Genetic Markers of Human Evolution Are Enriched in Schizophrenia

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Table S1. Genome-wide association studies samples with available summary statistics.

Phenotype		Sample Size (*N*)	Number of SNPs Total (NSS)
Central nervous system (CNS) disorders	Alzheimer's disease (1) (AD)	54,162	2,436,961 (382,008)
	Attention-deficit/hyperactivity disorder (2) (ADHD)	19,210	1,163,004 (192,272)
	Bipolar disorder (3) (BD)	16,731	2,406,338 (375,625)
	Major depressive disorder (4) (MDD)	18,759	1,170,068 (193,732)
	Migraine (5)	118,710	1,834,101 (301,046)
	Multiple sclerosis (6) (MS)	27,148	458,752 (77,506)
	Schizophrenia (PGC1) (7)	21,856	1,171,056 (193,841)
	Schizophrenia (PGC2) (8)	82,315	2,538,794 (395,798)
Anthropometric measures	Body mass index (9) (BMI)	123,865	2,400,377 (374,879)
	Height (10)	183,727	2,398,527 (374,673)
	Waist hip ratio (11) (WHR)	77,167	2,376,820 (370,838)
Cardiovascular disease (CVD) risk factors	Systolic blood pressure (12) (SBP)	203,056	2,382,073 (371,417)
	Total cholesterol (13) (TC)	100,184	2,508,369 (391,044)
	Triglycerides (13) (TG)	96,568	2,508,363 (391,050)
Immune-mediated diseases	Crohn's disease (14) (CD)	51,109	942,858 (162,435)
	Celiac disease (15) (CeD)	15,283	517,873 (86,870)
	Rheumatoid arthritis (16) (RA)	25,708	2,462,228 (385,820)
	Ulcerative colitis (17) (UC)	26,405	1,273,589 (209,118)

Genome-wide association studies analyzed. The table shows the phenotypes, the sample size (i.e. the number of subjects, *N*); the total number of SNPs entering our analyses and the number of SNPs with Neanderthal selective sweep scores (NSS, within parentheses). PGC: Psychiatric Genomics Consortium, results from the first edition of the schizophrenia study by the Psychiatric Genomics Consortium (PGC1) and the second larger edition of the schizophrenia PGC study (PGC2).

Table S2. Neanderthal selective sweep, squared *z*-score regression and binomial proportion test after removal of major histocompatibility complex SNPs.

GWAS	β (Min, Max)	Std. Error	*p*-Value	C.I.	BPT(p) 1%(Min, Max)
AD	-0.012 (-0.029, 0.012)	0.016	4.90E-01	-0.041, 0.021	2.5E-01 (7.6E-04, 5.9E-01)
ADHD	0.003 (-0.013, 0.017)	0.013	8.50E-01	-0.022, 0.027	4.4E-01 (3.5E-02, 6.2E-01)
BD	-0.004 (-0.020, 0.013)	0.01	7.40E-01	-0.023, 0.016	4.8E-01 (1.4E-02, 9.1E-01)
MDD	-0.017 (-0.034, -0.006)	0.012	2.10E-01	-0.042, 0.007	5.6E-01 (1.1E-01, 9.4E-01)
Migraine	-0.006 (-0.029, -0.001)	0.013	6.90E-01	-0.032, 0.020	7.4E-01 (2.3E-01, 9.2E-01)
MS	-0.008 (-0.034, 0.023)	0.019	7.00E-01	-0.046, 0.030	5.0E-01 (8.7E-03, 8.5E-01)
SCZ 1	-0.039 (-0.051, -0.024)	0.013	5.40E-03	-0.064, -0.015	1.6E-01 (1.6E-02, 6.1E-01)
SCZ 2	-0.069 (-0.076, -0.058)	0.01	**2.10E-09**	-0.089, -0.049	8.7E-02 (5.3E-06, 3.4E-01)
BMI	-0.050 (-0.061, -0.036)	0.016	4.50E-03	-0.079, -0.023	4.1E-01 (6.1E-02, 9.2E-01)
Height	-0.074 (-0.095, -0.058)	0.015	**8.80E-06**	-0.104, -0.045	1.1E-01 (3.4E-04, 6.9E-01)
WHR	-0.026 (-0.040, -0.019)	0.011	2.80E-02	-0.047, -0.005	2.3E-01 (7.0E-03, 5.1E-01)
SBP	-0.015 (-0.023, -0.003)	0.01	1.90E-01	-0.035, 0.005	3.7E-01 (9.4E-02, 7.3E-01)
TC	-0.001 (-0.019, 0.023)	0.019	9.60E-01	-0.038, 0.039	5.2E-01 (3.1E-01, 8.6E-01)
TG	-0.017 (-0.024, -0.003)	0.015	3.30E-01	-0.048, 0.014	4.3E-01 (8.1E-03, 8.3E-01)
CD	-0.025 (-0.050, 0.003)	0.019	2.50E-01	-0.062, 0.014	5.3E-01 (2.6E-01, 8.6E-01)
CeD	-0.000 (-0.024, 0.018)	0.018	9.90E-01	-0.037, 0.035	3.7E-01 (1.2E-01, 8.4E-01)
RA	-0.005 (-0.020, 0.009)	0.011	6.90E-01	-0.027, 0.017	5.6E-01 (2.0E-02, 8.8E-01)
UC	-0.017 (-0.028, 0.015)	0.015	3.20E-01	-0.047, 0.014	5.2E-01 (1.6E-01, 9.2E-01)

Phenotypes: psychiatric and other neurological diseases (Alzheimer's disease (AD), attention-deficit/hyperactivity disorder (ADHD), bipolar disorder (BD), major depressive disorder (MDD), migraine, multiple sclerosis (MS), first and second edition of the schizophrenia GWAS by the Psychiatric Genomic Consortium (SCZ1 and SCZ2)), anthropometric measures (body mass index (BMI), height, waist-hip ratio (WHR)), cardiovascular risk factors (systolic blood pressure (SBP), total cholesterol (TC), triglycerides (TG)), immune-mediated diseases (Crohn's disease (CD), celiac disease (CeD), rheumatoid arthritis (RA), ulcerative colitis (UC)).

Table S3. Neanderthal selective sweep, squared z-score regression and binomial proportion test using affiliation scores.

GWAS	β	Std. Error	*p*-Value	C.I. Lower	C.I. Upper	BPT(p) 1%
AD	0.000	0.013	9.75E-01	-0.025	0.024	2.20E-03
ADHD	0.005	0.013	7.42E-01	-0.017	0.029	6.00E-01
BD	0.008	0.009	4.19E-01	-0.009	0.025	7.10E-01
MDD	0.000	0.013	9.74E-01	-0.026	0.024	5.80E-01
Migraine	0.022	0.010	5.67E-02	0.001	0.042	4.00E-02
MS	0.022	0.021	3.52E-01	-0.024	0.062	5.40E-02
SCZ 1	0.022	0.013	1.33E-01	-0.003	0.048	2.70E-03
SCZ 2	0.053	0.009	4.03E-07	0.035	0.072	2.30E-06
BMI	-0.004	0.010	7.47E-01	-0.024	0.017	9.40E-04
Height	0.010	0.012	4.44E-01	-0.013	0.035	6.10E-04
WHR	0.004	0.009	6.71E-01	-0.013	0.022	2.90E-01
SBP	-0.008	0.009	4.13E-01	-0.026	0.009	1.40E-01
TC	0.017	0.016	3.62E-01	-0.015	0.051	1.00E-01
TG	0.006	0.016	7.33E-01	-0.025	0.036	5.40E-06
CD	0.003	0.022	9.14E-01	-0.036	0.043	7.10E-01
CeD	0.013	0.020	5.45E-01	-0.025	0.055	7.00E-01
RA	0.006	0.009	5.43E-01	-0.012	0.025	9.80E-02
UC	0.003	0.015	8.80E-01	-0.026	0.034	4.10E-01

Phenotypes: psychiatric and other neurological diseases (Alzheimer's disease (AD), attention-deficit/hyperactivity disorder (ADHD), bipolar disorder (BD), major depressive disorder (MDD), migraine, multiple sclerosis (MS), first and second edition of the schizophrenia GWAS by the Psychiatric Genomic Consortium (SCZ1 and SCZ2)), anthropometric measures (body mass index (BMI), height, waist-hip ratio (WHR)), cardiovascular risk factors (systolic blood pressure (SBP), total cholesterol (TC), triglycerides (TG)), immune-mediated diseases (Crohn's disease (CD), celiac disease (CeD), rheumatoid arthritis (RA), ulcerative colitis (UC)).

Table S4. SNPs associated with schizophrenia conditioned on Neanderthal selective sweep score.

SNP ID	Gene	HAZ	*p* Value	FDR	Cond FDR	NSS Replication Rate	NSS Rep SD	All SNPs Rep rate	All SNPs Rep SD	NSS	LD Count	Total LD	Ancestral Allele Frequency	PhyloP Primates	PhyloP Mammals	Hetero-zygosity	Function	Associated Phenotypes
rs946106	AGBL4	4.48	1.22E-04	9.22E-02	1.31E-04	NaN	NaN	0.176	0.090	-0.403	591 (97%)	253.3 (95%)	0.77 (27%)	0.37 (13%)	0.72 (41%)	0.14 (15%)	Encodes an ATP binding protein which is involved in metallocarb-oxypeptidase activity and tubulin binding	Celiac disease
rs2291409	AKT3	4.16	8.83E-04	1.97E-01	8.04E-04	NaN	NaN	0.330	0.128	-1.056	315 (87%)	161.4 (86%)	0.30 (7%)	-0.68 (43%)	-0.75 (53%)	0.14 (14%)	Encodes kinases involved in cell signalling in for insulin and growth factors	Melanoma, carcinomas, prostate cancer
rs10906984	AP3B2	4.732	1.47E-04	9.37E-02	1.62E-04	NaN	NaN	0.312	0.140	-0.129	254 (80%)	124.7 (79%)	-	-	-	-	Encodes a vesicle-coat protein complex. Some of which are expressed exclusively in neurons (18)	Carcinomas and melanomas
rs13084588	BBX	-3.695	3.30E-03	7.40E-01	6.97E-03	0.273	0.081	0.156	0.048	-0.314	126 (54%)	82.5 (64%)	0.87 (33%)	0.32 (6%)	0.80 (68%)	0.13 (11%)	Encodes for a protein	Lymphocytic gastritis
rs7901209	C10orf76	3.643	3.21E-03	7.40E-01	6.97E-03	0.237	0.081	0.135	0.051	-0.203	104 (46%)	54.8 (48%)	-	-	-	-	Might be involved in transcriptional regulation (19)	Alzheimer's
rs4369701	CDH11	4.258	2.73E-04	9.70E-02	2.53E-04	0.235	0.107	0.147	0.084	-0.166	75 (34%)	23.4 (20%)	-	-	-	-	Encodes membrane protein involved in cellular adhesion	Overexpressed in cancer cells
rs10926976	CEP170	5.078	4.80E-05	7.81E-02	7.94E-05	0.329	0.109	0.227	0.098	-0.742	353 (89%)	164.8 (87%)	0.49 (13%)	-0.70 (46%)	0.53 (13%)	0.13 (11%)	Encodes protein that is component of the centrosome and is involved in microtubule organization (20)	Ciliary dyskinesia
rs11688397	CUL3	-4.362	2.01E-04	9.50E-02	2.02E-04	NaN	NaN	NaN	NaN	-0.489	105 (47%)	64.7 (54%)	-	-	-	-	Protein coding gene	Blood vessel malformations
rs11123288	DPP10	-3.489	3.06E-03	7.40E-01	6.97E-03	0.290	0.089	0.170	0.073	-0.067	369 (90%)	128.6 (80%)	0.77 (26%)	-0.33 (2%)	-0.59 (23%)	0.13 (11%)	Encodes a membrane protein involved in functioning of voltage gated potassium channels (21)	Asthma, autism spectrum disorders
rs1421750	FLJ33630	-4.082	5.32E-04	1.23E-01	5.04E-04	NaN	NaN	0.166	0.086	-0.463	200 (72%)	100.3 (71%)	0.33 (8%)	-0.89 (60%)	-0.64 (35%)	0.16 (21%)	Not known but expressed in brain and other tissues	Cancer
rs17662328	FOXP1	-3.46	3.54E-03	7.40E-01	6.97E-03	NaN	NaN	0.225	0.136	-0.697	222 (76%)	121.1 (78%)	-	-	-	-	Encodes for protein in the forkhead box transcription factor family. Plays important roles in the regulation of transcription during both development and adulthood.	Mental retardation with language impairment and autistic features, and hypertonia
rs1127091	GATAD2B	-3.809	2.24E-03	5.36E-01	2.51E-03	0.275	0.085	0.154	0.047	-0.265	289 (84%)	144.6 (83%)	0.50 (13%)	2.11 (95%)	0.63 (22%)	0.13 (11%)	Zinc finger protein-coding gene	Mental retardation
rs2230653	HIST1H1C	3.891	2.70E-03	6.41E-01	3.94E-03	0.287	0.104	0.174	0.073	-0.321	41 (17%)	19.5 (16%)	0.97 (41%)	-2.37 (96%)	-1.26 (78%)	0.21 (39%)	Encodes for a histone protein	NA

SNP ID	Gene	HAZ	*p* Value	FDR	Cond FDR	NSS Replication Rate	NSS Rep SD	All SNPs Rep rate	All SNPs Rep SD	NSS	LD Count	Total LD	Ancestral Allele Frequency	PhyloP Primates	PhyloP Mammals	Hetero-zygosity	Function	Associated Phenotypes
rs5762416	KIAA1648	-3.7	3.01E-03	7.40E-01	6.97E-03	0.175	0.051	0.105	0.022	-0.024	189 (70%)	70.5 (58%)	0.50 (14%)	0.44 (24%)	0.47 (6%)	0.13 (13%)	Encodes protein that localizes in membrane	NA
rs254778	MEF2C	-4.671	2.00E-04	9.50E-02	2.02E-04	0.291	0.104	0.174	0.075	-0.245	159 (63%)	83.2 (64%)	-	-	-	-	Encodes for a trans-cription factor. Involved in myogenesis and vascular development (22)	severe psychomotor retardation
rs4799358	NOL4	-4.724	1.39E-04	9.22E-02	1.31E-04	NaN	NaN	NaN	NaN	-0.144	109 (48%)	42.9 (38%)	0.53 (14%)	-0.49 (24%)	0.74 (46%)	0.17 (26%)	Encodes for RNA binding nucleolar protein	Major depressive disorder, and cervical cancer
rs11190855	NRG3	3.551	2.24E-03	5.36E-01	2.51E-03	0.277	0.092	0.160	0.065	-0.506	345 (89%)	153.1 (85%)	0.90 (36%)	0.69 (53%)	0.74 (46%)	0.14 (17%)	Encodes ligands for the transmembrane tyrosine kinase receptors	Schizophrenia, Hirschsprung's disease
rs4971695	NRXN1	4.429	4.06E-04	1.08E-01	4.00E-04	0.313	0.093	0.185	0.077	-0.745	96 (43%)	33.5 (30%)	0.76 (26%)	-0.31 (0%)	0.95 (95%)	0.17 (28%)	Encodes proteins which works in the central nervous system (23)	Schizophrenia, autism, and intellectual disability
rs1153877	PCCB	-4.767	4.55E-05	7.81E-02	7.94E-05	NaN	NaN	NaN	NaN	-0.15	605 (97%)	241.7 (94%)	0.60 (17%)	-2.94 (98%)	-3.09 (99%)	0.18 (29%)	Encodes protein	Propionic acidemia type II, encephalopathy
rs1345154	PPP2R3A	-3.986	5.91E-04	1.52E-01	6.36E-04	NaN	NaN	NaN	NaN	-0.186	46 (20%)	33.3 (30%)	-	-	-	-	Codes one of the regulatory subunits of the protein phosphatase, calcium ion binding	NA
rs10400055	SORCS3	3.757	2.52E-03	6.41E-01	3.94E-03	NaN	NaN	0.162	0.068	-0.557	514 (95%)	211.0 (92%)	-	-	-	-	Encodes a vacuolar protein expressed in the central nervous system involved in neuropeptide signaling pathway	Alzheimer's disease
rs1878874	SOX2OT	NaN	2.00E-05	4.96E-02	1.19E-04	0.112	0.011	0.079	0.004	-1.533	96 (43%)	33.7 (30%)	-	-	-	-	Long non-coding RNA expressed in zones of neurogenesis (24)	Anopthalmia
rs10492904	TK2	NaN	2.97E-03	7.40E-01	6.97E-03	0.111	0.010	0.078	0.004	-1.106	240 (79%)	77.0 (61%)	0.14 (3%)	-0.60 (36%)	0.74 (45%)	0.05 (0%)	Encodes a kinase and is required for mitochon-drial DNA synthesis	Mitochondrial DNA depletion syndrome
rs2196806	VRK2	4.252	7.62E-04	1.97E-01	8.04E-04	NaN	NaN	0.224	0.120	-0.006	292 (85%)	128.3 (80%)	0.89 (35%)	-1.23 (76%)	-1.23 (77%)	0.17 (28%)	Encodes a protein that acts as an effector of signaling pathways, regulating apoptosis and tumor cell growth	Schizophrenia/Bi polar disorder
rs7556184	XPR1	3.645	1.70E-03	4.33E-01	1.76E-03	0.258	0.081	0.146	0.050	-0.075	126 (54%)	73.2 (59%)	-	-	-	-	Encodes protein involved in transmem-brane signaling receptor activity and G-protein coupled receptor activity.	NA
rs7856690	ZCCHC7	NaN	1.84E-04	9.50E-02	2.02E-04	0.111	0.010	0.078	0.004	-0.601	254 (80%)	139.4 (82%)	-	-	-	-	Encodes for a zinc finger protein involved in nucleic acid binding (25)	Autoimmune disorders
rs11888068	ZNF804A	-4.137	4.44E-04	1.08E-01	4.00E-04	NaN	NaN	NaN	NaN	-0.467	131 (56%)	56.5 (49%)	0.72 (23%)	-0.47 (21%)	-0.56 (15%)	0.13 (12%)	Encodes for a zinc finger protein	Schizophrenia/ Bipolar disorder

Given are: genes in association, based on their proximity to the SNP; human (non ancestral) allele z-score (HAZ); SNP association *p*-value, SNP false discovery rate (FDR), SNP conditional false discovery rate (condFDR), Neanderthal selective sweep (NSS) score, linkage disequilibrium (LD) count, i.e. number of 1000G SNPs within 1 Mb and with an LD $r^2 \geq 0.2$ (in parentheses, percentage of SNPs with LD count below that); total LD, i.e. sum of the LD r^2 with the aforesaid 1000G SNPs (in parentheses, percentage of SNPs with total LD below that); ancestral allele frequency; phyloP44wayPrimate acceleration/conservation score from the UCSC genome browser (in parentheses, percentage of SNPs with absolute score below that); phyloP44wayPlacMammal acceleration/conservation score from the UCSC genome browser (in parentheses, percentage of SNPs with absolute score below that); heterozygosity (in parentheses, percentage of SNPs with heterozygosity below that); known functions and phenotypes associated with the variant.

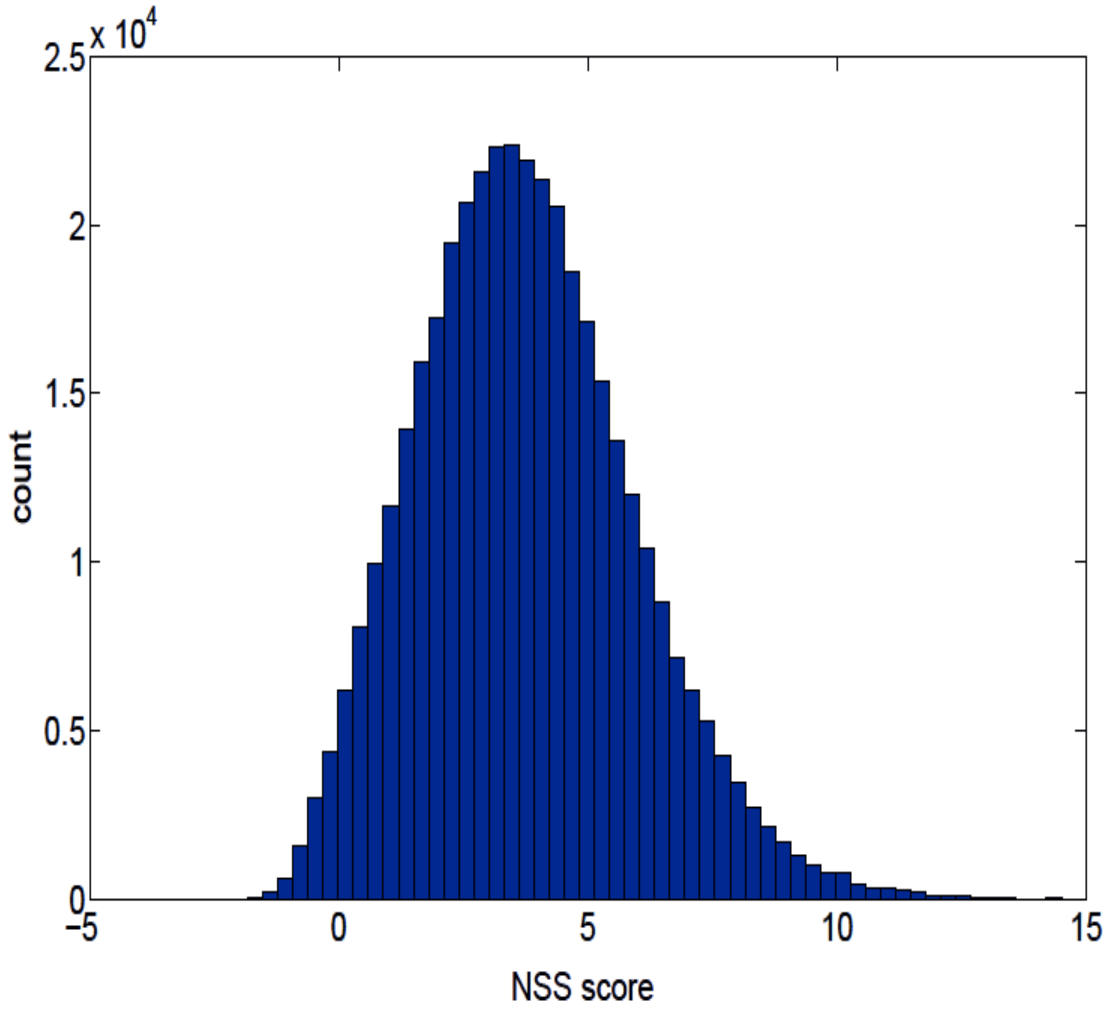

Fig. S1. Distribution of Neanderthal selective sweep scores. The Neanderthal selective sweep (NSS) score track was downloaded from the UCSC genome browser (S-scores, track ntSssZScorePMVar, http://genome.ucsc.edu). This track consists of two entries per SNP, which the authors call (z score + variance) and (z score – variance). Since a negative NSS-score is expected to indicate a possible positive selection in humans, the (z-score + variance) entries are conservative measures of positive selection likelihood. These were extracted for all SNPs in the genome-wide association studies of interest (**Table S1**) and follow the distribution illustrated here.

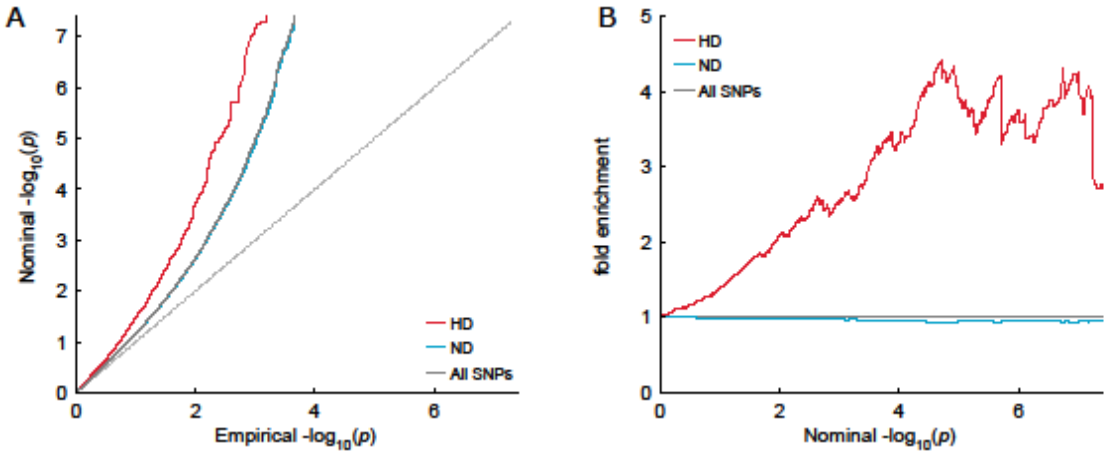

Fig. S2. Q-Q and fold enrichment plots of schizophrenia stratified according to Neanderthal selective sweep score after exclusion of MHC SNPs. Reported are (**A**) quantile-quantile (Q-Q) and (**B**) fold enrichment plots of GWAS summary statistics *p*-values for schizophrenia, stratified on the basis of Neanderthal selective sweep scores after removing SNPs in the major histocompatibility complex (MHC) from the analysis. The enrichment of the human divergent (HD) category, represented by its deflection from the diagonal (**A**), is still clear, suggesting that the MHC does not have a great effect on the enrichment of HD SNPs (**Fig. 1**). The non-divergent (ND) SNPs also show unchanged deflection from the baseline (**B**; All SNPs). This suggests that there is no relevant overlap among MHC SNPs and the SCZ susceptibility SNPs in human divergent regions.

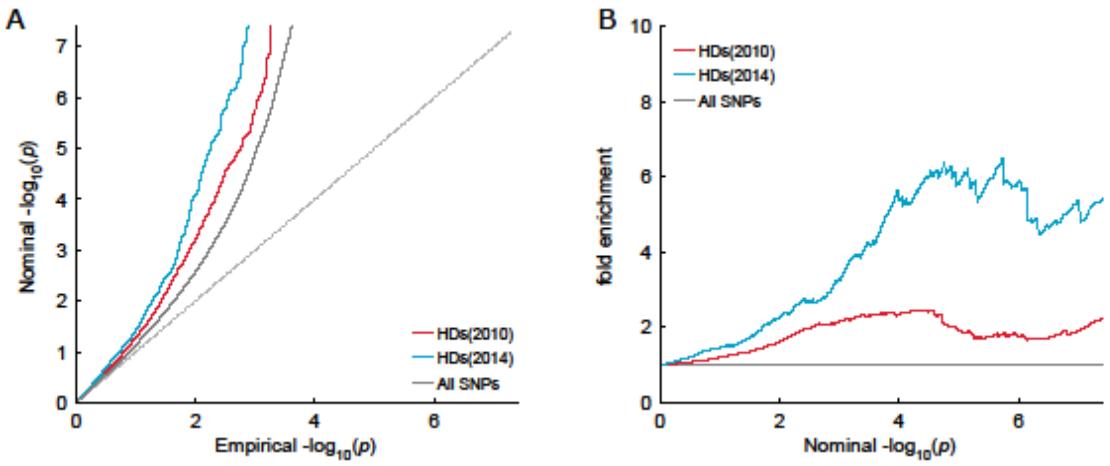

Fig. S3. Q-Q and fold enrichment plots of schizophrenia stratified according to Neanderthal selective sweep region affiliation scores after Green *et al.* (26) and Prüfer *et al.* (27). Reported are (**A**) quantile-quantile (Q-Q) and (**B**) fold enrichment plots of genome-wide association study summary statistics *p*-values for schizophrenia, stratified based on Neanderthal selective sweep scores (NSS). The strata are determined here by LD-informed annotation scores for DNA regions significantly (top 5%) likely to have undergone recent positive selection in humans. The DNA regions were identified using respectively the draft sequence of the Neanderthal genome (HDs2010) by Green *et al.* 2010 (26) and the complete sequence of the Neanderthal genome (HDs2014) by Prüfer *et al.* 2014 (27). The enrichment plot (**B**) shows 2-7 fold enrichment for SNPs in regions with significantly negative NSS score, i.e. the human divergent (HD) SNPs stratum, compared with all SNPs (All SNPs).

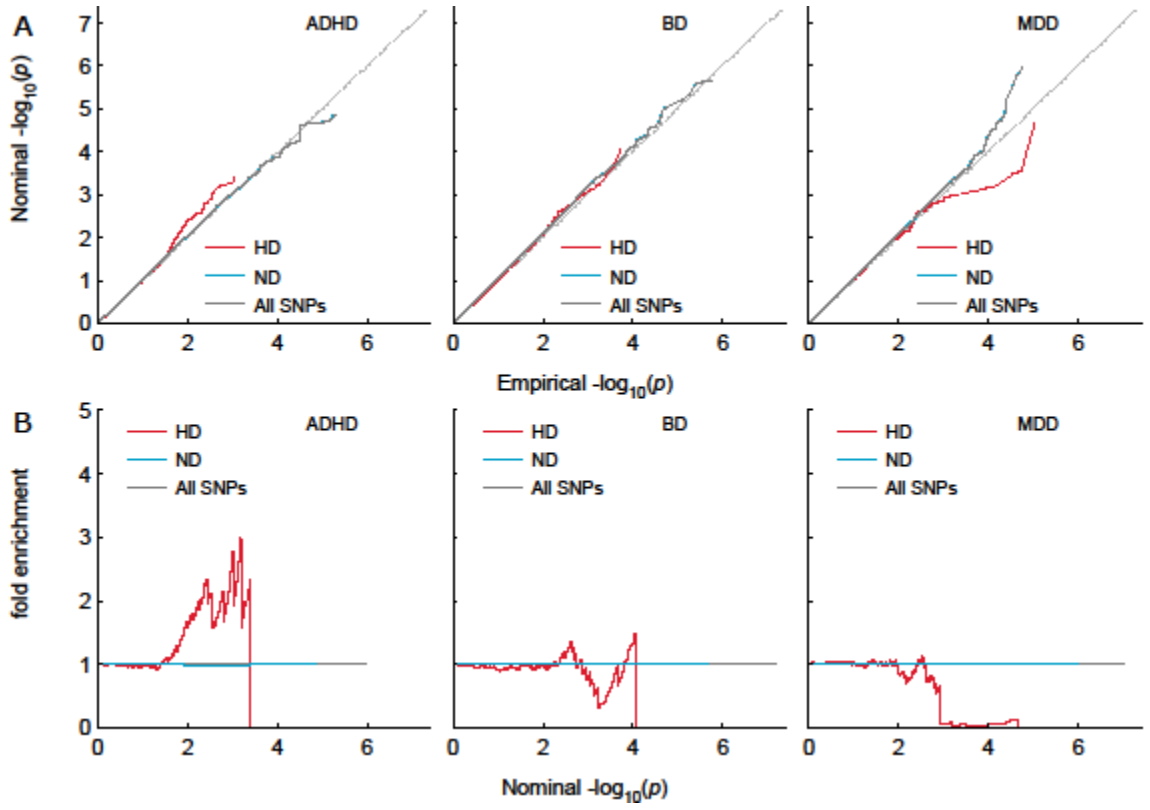

Fig. S4. Q-Q and fold enrichment plots of three psychiatric phenotypes stratified according to Neanderthal selective sweep scores. Phenotypes: attention-deficit/hyperactivity disorder (ADHD), bipolar disorder (BD) and major depressive disorder (MDD). (**A**) The quantile-quantile (Q-Q) plots show genome-wide association studies summary statistics *p*-values of SNPs tagging human divergent regions (HD), non-divergent (ND) regions as well as all SNPs (All SNPs). As observed for non-psychiatric phenotypes (**Fig. 2**), there is no indication of enrichment the likes of that seen for schizophrenia in (**Fig. 1**). (**B**) The fold enrichment counterparts of the Q-Q plots in (**A**) emphasize the association enrichment. ADHD in particular does present some deflection but the number of SNPs involved is too exiguous to result in any significant association as measured by the regression analysis (**Table S2**).

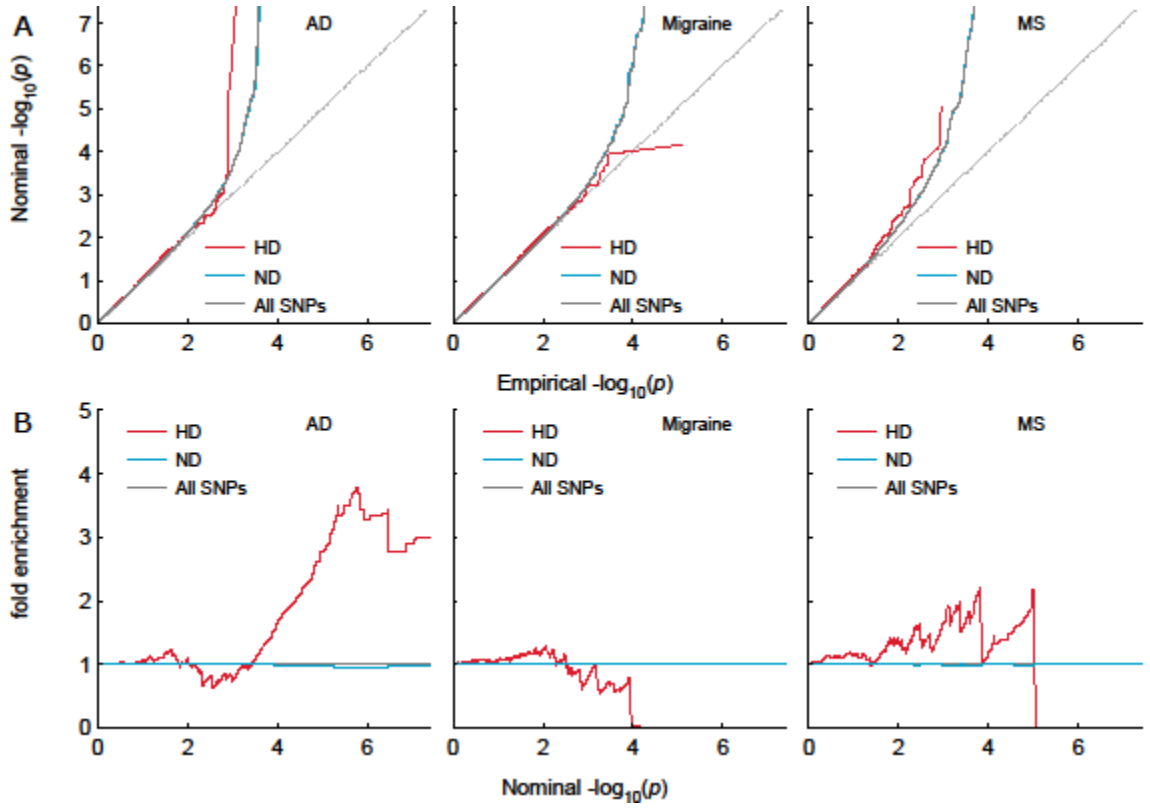

Fig. S5. Q-Q and fold enrichment plots of three neurological phenotypes stratified according to Neanderthal selective sweep scores. Phenotypes: Alzheimer's disease (AD), migraine and multiple sclerosis (MS). (**A**) The quantile-quantile (Q-Q) plots show genome-wide association studies summary statistics *p*-values of SNPs tagging human divergent regions (HD), non-divergent (ND) regions as well as all SNPs (All SNPs). As observed for other phenotypes (**Fig. 2**), there is no indication of enrichment the likes of that seen for schizophrenia in (**Fig. 1**). (**B**) The fold enrichment counterparts of the Q-Q plots in (**A**) emphasize the association enrichment or rather the lack thereof.

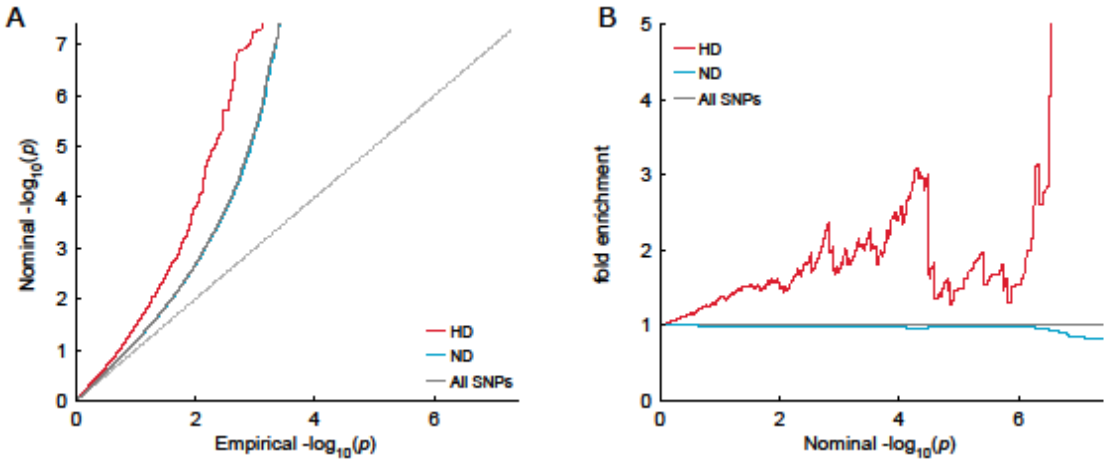

Fig. S6. Q-Q and fold enrichment plots of the first edition of the schizophrenia genome-wide association study by the Psychiatric Genomic Consortium stratified according to Neanderthal selective sweep scores. Reported are (**A**) quantile-quantile (Q-Q) and (**B**) fold enrichment plots of first edition of the Psychiatric Genomic Consortium (PGC) schizophrenia genome-wide association studies. The enrichment is not as strong as seen with the larger second edition of the PGC schizophrenia GWAS (**Fig. 1**) but is confirmed by a nominally significant association between squared z-scores and Neanderthal selective sweep scores (**Table 1**).

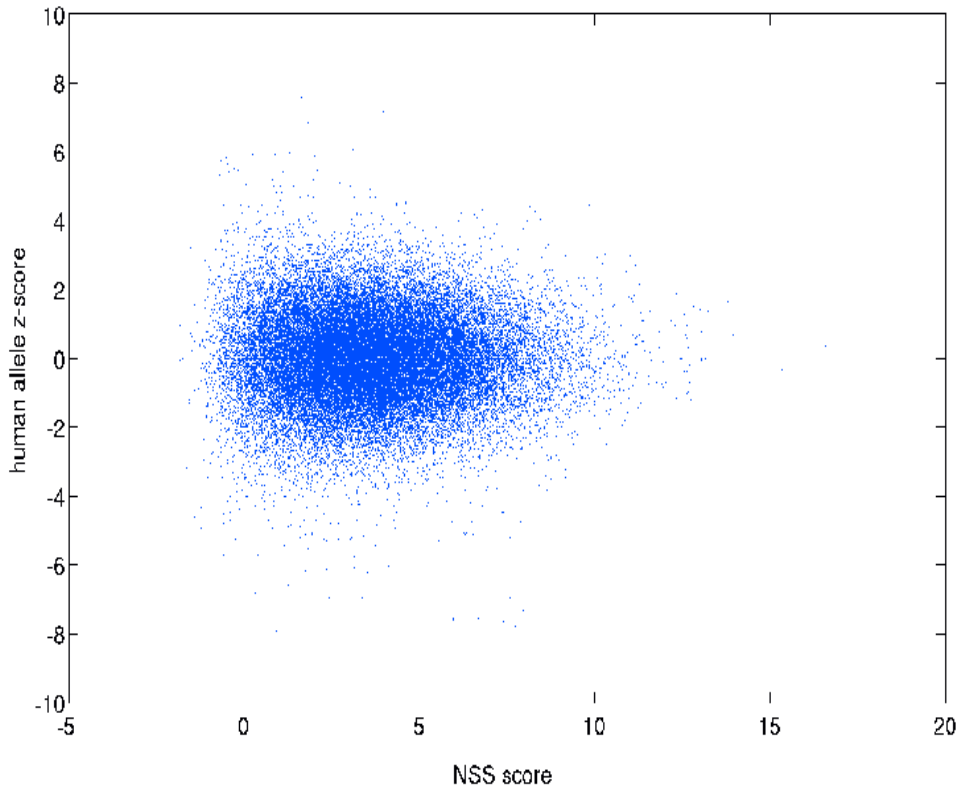

Fig. S7. Direction of effect for human allele z-score versus Neanderthal selective sweep score. No obvious directional preponderance can be discerned in the correlation between Neanderthal selective sweep score (NSS) and effect of the non-ancestral allele on schizophrenia. A linear regression of z scores versus NSS scores does not yield any significant results.

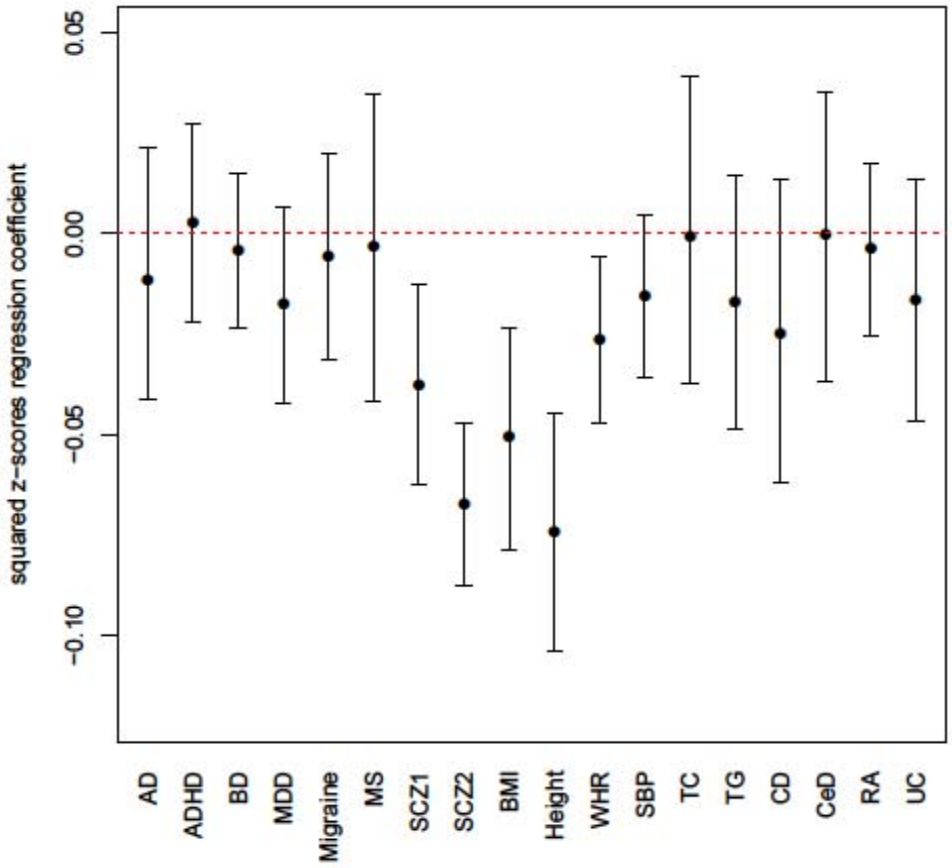

Fig. S8. Effect size comparison. Squared z-scores logarithm Neanderthal selective sweep score regression coefficients (mean ± SE) for phenotypes: psychiatric and other neurological diseases (Alzheimer's disease (AD), attention-deficit/hyperactivity disorder (ADHD), bipolar disorder (BD), major depressive disorder (MDD), migraine, multiple sclerosis (MS), first and second edition of the schizophrenia GWAS by the Psychiatric Genomic Consortium (SCZ1 and SCZ2)), body mass index (BMI), height, waist-hip ratio (WHR), systolic blood pressure (SBP), total cholesterol (TC), triglycerides (TG), Crohn's disease (CD), celiac disease (CeD), rheumatoid arthritis (RA), ulcerative colitis (UC). For sample sizes in the respective genome-wide association studies, see **Table S1**.

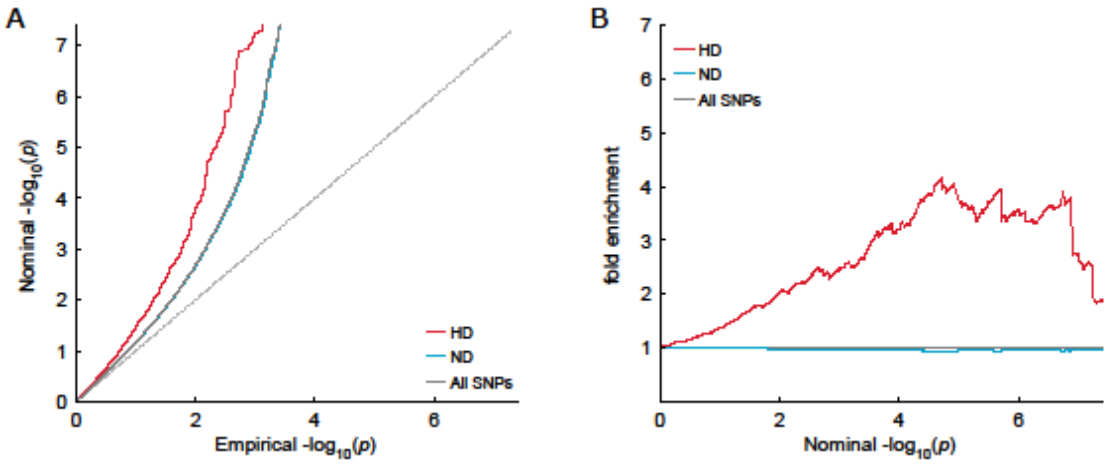

Fig. S9. Q-Q and fold enrichment plots of schizophrenia autosome and X chromosome genome-wide association study stratified according to Neanderthal selective sweep score. Reported are (**A**) quantile-quantile (Q-Q) and (**B**) fold enrichment plots of autosome and X chromosome GWAS summary statistics *p*-values for schizophrenia, stratified based on Neanderthal selective sweep score. The enrichment of the human divergent (HD) category, represented by its deflection from the diagonal (**A**), is still clear and we do not see comparable differences from the analysis devoid of the X chromosome (**Fig. 1**). The non-divergent (ND) SNPs also show unchanged deflection from the baseline (All SNPs).

Supplemental Methods & Materials

Confounding Factors

Possible confounding factors that might influence the results are addressed in the analyses: the effect size computed in the regression analysis typical of most SNP association studies depends on the SNP's frequency *f* through its genotypic variance *2f (1-f)*. A SNP's frequency or its genotypic variance can therefore constitute confounders if other factors, e.g. the covariates, used in the enrichment analysis are correlated with them. It is possible that SNPs that underwent positive selection after divergence from Neanderthal have unusual frequency distributions. All analyses are therefore carried out while controlling for genotypic variance. The chromosomal linkage disequilibrium (LD) structure is another feature that undergoes differential amounts of transformations depending on the type of selection pressure and is therefore controlled for in the analyses as well.

Major Histocompatibility Complex (MHC)

The MHC has been implicated in schizophrenia as well as a number of other phenotypes, particularly immune-mediated diseases. The evolution of MHC itself may have involved segmental duplication and other large scale genetic variations (28). It is therefore reasonable to suspect that SNPs in these regions might be driving some of the enrichment results. By removing the MHC region (chromosome 6 region between genomic positions 25652429 and 33421466 in the hg19 assembly) from the analyses, we aim at identifying their contribution to the enrichment patterns.

Replication

The z-scores of each of the 52 original sub-studies contributing to the schizophrenia meta-analysis (8) were independently adjusted using intergenic inflation control: the inflation factor, λ_{GC}, was estimated as the median squared z-score across intergenic SNPs divided by the expected median of a chi-square distribution with one degree of freedom. The 52 sub-studies were then subdivided into two groups of 26 in 50 different ways, the first group, D_k, $k = 1\ldots100$, serving as discovery group, the second, R_k, $k = 1\ldots100$, as replication group. Average discovery and replication z-scores were computed for all SNPs and all 50 subdivisions

$$\overline{Z}_{D_k} = \frac{1}{\sqrt{N_{\text{eff}}^{D_k}}} \sum_{i \in D_k} Z_i \sqrt{N_{\text{eff}}^{(i)}}, \quad \overline{Z}_{R_k} = \frac{1}{\sqrt{N_{\text{eff}}^{R_k}}} \sum_{i \in R_k} Z_i \sqrt{N_{\text{eff}}^{(i)}}, \quad \text{with } D_k, R_k \subset \{1,\ldots,8\}, \text{ and } k = 1,\ldots,50$$

where

$$N_{\text{eff}}^{(i)} = \frac{N_{\text{cases}}^{(i)} N_{\text{controls}}^{(i)}}{N_{\text{cases}}^{(i)} + N_{\text{controls}}^{(i)}}, \quad \text{and } N_{\text{eff}}^{R_k} = \sum_{i \in R_k} N_{\text{eff}}^{(i)}, \; N_{\text{eff}}^{D_k} = \sum_{i \in D_k} N_{\text{eff}}^{(i)}.$$

The average Z-scores were converted to *p*-values using the standard normal cumulative distribution function Φ. Two-tailed discovery *p*-values were calculated as $p_D = 1\text{-}\Phi(|Z_D|) + \Phi(-|Z_D|) = 2*\Phi(-|Z_D|)$, one-tailed replication *p*-values preserving the signs of the discovery Z-scores were calculated as $p_R = \Phi(\text{sgn}(Z_D) * Z_R)$.

Conditional False Discovery Rate (condFDR)

The observed enrichment can be directly interpreted in terms of the Bayesian FDR (29). Specifically, for a given *p*-value cutoff, the FDR is defined as

$$\text{FDR}(p) = \pi_0 F_0(p)/F(p),$$

where π_0 is the proportion of null SNPs, F_0 is the null cumulative distribution function (cdf), and F is the cdf of all SNPs, both null and non-null. Under the null hypothesis, $F_0(p) = p$ is the cdf of the uniform distribution on the unit interval [0,1], so

$$\mathrm{FDR}(p) = \pi_0 p / F(p).$$

F is estimated by the empirical cdf $q = N_p/N$, where N_p is the number of SNPs with p-values less than or equal to p, and N is the total number of SNPs. If π_0 is close to one, as is likely true for most GWASs, a reasonable conservative estimate of FDR is p/q. The negative decadic logarithm of this FDR estimate is $\log10(q) - \log10(p)$ which coincides with the Q-Q plot's deflection from the null line.

The condFDR is conservatively estimated as $\mathrm{FDR}(p \mid x) = p / F(p \mid x)$, where x is the value of a given annotation X, and $F(p \mid x)$ is the cdf of p conditional on the annotation $X = x$. If SNPs are enriched for associations according to levels of X, then $F(p \mid x) > F(p)$ for a given p and hence $\mathrm{FDR}(p \mid x) < \mathrm{FDR}(p)$.

Upon binning and averaging the conditional FDR values obtained from ten sets of LD-blocks representative SNPs, we constructed a two-dimensional look-up table reporting conditional FDR as a function of the SCZ association p-value and the NSS score. Through smoothing via interpolation of the look-up table, we then assigned each SNP a conditional FDR value for SCZ (denoted by condFDR).

Censored Analysis

Many of the 108 schizophrenia GWAS hits lie within or around genes that are involved in the biochemistry of neural cells. The genome regions that have undergone a selective sweep according to the NSS score have also been shown to contain genes involved with brain functions.

(26). Affiliation to the brain genes that populate the 108 loci may therefore be confounding the results we observe for the enrichment of NSS regions of the genome. We wanted to see to what extent the results are driven by the 108 schizophrenia GWAS hits. To this end, we repeated the analyses after censoring the GWAS summary stats. Specifically, we excluded from the analyses all SNPs falling less than 1Mbase from any of the reported loci and having an LD ($r^2 > 0.2$) with any of the SNPs therein.

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Supplemental References

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2. Neale BM, Medland SE, Ripke S, Asherson P, Franke B, Lesch KP, *et al.* (2010): Meta-Analysis of Genome-Wide Association Studies of Attention-Deficit/Hyperactivity Disorder. *J Am Acad Child Adolesc Psychiatry*. 49:884-897.

3. Psychiatric GCBDWG (2011): Large-Scale Genome-Wide Association Analysis of Bipolar Disorder Identifies a New Susceptibility Locus near Odz4. *Nat Genet*. 43:977-983.

4. Ripke S, Wray NR, Lewis CM, Hamilton SP, Weissman MM, Breen G, *et al.* (2013): A Mega-Analysis of Genome-Wide Association Studies for Major Depressive Disorder. *Mol Psychiatry*. 18:497-511.

5. Anttila V, Winsvold BS, Gormley P, Kurth T, Bettella F, McMahon G, *et al.* (2013): Genome-Wide Meta-Analysis Identifies New Susceptibility Loci for Migraine. *Nat Genet*. 45:912-917.

6. Sawcer S, Hellenthal G, Pirinen M, Spencer CC, Patsopoulos NA, Moutsianas L, *et al.* (2011): Genetic Risk and a Primary Role for Cell-Mediated Immune Mechanisms in Multiple Sclerosis. *Nature*. 476:214-219.

7. Ripke S, O'Dushlaine C, Chambert K, Moran JL, Kahler AK, Akterin S, *et al.* (2013): Genome-Wide Association Analysis Identifies 13 New Risk Loci for Schizophrenia. *Nat Genet*. 45:1150-1159.

8. Schizophrenia Working Group of the Psychiatric Genomics C (2014): Biological Insights from 108 Schizophrenia-Associated Genetic Loci. *Nature*. 511:421-427.

9. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, *et al.* (2010): Association Analyses of 249,796 Individuals Reveal 18 New Loci Associated with Body Mass Index. *Nat Genet*. 42:937-948.

10. Lango Allen H, Estrada K, Lettre G, Berndt SI, Weedon MN, Rivadeneira F, *et al.* (2010): Hundreds of Variants Clustered in Genomic Loci and Biological Pathways Affect Human Height. *Nature*. 467:832-838.

11. Heid IM, Jackson AU, Randall JC, Winkler TW, Qi L, Steinthorsdottir V, *et al.* (2010): Meta-Analysis Identifies 13 New Loci Associated with Waist-Hip Ratio and Reveals Sexual Dimorphism in the Genetic Basis of Fat Distribution. *Nat Genet*. 42:949-960.

12. Ehret GB, Munroe PB, Rice KM, Bochud M, Johnson AD, Chasman DI, *et al.* (2011): Genetic Variants in Novel Pathways Influence Blood Pressure and Cardiovascular Disease Risk. *Nature*. 478:103-109.

13. Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, *et al.* (2010): Biological, Clinical and Population Relevance of 95 Loci for Blood Lipids. *Nature*. 466:707-713.

14. Franke A, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, *et al.* (2010): Genome-Wide Meta-Analysis Increases to 71 the Number of Confirmed Crohn's Disease Susceptibility Loci. *Nat Genet*. 42:1118-1125.

15. Dubois PC, Trynka G, Franke L, Hunt KA, Romanos J, Curtotti A, *et al.* (2010): Multiple Common Variants for Celiac Disease Influencing Immune Gene Expression. *Nat Genet*. 42:295-302.

16. Stahl EA, Raychaudhuri S, Remmers EF, Xie G, Eyre S, Thomson BP, *et al.* (2010): Genome-Wide Association Study Meta-Analysis Identifies Seven New Rheumatoid Arthritis Risk Loci. *Nat Genet*. 42:508-514.

17. Anderson CA, Boucher G, Lees CW, Franke A, D'Amato M, Taylor KD, *et al.* (2011): Meta-Analysis Identifies 29 Additional Ulcerative Colitis Risk Loci, Increasing the Number of Confirmed Associations to 47. *Nat Genet*. 43:246-252.

18. Grabner CP, Price SD, Lysakowski A, Cahill AL, Fox AP (2006): Regulation of Large Dense-Core Vesicle Volume and Neurotransmitter Content Mediated by Adaptor Protein 3. *Proc Natl Acad Sci U S A*. 103:10035-10040.

19. Weinberg MS, Barichievy S, Schaffer L, Han J, Morris KV (2007): An Rna Targeted to the Hiv-1 Ltr Promoter Modulates Indiscriminate Off-Target Gene Activation. *Nucleic Acids Res*. 35:7303-7312.

20. Guarguaglini G, Duncan PI, Stierhof YD, Holmström T, Duensing S, Nigg EA (2005): The Forkhead-Associated Domain Protein Cep170 Interacts with Polo-Like Kinase 1 and Serves as a Marker for Mature Centrioles. *Mol Biol Cell*. 16:1095-1107.

21. Girirajan S, Dennis Megan Y, Baker C, Malig M, Coe Bradley P, Campbell Catarina D, *et al.* (2013): Refinement and Discovery of New Hotspots of Copy-Number Variation Associated with Autism Spectrum Disorder. *Am J Hum Genet*. 92:221-237.

22. Nowakowska BA, Obersztyn E, Szymanska K, Bekiesinska-Figatowska M, Xia Z, Ricks CB, *et al.* (2010): Severe Mental Retardation, Seizures, and Hypotonia Due to Deletions of Mef2c. *Am J Med Genet B Neuropsychiatr Genet*. 153b:1042-1051.

23. Duong L, Klitten LL, Moller RS, Ingason A, Jakobsen KD, Skjodt C, *et al.* (2012): Mutations in Nrxn1 in a Family Multiply Affected with Brain Disorders: Nrxn1 Mutations and Brain Disorders. *Am J Med Genet B Neuropsychiatr Genet*. 159b:354-358.

24. Amaral PP, Neyt C, Wilkins SJ, Askarian-Amiri ME, Sunkin SM, Perkins AC, *et al.* (2009): Complex Architecture and Regulated Expression of the Sox2ot Locus During Vertebrate Development. *RNA*. 15:2013-2027.

25. Sartoris S, Brendolan A, Degola A, Testi MG, Chignola R, Scarpa A, *et al.* (2000): Analysis of Ciita Encoding Air-1 Gene Promoters in Insulin-Dependent Diabetes Mellitus and Rheumatoid Arthritis Patients from the Northeast of Italy: Absence of Sequence Variability. *Hum Immunol*. 61:599-604.

26. Green RE, Krause J, Briggs AW, Maricic T, Stenzel U, Kircher M, *et al.* (2010): A Draft Sequence of the Neandertal Genome. *Science*. 328:710-722.

27. Prufer K, Racimo F, Patterson N, Jay F, Sankararaman S, Sawyer S, *et al.* (2014): The Complete Genome Sequence of a Neanderthal from the Altai Mountains. *Nature*. 505:43-49.

28. Kulski JK, Gaudieri S, Bellgard M, Balmer L, Giles K, Inoko H, *et al.* (1997): The Evolution of Mhc Diversity by Segmental Duplication and Transposition of Retroelements. *J Mol Evol*. 45:599-609.

29. Storey JD (2003): The Positive False Discovery Rate: A Bayesian Interpretation and the Q-Value. *Ann Stat*. 31:2013-2035.