and (B) pseudogenes within the regulatory domain encompassing genomewide significant loci on chromosome 10.

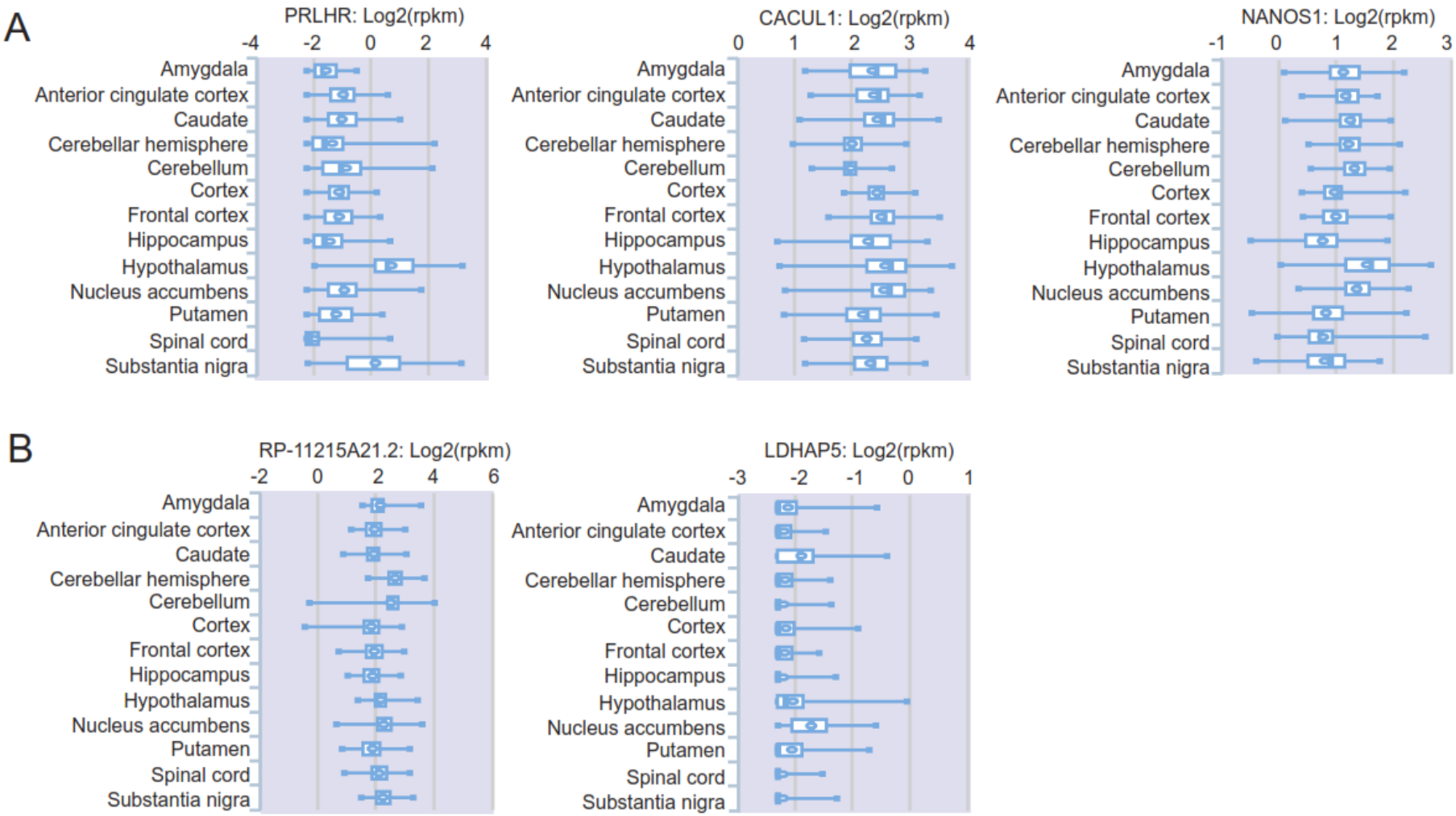


Figure S5. Conservation across primates (but not other vertebrates) for rs1409568.

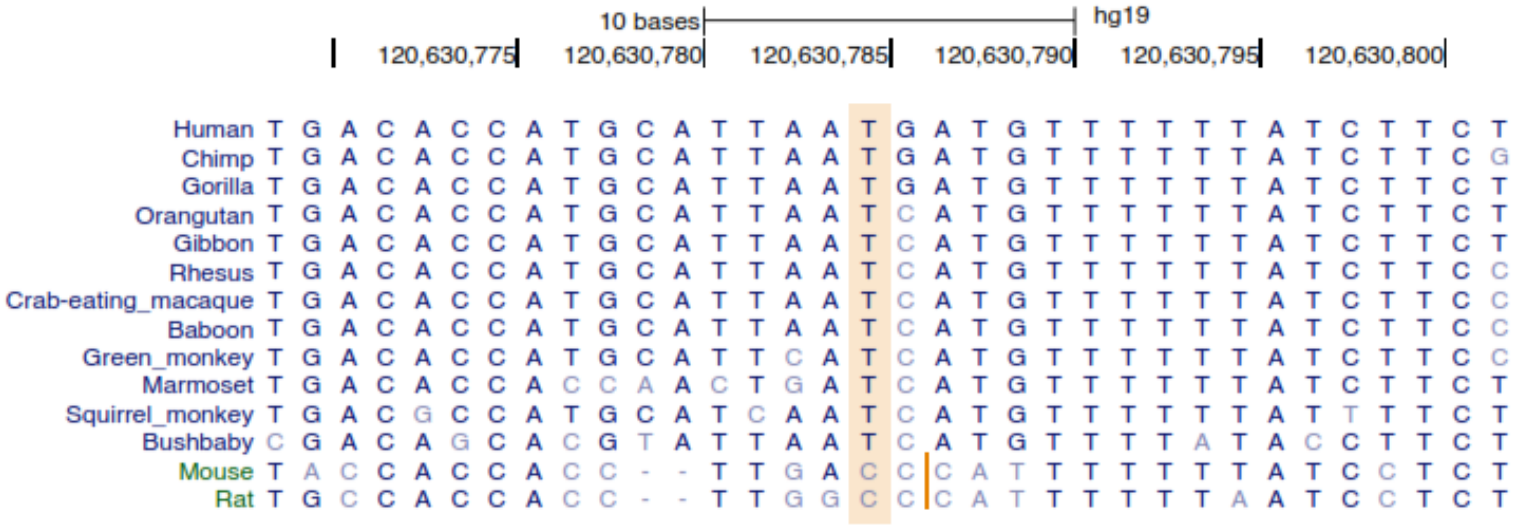
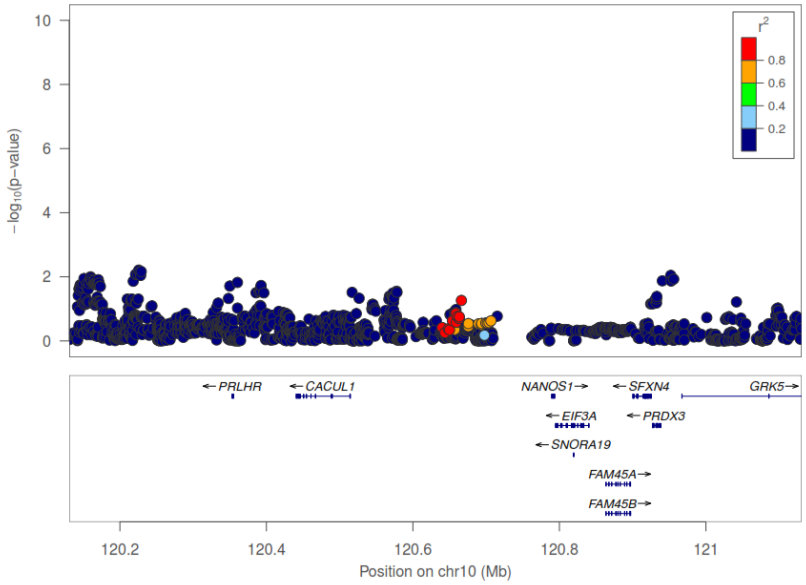
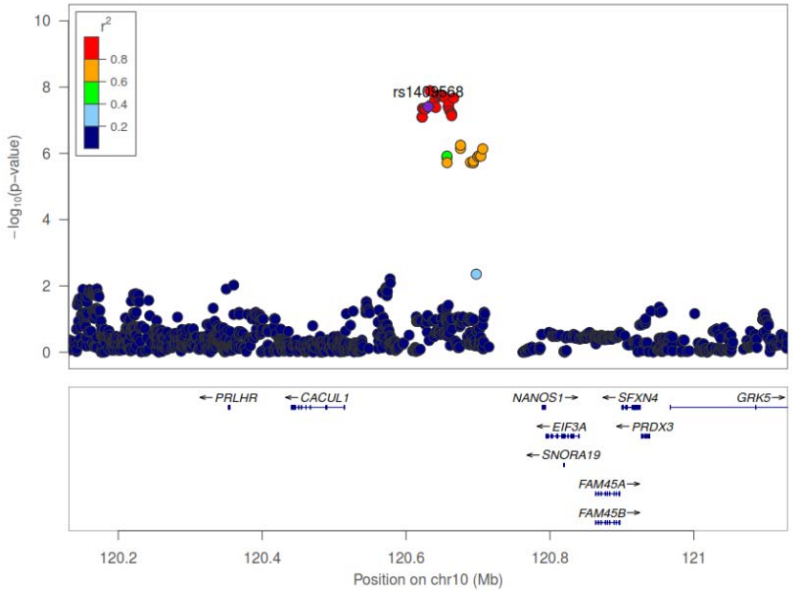


Figure S6. Regional association plots of chromosome 10 region based on: PANEL A: conditional analyses that included rs1409568 as a covariate in each discovery sample; and PANEL B: analysis from full meta-analysis without inclusion of rs1409568 as a covariate, showing its significance.



PANEL A



PANEL B

Figure S7. A) rs1409568 C-allele carriers display increased volume in a cluster of the right hippocampus (p-fwe=0.007). B) Participants who reported ever using cannabis display increased volume in a cluster of the left hippocampus (p-fwe=0.002). Results are displayed at p-fwe<0.05.

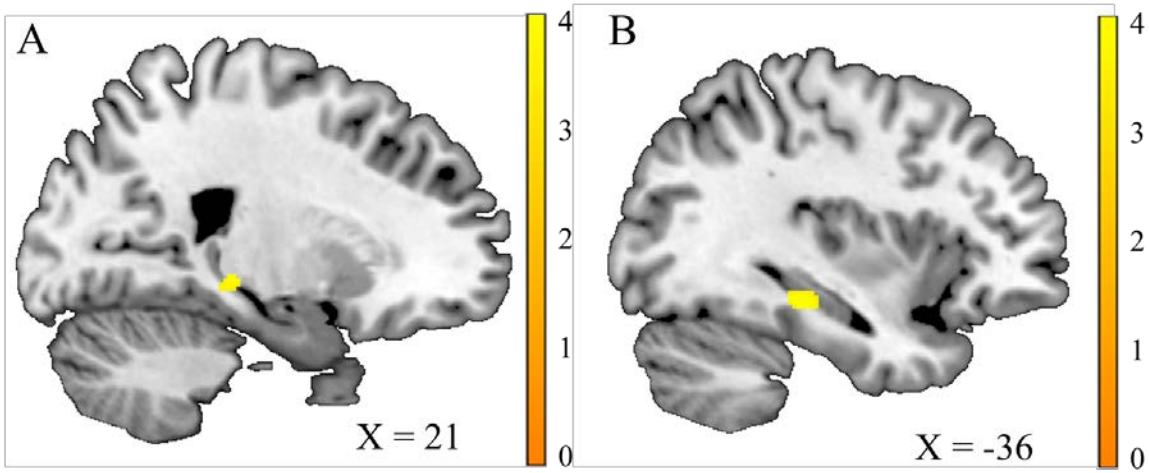


Figure S8. Linkage disequilibrium (LD) plots for genomewide significant SNPs using 1000 Genomes reference panel data for CEU and ASW populations (value shown is r^2; darker color represents higher r^2)