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Supplemental Data

Genome-wide Association Study Identifies Genetic Variation in Neurocan as a Susceptibility Factor for Bipolar Disorder

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Table S1. Evidence for Association at the *ANK3* Locus in Previous Studies of BD and in Cichon, Mühleisen et al.

Previous GWAS					GWAS of this study	
SNP	**Sample**	**Study**	**P value**	**OR (allele)**	**TREND P**	**OR (allele)**
rs10994336	WTCCC + STEP-UCL + ED-DUB-STEP2	Ferreira et al. (2008)[4]	9.1×10^{-9}	1.45 (T)	0.131 (imp)	1.22 (T)
rs10994336	German	Schulze et al. (2009)[8]	0.0001	1.70 (T)		
	NIMH waves 1-4		> 0.05			
	NIMH wave 5		> 0.05			
	three-sample meta-analysis		1.7×10^{-5}	1.54 (T)		
rs10994336	GSK	Scott, Muglia et al. (2009)[5]	0.042	1.37 (n.a.)		
	GSK + NIMH waves 1-5		0.012	1.40 (n.a.)		
rs1938526	WTCCC + STEP-UCL + ED-DUB-STEP2	Ferreira et al. (2008)[4]	1.3×10^{-8}	1.40 (G)	0.0766	1.25 (G)
rs9804190	German	Schulze et al. (2009)[8]	0.0006	1.34 (C)	5.93×10^{-4}	1.32 (C)
	NIMH waves 1-4		0.050	1.24 (C)		
	NIMH wave 5		0.017	1.38 (C)		
	three-sample meta-analysis		3×10^{-6}	1.32 (C)		

NIMH, National Institute of Mental Health; OR, odds ratio; n.a., not available; TREND, Cochran-Armitage trend test; imp, Imputation was performed using MACH (version 1.0.16) (Y. Li and G.R. Abecasis, 2006, Am. Soc. Hum. Genet. abstract) with phased haplotypes from the 60 CEU founders (HapMap phase II, release 22) as a reference. MACH quality score was > 95%.

Table S2. Genome-wide Datasets of BD for Extraction of *NCAN* rs1064395 Genotypes (Replication II)

Sample	Patients	Controls	Genotyping Platform	rs1064395 Imputed?	Study
GAIN-EA / TGEN1[a]	2,189	1,434	A6	No	Smith, Bloss et al. (2009);[6] BiGS
WTCCC-BD / Exp. Ref. Grp.	1,868	14,311	A500	No	WTCCC (2007)[1]
Germany III[b]	501	866	I550, I610Q, I660Q, IO1Q	No	Muglia et al. (2010);[43] Cichon, Mühleisen et al.
France[c]	484	1,823	I300, I550, I610Q	Yes	Etain et al. (2010);[44] Cichon, Mühleisen et al.
Iceland[d]	422	11,487	I300	Yes	Thorgeirsson et al. (2003);[45] deCODE
Australia[e]	390	1,530	I610Q	No	McAuley et al. (2009);[46] Mitchell et al. (2009);[47] Medland et al. (2009);[48] Cichon, Mühleisen et al.
Norway (TOP)	203	372	A6	No	Djurovic et al. (2010);[49] Athanasiu et al. (2010)[50]

[a] GAIN-EA data have been described in a previous study.[6] TGEN1 samples were genotyped and quality-controlled at the Translational Genomics Research Institute (Phoenix, USA): There were 1,190 patients and 401 controls for association analysis and SNP rs1064395 passed filters for CR (> 95%), MAF > 1%, HWE ($p < 1 \times 10^{-6}$). GAIN-EA/TGEN1 datasets are part of the BiGS consortium.

[b] Patients were recruited from consecutive admissions to psychiatric hospitals (in Wiesloch, Würzburg, Dresden, and Tübingen, Germany). They were genotyped at the Life & Brain Center (Bonn, Germany). Control genotypes were extracted from a published study[43]. Using the QC protocol described for replication I, 4 patients and 9 controls were excluded.

[c] Patients have been reported previously.[44] Controls were genotyped at the Centre National de Génotypage (Evry, France). 13 patients and 65 controls were excluded (QC protocol of replication I). Imputation was performed using MACH (version 1.0.16) (Y. Li and G.R. Abecasis, 2006, Am. Soc. Hum. Genet. abstract) with phased haplotypes from the 60 HapMap-CEU founders (release 22) as a reference. MACH quality score was > 95%.

[d] About 27% of the patients have been reported previously.[45] Controls were recruited by various genetic programs at deCODE genetics (Reykjavik, Iceland). For imputation, an algorithm was written that is based on the IMPUTE model[51] and phased haplotype data, generated in the Icelandic population.[52] The IMPUTE info score was 98.9%.

[e] Patients were described in previous studies.[46,47] They were genotyped at the Life & Brain Center (Bonn, Germany). Controls are parents of adolescent twins who participated in a longitudinal study of a variety of phenotypes including melanoma risk factors, cognition and personality, but have not been selected for any particular phenotype. They were genotyped in a previous study.[48] 10 patients and no control were excluded (QC protocol of replication I).

The following abbreviations are used: A500, Affymetrix GeneChip 500K Mapping Array Set (NspI + StyI); A6, Affymetrix Genome-wide Human SNP Array 6.0; BiGS, Bipolar Disorder Genome Study Consortium; CNG, Centre National de Génotypage (Evry, France); deCODE, deCODE genetics (Reykjavík, Iceland); Exp. Ref. Grp., Expanded Reference Group for WTCCC-BD;[1] GAIN-EA, BD sample with European ancestry from the Genetic Association Information Network;[6] I300, Illumina HumanHap300; I550, Illumina HumanHap550; I610Q, Illumina Human610-Quad; I660Q, Illumina Human660W-Quad; IO1Q, Illumina HumanOmni1-Quad; TGEN1, Translational Genomics Research Institute genotyping wave 1 (Phoenix, USA); TOP, Thematically Organized Psychosis Study (Oslo, Norway).

Table S3. Association Results from the GWAS of BD, the Replication Step I Using Six Independent European Samples, and the Combined Analysis

SNP data		Association data														
		GWAS					Replication I					Combined analysis (GWAS + Replication I)				
		TREND			MAF		CMH (K = 6)			MAF		CMH (K = 6)			MAF	
Marker, minor allele	Band	RK	P	OR	Patients (682)	Controls (1,300)	RK	P	OR	Patients (1,729)	Controls (2,313)	RK	P	OR	Patients (2,411)	Controls (3,613)
rs1064395, A	19p13.11	4	3.42×10^{-6}	1.53	0.19	0.14	1	**4.61×10^{-4}**	1.23	0.20	0.16	1	3.02×10^{-8}	1.31	0.195	0.153
rs11764590, T	7p22.3	2	1.30×10^{-6}	1.47	0.27	0.20	2	**0.0020**	1.18	0.26	0.22	2	1.28×10^{-7}	1.26	0.260	0.216
rs10278591, T	7p22.3	8	6.05×10^{-6}	1.43	0.27	0.21	5	**0.0348**	1.12	0.26	0.23	3	1.81×10^{-5}	1.21	0.260	0.224
rs6547829, T	2p23.2	73	7.21×10^{-5}	1.59	0.11	0.07	3	**0.0134**	1.22	0.09	0.08	4	2.50×10^{-5}	1.32	0.096	0.076
rs985409, G	7q22.1	62	6.52×10^{-5}	1.31	0.45	0.38	4	**0.0206**	1.11	0.47	0.44	5	3.89×10^{-5}	1.17	0.463	0.422
rs2209263, A	9q21.31	33	3.44×10^{-5}	0.73	0.24	0.30	8	**0.0436**	0.90	0.26	0.28	6	5.58×10^{-5}	0.84	0.256	0.290
rs779279, A	3q28	42	4.25×10^{-5}	0.76	0.41	0.48	7	**0.0402**	0.91	0.46	0.48	7	6.39×10^{-5}	0.86	0.447	0.481
rs9322993, T	14q21.1	74	7.56×10^{-5}	1.75	0.07	0.04	6	**0.0382**	1.23	0.06	0.05	8	7.54×10^{-5}	1.37	0.065	0.048
rs422159, A	17p13.3	36	3.76×10^{-5}	1.33	0.43	0.36	10	0.0560	1.09	0.39	0.37	9	8.92×10^{-5}	1.16	0.401	0.367
rs11577112, G	1p36.13	15	9.85×10^{-6}	1.50	0.18	0.13	12	0.1138	1.10	0.16	0.15	10	1.57×10^{-4}	1.21	0.169	0.142
rs3996329, T	7p22.3	17	1.32×10^{-5}	1.45	0.23	0.17	11	0.1124	1.09	0.21	0.20	11	1.72×10^{-4}	1.19	0.217	0.187
rs6488297, A	12p13.2	6	3.71×10^{-6}	1.51	0.20	0.14	19	0.2994	1.07	0.17	0.16	12	5.52×10^{-4}	1.19	0.178	0.154
rs2654205, C	15q25.2	66	6.66×10^{-5}	1.35	0.30	0.25	15	0.1612	1.08	0.26	0.25	13	6.25×10^{-4}	1.16	0.272	0.248
rs508208, G	1q42.3	11	7.35×10^{-6}	0.73	0.33	0.41	21	0.3894	0.96	0.37	0.38	14	9.39×10^{-4}	0.88	0.359	0.389
rs2774339, T	1q42.3	1	1.02×10^{-6}	0.71	0.33	0.42	28	0.5772	0.97	0.37	0.38	15	1.08×10^{-3}	0.88	0.359	0.390
rs4844367, A	Xq13.1	4	1.89×10^{-4}	0.75	0.41	0.49	13	0.1454	0.93	0.44	0.46	16	1.11×10^{-3}	0.87	0.433	0.468
rs6821225, C	4q31.22	40	4.07×10^{-5}	1.31	0.43	0.36	16	0.2750	1.05	0.38	0.37	17	1.71×10^{-3}	1.13	0.393	0.369
rs281413, A	19p13.2	46	4.82×10^{-5}	0.72	0.19	0.25	17	0.2806	0.94	0.23	0.24	18	1.86×10^{-3}	0.87	0.221	0.241
rs7297212, A	12p13.31	27	2.40×10^{-5}	1.56	0.13	0.09	20	0.3676	1.07	0.13	0.12	19	2.23×10^{-3}	1.19	0.128	0.107
rs930906, A	Xp22.13	3	1.26×10^{-4}	2.70	0.03	0.01	14	0.1596	1.23	0.03	0.03	20	2.28×10^{-3}	1.47	0.033	0.021
rs7023951, T	9q32	38	3.86×10^{-5}	1.37	0.28	0.22	23	0.4202	1.05	0.23	0.22	21	2.66×10^{-3}	1.14	0.240	0.221
rs4743473, A	9q31.1	25	2.37×10^{-5}	1.32	0.49	0.42	27	0.5348	1.03	0.42	0.42	22	3.93×10^{-3}	1.12	0.443	0.419
rs10500683, C	11p15.4	35	3.75×10^{-5}	0.76	0.45	0.52	25	0.5162	0.97	0.47	0.48	23	4.19×10^{-3}	0.90	0.468	0.496
rs6506625, A	18p11.22	44	4.40×10^{-5}	0.75	0.36	0.42	26	0.5240	0.97	0.41	0.41	24	4.94×10^{-3}	0.90	0.392	0.415
rs1435442, C	4q35.1	7	5.90×10^{-6}	1.42	0.29	0.22	30	0.7192	1.02	0.26	0.26	25	5.11×10^{-3}	1.13	0.271	0.247
rs502224, T	11q13.1	32	3.10×10^{-5}	1.43	0.21	0.16	33	0.7962	1.02	0.17	0.17	26	9.15×10^{-3}	1.14	0.185	0.166
rs16954276, T	15q23	3	2.83×10^{-6}	0.58	0.08	0.13	41	0.8144	1.02	0.11	0.11	27	0.0119	0.86	0.099	0.115
rs1889339, C	9q22.31	12	7.60×10^{-6}	1.43	0.25	0.19	46	0.9660	0.998	0.20	0.20	28	0.0200	1.12	0.213	0.195

Table S3 (continued)

SNP data		Association data														
		GWAS					Replication I					Combined analysis (GWAS + Replication I)				
		TREND			MAF		CMH (K = 6)			MAF		CMH (K = 6)			MAF	
Marker, minor allele	Band	RK	P	OR	Patients (682)	Controls (1,300)	RK	P	OR	Patients (1,729)	Controls (2,313)	RK	P	OR	Patients (2,411)	Controls (3,613)
rs9944047, C	14q32.2	57	6.33×10^{-5}	0.76	0.44	0.51	32	0.7440	0.99	0.45	0.45	29	0.0121	0.91	0.446	0.474
rs6943047, T	7p11.2	16	1.14×10^{-5}	1.50	0.18	0.12	48	1.0000	1.00	0.14	0.14	30	0.0128	1.14	0.148	0.133
rs2398820, G	9q22.31	20	1.70×10^{-5}	1.34	0.42	0.35	47	0.9826	0.99	0.38	0.37	31	0.0155	1.10	0.389	0.365
rs11242396, G	5q31.2	14	9.54×10^{-6}	1.38	0.33	0.27	45	0.8961	0.99	0.27	0.27	32	0.0164	1.11	0.286	0.271
rs1317266, G	4q32.1	50	5.48×10^{-5}	1.38	0.25	0.19	34	0.9184	1.01	0.21	0.21	33	0.0175	1.12	0.221	0.203
rs1931364, A	9q22.31	26	2.40×10^{-5}	1.45	0.20	0.15	43	0.8423	0.99	0.16	0.16	34	0.0249	1.12	0.167	0.154
rs7229918, G	18q22.3	47	5.08×10^{-5}	1.35	0.32	0.26	44	0.8914	0.99	0.29	0.29	35	0.0298	1.10	0.300	0.281
rs10426528, T	19q13.31	67	6.69×10^{-5}	1.31	0.45	0.38	42	0.8296	0.99	0.39	0.39	36	0.0358	1.08	0.405	0.390
rs10231989, C	7q21.3	28	2.78×10^{-5}	1.33	0.42	0.35	38	0.7172	0.98	0.37	0.37	37	0.0390	1.08	0.381	0.361
rs6715508, T	2q33.2	13	9.37×10^{-6}	1.45	0.23	0.17	36	0.5774	0.97	0.19	0.20	38	0.0422	1.10	0.201	0.188
rs1725262, C	1p36.23	34	3.69×10^{-5}	1.35	0.31	0.25	39	0.7453	0.98	0.27	0.27	39	0.0444	1.09	0.284	0.266
rs4461243, A	2p22.2	63	6.62×10^{-5}	1.31	0.41	0.35	40	0.7949	0.99	0.38	0.39	40	0.0451	1.08	0.390	0.372
rs17530034, A	2q14.3	10	6.75×10^{-6}	0.52	0.05	0.08	31	0.3629	1.09	0.07	0.07	41	0.0689	0.87	0.063	0.073
rs7268, T	5q31.3	72	7.04×10^{-5}	1.30	0.52	0.45	37	0.5970	0.98	0.49	0.49	42	0.0721	1.07	0.498	0.477
rs12123953, T	1p31.1	60	6.38×10^{-5}	1.46	0.17	0.12	35	0.5465	0.96	0.15	0.15	43	0.0866	1.09	0.153	0.142
rs843319, G	6p22.3	45	4.45×10^{-5}	1.35	0.33	0.27	29	0.3004	0.95	0.31	0.32	44	0.166	1.06	0.318	0.304
rs6767011, A	3p22.3	18	1.42×10^{-5}	1.54	0.15	0.10	22	0.2001	0.91	0.11	0.12	45	0.185	1.08	0.121	0.114
rs4849303, T	2q13	52	5.63×10^{-5}	0.76	0.43	0.50	24	0.2354	1.06	0.49	0.48	46	0.200	0.95	0.475	0.486
rs1203860, A	4p16.3	31	3.08×10^{-5}	1.40	0.26	0.20	18	0.1493	0.92	0.22	0.23	47	0.238	1.05	0.232	0.223
rs705648, C	2q35	69	6.76×10^{-5}	1.35	0.30	0.24	9	**0.0277**	0.90	0.29	0.31	48	0.732	1.01	0.291	0.282

Minor allele, refers to dbSNP build 130 and was determined for patients and controls in each analysis; RK (GWAS), rank refers to the rank space between 1 and 75 of all autosomal SNPs and the rank space between 1 and 4 of all X chromosomal markers; P (GWAS), autosomal markers were analyzed using the Cochran-Armitage test (TREND) and X-chromosomal markers were analyzed using the Wald test; MAF, minor allele (MA) frequency; OR, odds ratio referring to minor allele; P (replication), autosomal and X chromosomal markers were analyzed using the Cochran-Mantel-Haenszel (CMH) test (highlighted in bold if $p < 0.05$); P (combined analysis), autosomal markers were analyzed using the CMH; K, CMH's cluster variable.

Table S4. Individual Association Results for the Nine GWAS SNPs with Evidence for Association in the Replication Step I (to Investigate the Contribution of each Sample to Each Association, CMH was Performed Across each Combination of 5 out of 6 European Samples)

SNP data	Replication I																						
	Germany II							Poland							Spain								
	TREND		CMH (K = 5)			MAF		TREND		CMH (K = 5)			MAF		TREND		CMH (K = 5)			MAF	
Marker	P	OR	P	OR	M	Pat (361)	Con (755)	P	OR	P	OR	M	Pat (411)	Con (504)	P	OR	P	OR	M	Pat (297)	Con (391)
rs1064395	**0.0490**	1.275	**0.0034**	1.218	A	0.17	0.14	0.1354	1.207	**0.0014**	1.236	A	0.17	0.15	**0.0317**	1.320	**0.0048**	1.207	A	0.26	0.21
rs11764590	0.8182	1.025	**0.0006**	1.236	T	0.24	0.23	0.0692	1.222	**0.0110**	1.167	T	0.25	0.21	0.2710	1.156	**0.0038**	1.184	T	0.23	0.21
rs10278591	0.6418	0.952	**0.0070**	1.180	T	0.23	0.24	0.0840	1.209	0.1478	1.092	T	0.27	0.23	0.1400	1.213	0.0992	1.101	T	0.25	0.21
rs6547829	0.1780	1.219	**0.0378**	1.223	T	0.11	0.09	0.1754	1.267	**0.0366**	1.210	T	0.09	0.07	0.5406	1.119	**0.0140**	1.250	T	0.11	0.10
rs985409	0.2272	1.126	0.0546	1.107	G	0.47	0.44	0.1846	1.148	0.0642	1.102	G	0.45	0.42	0.4351	0.912	0.0612	1.116	A	0.48	0.49
rs2209263	0.2378	0.885	0.1014	0.907	A	0.26	0.28	**0.0122**	0.772	0.3712	0.948	A	0.28	0.33	0.5970	1.074	**0.0146**	0.872	A	0.24	0.23
rs779279	0.4708	0.936	0.0508	0.901	A	0.46	0.47	0.2433	1.120	0.1840	0.915	C	0.47	0.45	0.6016	0.943	**0.0440**	0.903	A	0.38	0.39
rs9322993	0.3232	1.212	0.0674	1.232	T	0.06	0.05	0.4360	1.183	0.0538	1.239	T	0.06	0.05	0.2322	1.272	0.0836	1.214	T	0.08	0.07

	Russia							Romania							Bosnia-Herzegovina / Serbia						
	TREND		CMH (K = 5)			MAF		TREND		CMH (K = 5)			MAF		TREND		CMH (K = 5)			MAF	
Marker	P	OR	P	OR	M	Pat (326)	Con (329)	P	OR	P	OR	M	Pat (227)	Con (221)	P	OR	P	OR	M	Pat (107)	Con (113)
rs1064395	0.9010	1.018	**0.0002**	1.278	A	0.18	0.17	**0.0484**	1.381	**0.0024**	1.211	A	0.21	0.17	0.4472	1.201	**0.0006**	1.232	A	0.21	0.18
rs11764590	0.0764	1.246	**0.0096**	1.165	T	0.29	0.25	0.0528	1.343	**0.0098**	1.158	T	0.28	0.23	0.2606	1.280	**0.0036**	1.173	T	0.26	0.22
rs10278591	0.2064	1.171	0.0812	1.108	T	0.28	0.25	0.2962	1.177	0.0612	1.111	T	0.26	0.23	0.9760	1.007	**0.0304**	1.126	T	0.24	0.24
rs6547829	0.6188	1.114	**0.0136**	1.239	T	0.07	0.06	0.0770	1.500	**0.0464**	1.188	T	0.11	0.07	0.7190	1.161	**0.0142**	1.224	T	0.06	0.05
rs985409	0.2792	1.140	**0.0440**	1.107	G	0.45	0.41	0.6790	1.062	**0.0214**	1.119	G	0.46	0.45	0.9667	0.992	**0.0166**	1.120	G	0.47	0.47
rs2209263	0.8870	0.982	**0.0316**	0.886	A	0.27	0.27	0.5206	0.908	0.0552	0.901	A	0.25	0.27	0.6052	0.893	0.0514	0.902	A	0.27	0.29
rs779279	0.3497	1.110	0.1356	0.912	C	0.49	0.48	0.5386	0.921	0.0500	0.909	A	0.42	0.44	0.1826	0.783	0.0722	0.918	A	0.44	0.50
rs9322993	0.8837	0.966	**0.0190**	1.290	T	0.06	0.06	0.4696	1.279	0.0518	1.222	T	0.05	0.04	**0.0212**	2.725	0.1102	1.176	T	0.08	0.03

P, p value highlighted in bold if p < 0.05; TREND, Cochran-Armitage test; OR, odds ratio referring to minor allele (highlighted in yellow when OR was in the opposite direction to GWAS); M, minor allele refers to dbSNP build 130 and was determined for patients (Pat) and controls (Con) in each analysis (highlighted in orange when minor allele has changed with respect to GWAS); CMH, Cochran-Mantel-Haenszel test; K, CMH's cluster variable.

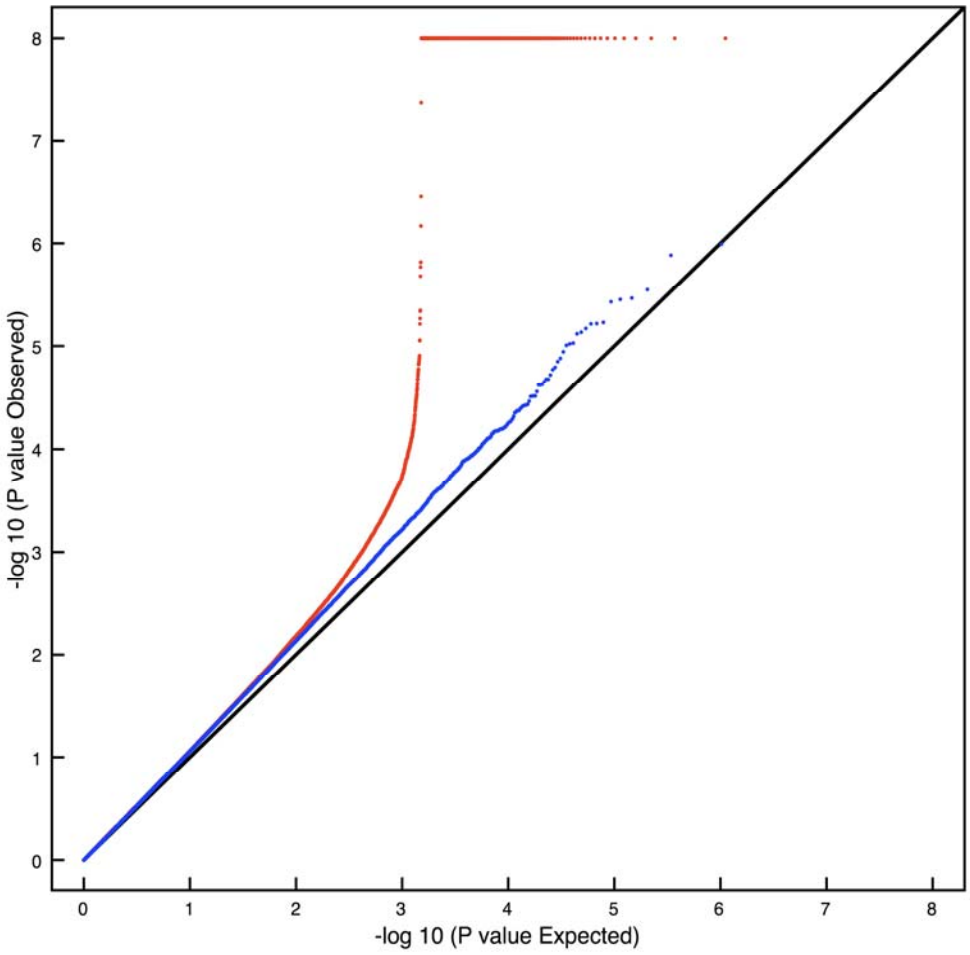


Figure S1. Quantile-Quantile (QQ) Plot of Genome-wide Association Data
QQ plot of TREND test p values from autosomal SNPs before (red curve) and after (blue curve) application of all QC filters; SNPs for which the test statistic exceeded an observed –log(p) of 8 are fixed to 8. After filtering (blue curve), we observed a good adherence of data points to the line of expectance. This implies that spurious associations, characterized by an increase in the number of potential highly significant p values, were systematically removed. All remaining slight deviations from the line of expectance in the extreme tail are presumed to reflect true-positive genetic effects.

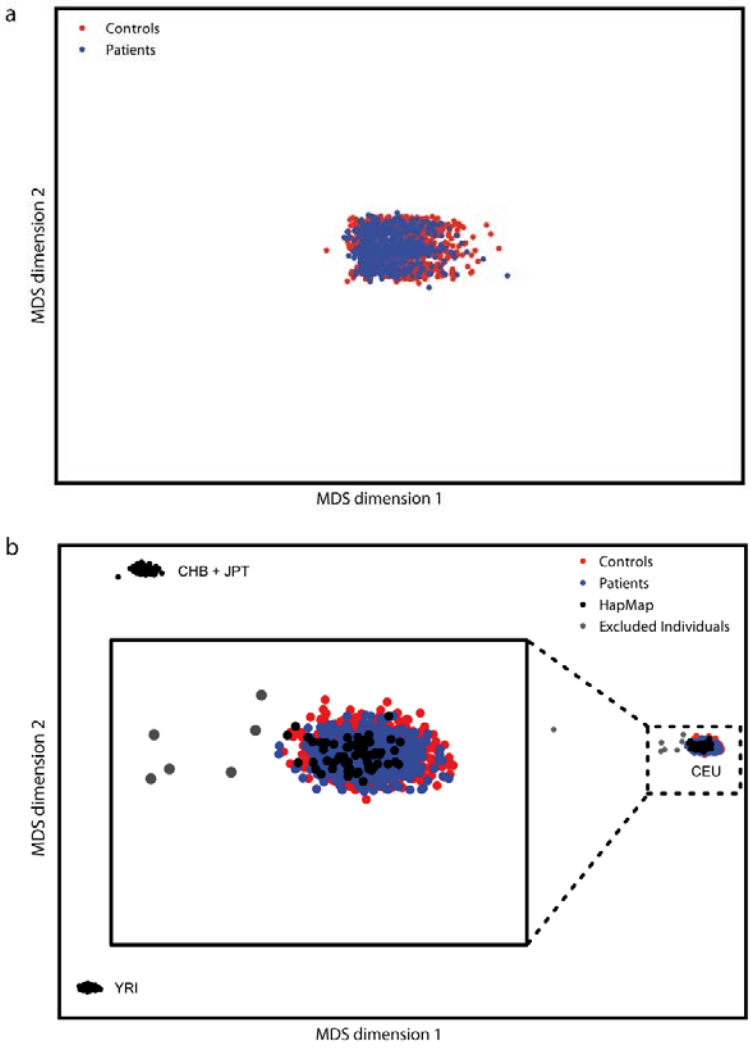


Figure S2. Multi-Dimensional Scaling Analysis Based on Identity-By-State Distances
(a) Between patients and controls from our GWAS sample and (b) between the GWAS sample and unrelated individuals from the four ethnically diverse HapMap panels (CHB, Han Chinese in Beijing, China; JPT, Japanese in Tokyo, Japan; CEU: Utah residents with Northern and Western European ancestry from the CEPH collection; YRI, Yoruba in Ibadan, Nigeria; phase II data). Only the first two dimensions are plotted, and each dot represents one individual. Seven individuals, who were either outliers within our GWAS sample and/or of non-European ancestry, were excluded from further analysis (grey dots).

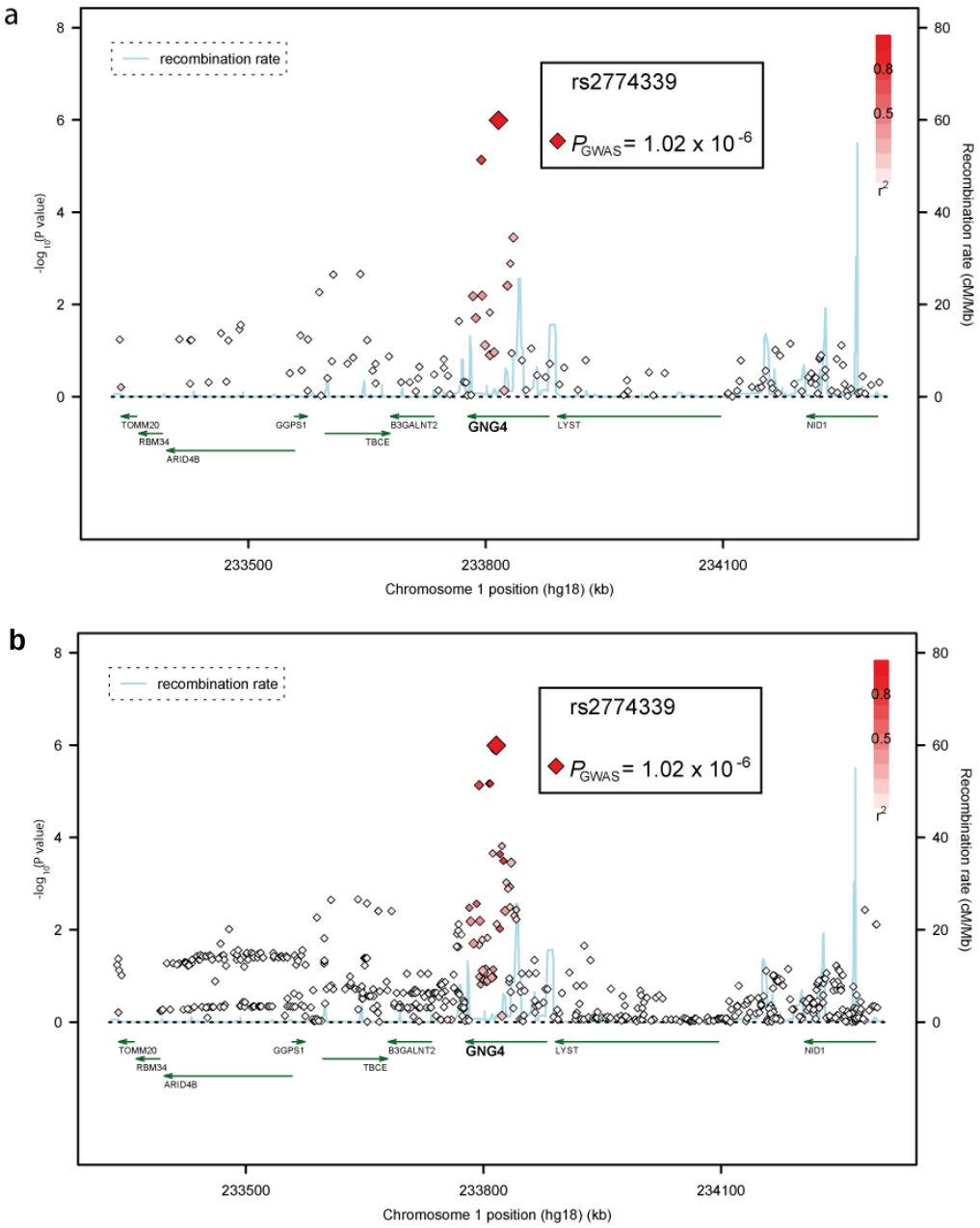
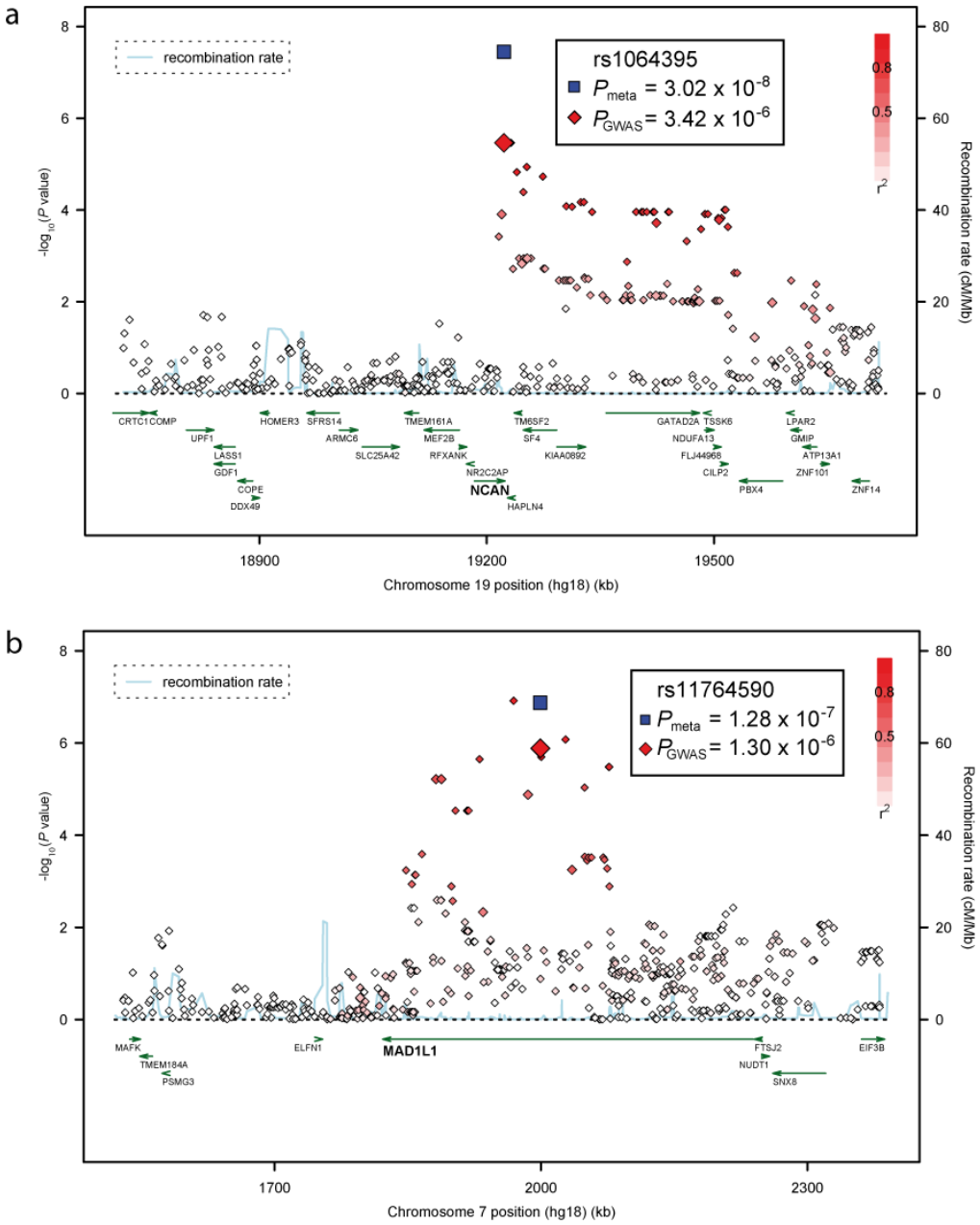
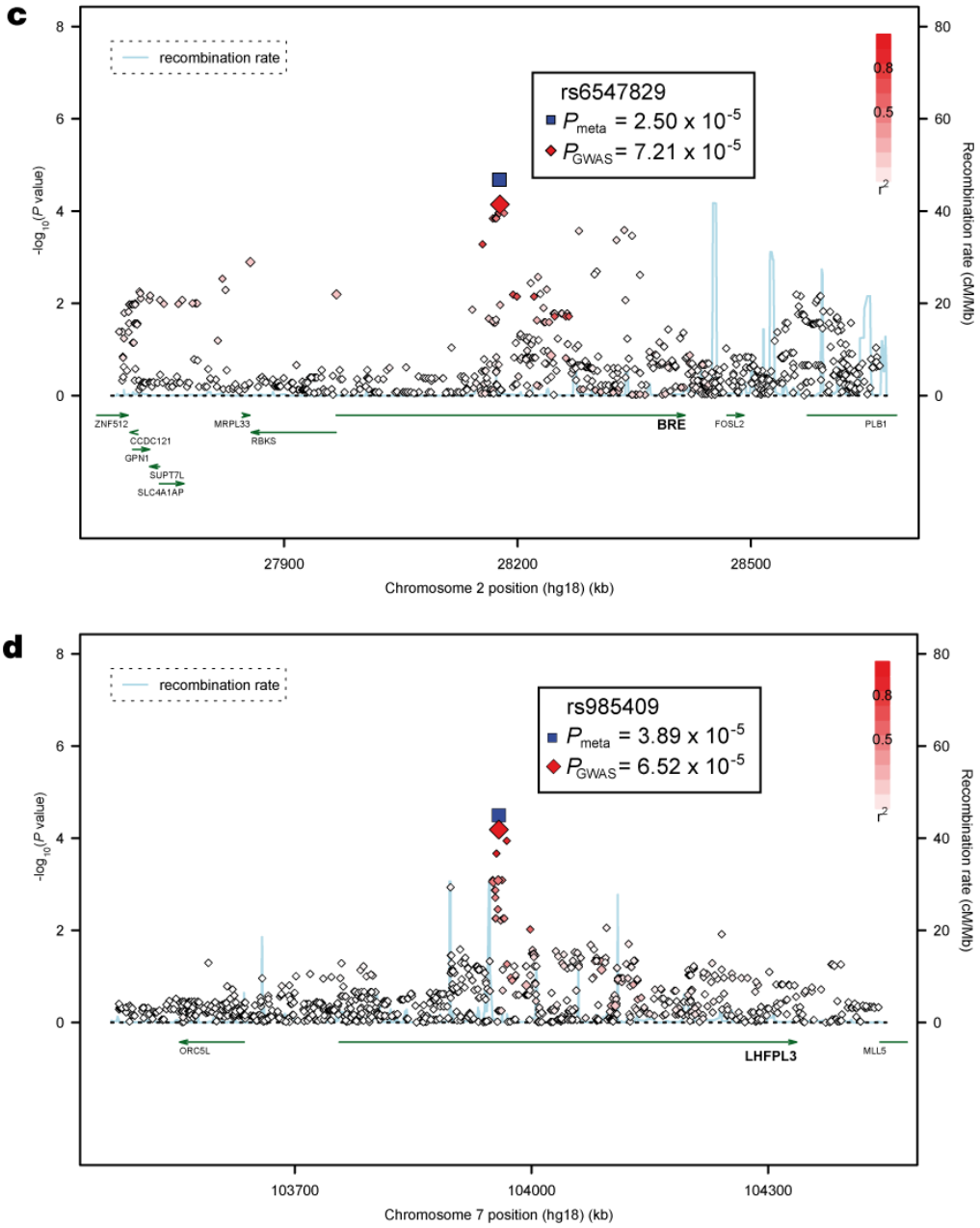
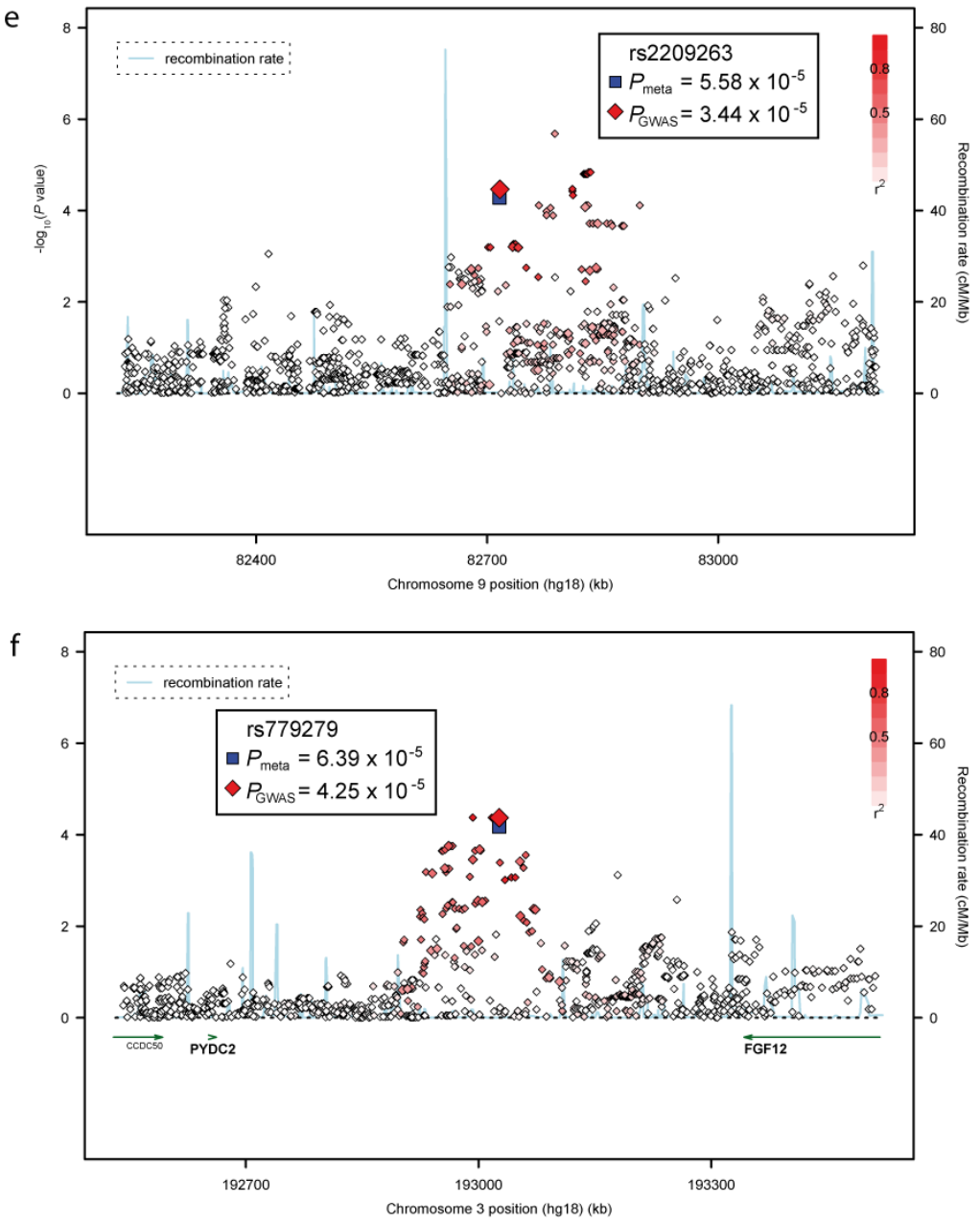


Figure S3. Regional Association Plots Displaying *GNG4* rs2774339 which was not Supported in the Replication Step I Using (a) Genotyped and (b) Imputed and Genotyped SNPs

TREND p values from SNPs are plotted against positions from the March 2006 human reference sequence, annotated by RefSeq genes. The most associated marker from the GWAS is indicated by an enlarged red diamond which is centered in a genomic window of around 1 Mb. The corresponding CMH p value from the combined analysis (p_{meta}) is given by an enlarged blue diamond. The strength of LD (in r^2) between the top SNP and its adjacent markers is demonstrated by the red (high) to white (low) color bar (top right corner). The recombination rate (second y axis) is plotted in light blue, according to HapMap-CEU. RAPs were generated using SNAP.[43]


a
recombination rate
rs1064395
P_{meta} = 3.02 x 10^{-8}
P_{GWAS} = 3.42 x 10^{-6}
r^2
0.8
0.5
-log10(P value)
Recombination rate (cM/Mb)
CRTC1COMP
HOMER3
SFRS14
TMEM161A
TM6SF2
GATAD2A
TSSK6
LPAR2
UPF1
ARMC6
MEF2B
SF4
NDUFA13
GMIP
LASS1
SLC25A42
RFXANK
KIAA0892
FLJ44966
ATP13A1
GDF1
NR2C2AP
CILP2
ZNF101
COPE
NCAN
PBX4
ZNF14
DDX49
HAPLN4
18900
19200
19500
Chromosome 19 position (hg18) (kb)
b
recombination rate
rs11764590
P_{meta} = 1.28 x 10^{-7}
P_{GWAS} = 1.30 x 10^{-6}
r^2
0.8
0.5
-log10(P value)
Recombination rate (cM/Mb)
MAFK
ELFN1
MAD1L1
FTSJ2
EIF3B
TMEM184A
NUDT1
PSMG3
SNX8
1700
2000
2300
Chromosome 7 position (hg18) (kb)


c
recombination rate
rs6547829
P_{meta} = 2.50 x 10^{-5}
P_{GWAS} = 7.21 x 10^{-5}
r^2
0.8
0.5
-log10(P value)
Recombination rate (cM/Mb)
ZNF512
CCDC121
GPN1
SUPT7L
SLC4A1AP
MRPL33
RBKS
BRE
FOSL2
PLB1
27900
28200
28500
Chromosome 2 position (hg18) (kb)
d
recombination rate
rs985409
P_{meta} = 3.89 x 10^{-5}
P_{GWAS} = 6.52 x 10^{-5}
r^2
0.8
0.5
-log10(P value)
Recombination rate (cM/Mb)
ORC5L
LHFPL3
MLL5
103700
104000
104300
Chromosome 7 position (hg18) (kb)


e
recombination rate
rs2209263
P_{meta} = 5.58 x 10^{-5}
P_{GWAS} = 3.44 x 10^{-5}
0.8
0.5
r^2
-log$_{10}$(P value)
Recombination rate (cM/Mb)
82400
82700
83000
Chromosome 9 position (hg18) (kb)
f
recombination rate
rs779279
P_{meta} = 6.39 x 10^{-5}
P_{GWAS} = 4.25 x 10^{-5}
CCDC50
PYDC2
FGF12
192700
193000
193300
Chromosome 3 position (hg18) (kb)

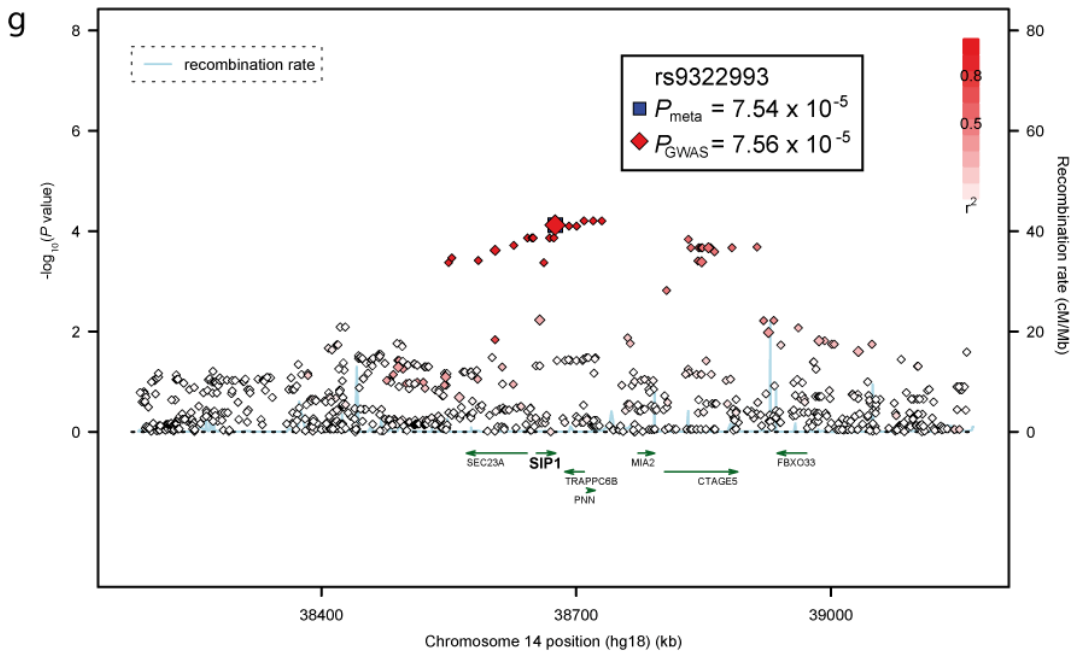
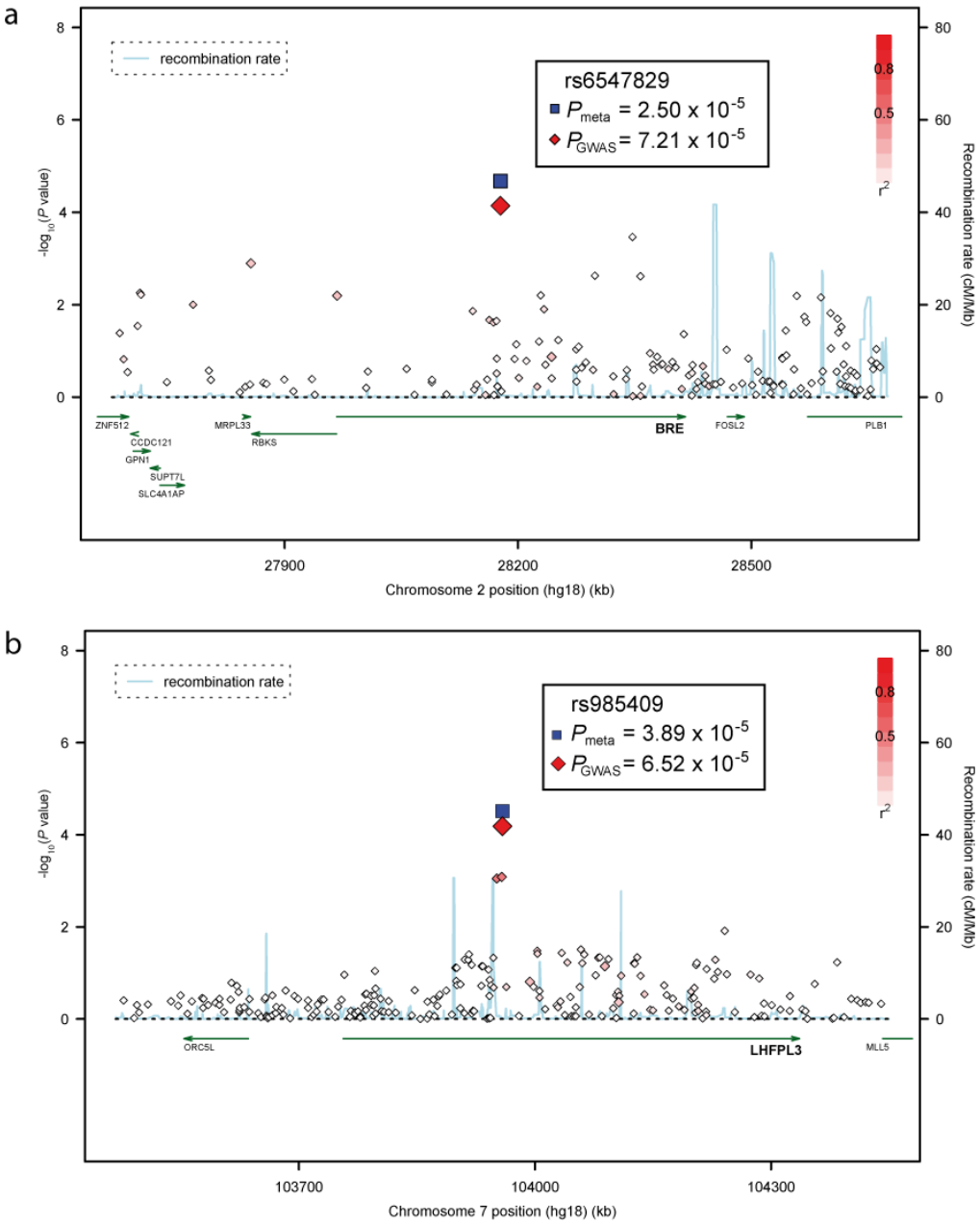
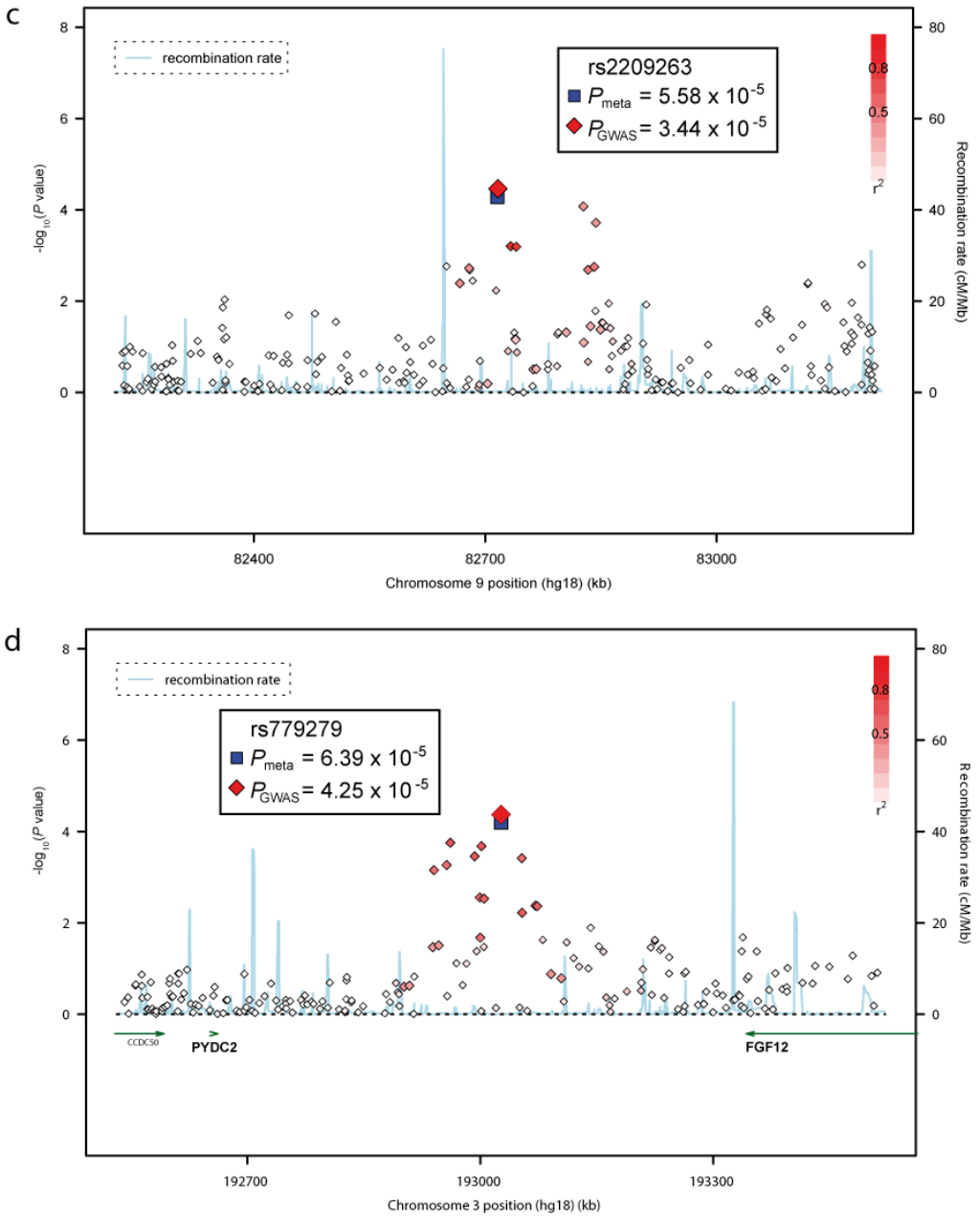


Figure S4. Regional Association Plots Displaying All Seven Loci (a-g) with Evidence for Association in the Replication Step I Using Imputed and Genotyped SNPs.
A description of this figure is provided in Figure S3.


a
recombination rate
rs6547829
P_{meta} = 2.50 x 10^{-5}
P_{GWAS} = 7.21 x 10^{-5}
0.8
0.5
r^2
-log$_{10}$(p value)
Recombination rate (cM/Mb)
ZNF512
CCDC121
GPN1
SUPT7L
SLC4A1AP
MRPL33
RBKS
BRE
FOSL2
PLB1
27900
28200
28500
Chromosome 2 position (hg18) (kb)
b
recombination rate
rs985409
P_{meta} = 3.89 x 10^{-5}
P_{GWAS} = 6.52 x 10^{-5}
0.8
0.5
r^2
-log$_{10}$(p value)
Recombination rate (cM/Mb)
ORC5L
LHFPL3
MLL5
103700
104000
104300
Chromosome 7 position (hg18) (kb)


c
recombination rate
rs2209263
P_{meta} = 5.58 x 10^{-5}
P_{GWAS} = 3.44 x 10^{-5}
0.8
0.5
r^2
-log (P_{10} value)
Recombination rate (cM/Mb)
82400
82700
83000
Chromosome 9 position (hg18) (kb)
d
recombination rate
rs779279
P_{meta} = 6.39 x 10^{-5}
P_{GWAS} = 4.25 x 10^{-5}
CCDC50
PYDC2
FGF12
192700
193000
193300
Chromosome 3 position (hg18) (kb)

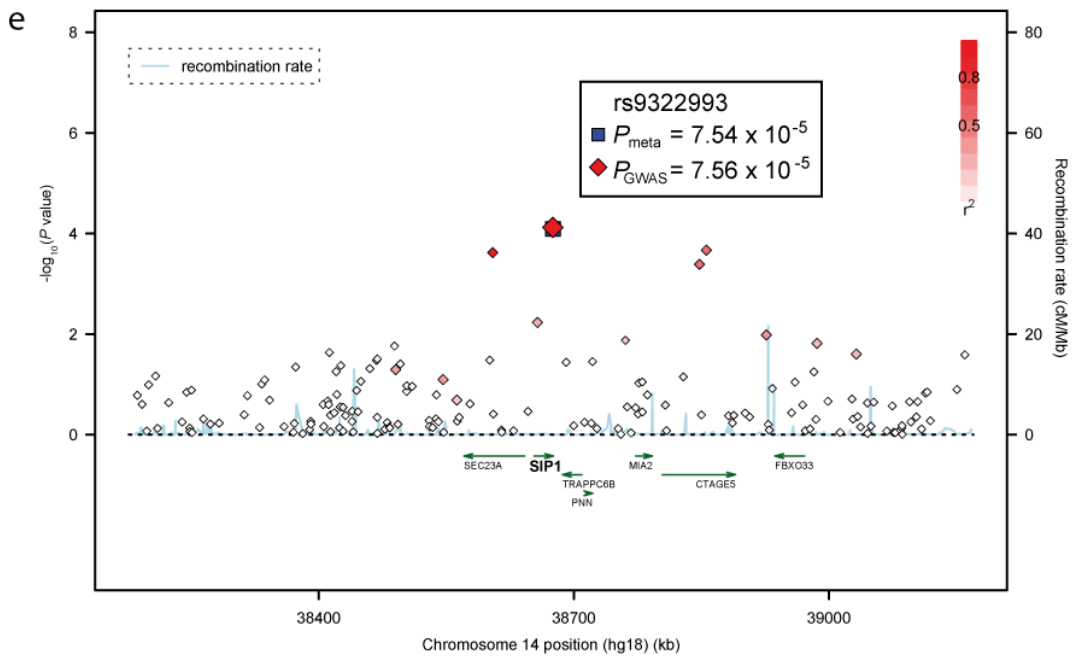


Figure S5. Regional Association Plots Displaying the Five Additional Loci (a-e) with Evidence for Association in the Replication Step I.
A description of this figure is provided in Figure S3.

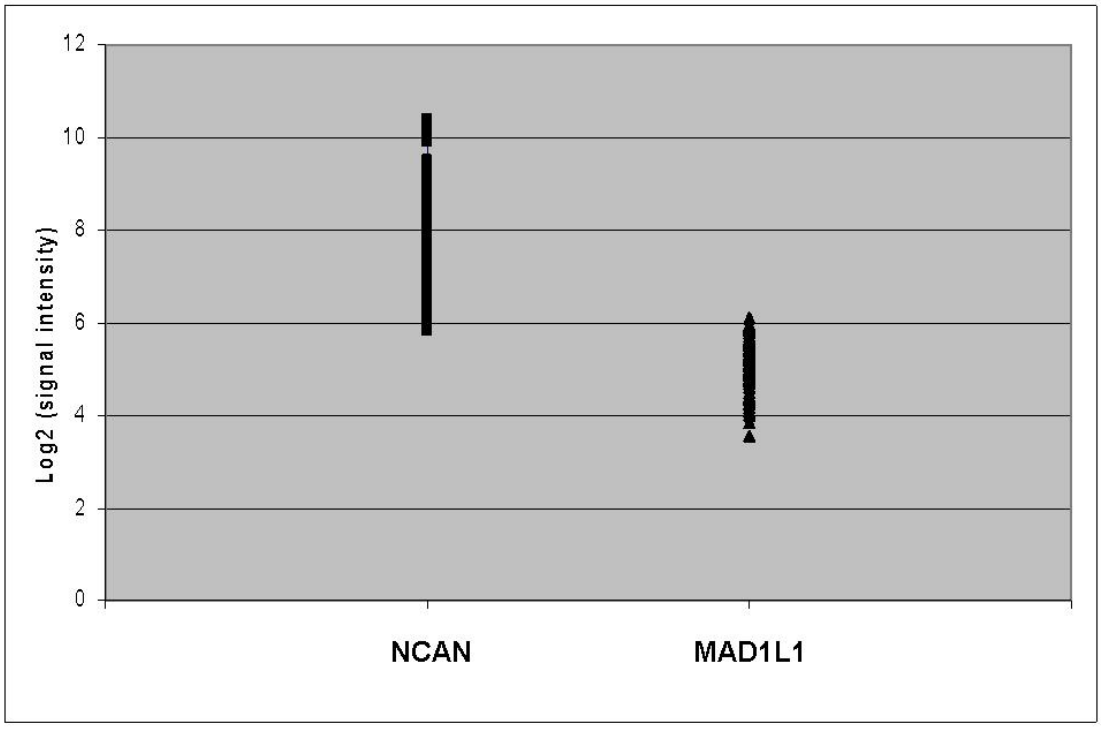


Figure S6. Transcriptional Expression of *NCAN* and *MAD1L1* in Human Hippocampus Tissue
Whole-genome expression analysis with HumanHT-12 Expression BeadArrays (n=148; Illumina, San Diego, USA) showed that *NCAN* (black boxes) was expressed in the hippocampus tissue with an average $\log_2$ ratio = 7.99 of signal intensities with a standard deviation of 0.8 (intensities, min = 5.82 and max = 10.4). Expression of *MAD1L1* (black triangles) in the human hippocampus showed an average $\log_2$ ratio = 5.21 of signal intensities with a standard deviation of 0.46 (intensities, min = 3.55 and max = 6.1). The expression profile was background-subtracted and average-normalized using Illumina's GenomeStudio software.

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