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IMMEDIATE COMMUNICATION

Convergent functional genomics of schizophrenia: from comprehensive understanding to genetic risk prediction

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We have used a translational convergent functional genomics (CFG) approach to identify and prioritize genes involved in schizophrenia, by gene-level integration of genome-wide association study data with other genetic and gene expression studies in humans and animal models. Using this polyevidence scoring and pathway analyses, we identify top genes (DISC1, TCF4, MBP, MOBP, NCAM1, NRCAM, NDUFV2, RAB18, as well as ADCYAP1, BDNF, CNR1, COMT, DRD2, DTNBP1, GAD1, GRIA1, GRIN2B, HTR2A, NRG1, RELN, SNAP-25, TNIK), brain development, myelination, cell adhesion, glutamate receptor signaling, G-protein–coupled receptor signaling and cAMP-mediated signaling as key to pathophysiology and as targets for therapeutic intervention. Overall, the data are consistent with a model of disrupted connectivity in schizophrenia, resulting from the effects of neurodevelopmental environmental stress on a background of genetic vulnerability. In addition, we show how the top candidate genes identified by CFG can be used to generate a genetic risk prediction score (GRPS) to aid schizophrenia diagnostics, with predictive ability in independent cohorts. The GRPS also differentiates classic age of onset schizophrenia from early onset and late-onset disease. We also show, in three independent cohorts, two European American and one African American, increasing overlap, reproducibility and consistency of findings from single-nucleotide polymorphisms to genes, then genes prioritized by CFG, and ultimately at the level of biological pathways and mechanisms. Finally, we compared our top candidate genes for schizophrenia from this analysis with top candidate genes for bipolar disorder and anxiety disorders from previous CFG analyses conducted by us, as well as findings from the fields of autism and Alzheimer. Overall, our work maps the genomic and biological landscape for schizophrenia, providing leads towards a better understanding of illness, diagnostics and therapeutics. It also reveals the significant genetic overlap with other major psychiatric disorder domains, suggesting the need for improved nosology.

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INTRODUCTION

'Things fall apart; the center cannot hold'

– WB Yeats, The Second Coming

Schizophrenia is a devastating disorder affecting ~1% of the population. While there is clear evidence for roles for both genes and environment, a comprehensive biological understanding of the disorder has been elusive so far. Most notably, there has been until recently a lack of concerted integration across functional and genetic studies, and across human and animal model studies, resulting in missed opportunities to see the whole picture.

As part of a translational convergent functional genomics (CFG) approach, developed by us over the last decade,[1–5] and expanding upon our earlier work on identifying genes for schizophrenia[6] and biomarkers for psychosis,[7] we set out to comprehensively identify candidate genes, pathways and mechanisms for schizophrenia, integrating the available evidence in the field to date. We have used data from published genome-wide association studies (GWAS) data sets for schizophrenia.[8,9] We integrated those data with gene expression data—human postmortem brain gene expression data, human induced pluripotent stem cell-derived neuronal cells[10] and human blood gene expression data[7] published by others and us, as well as with relevant animal model brain and blood gene expression data generated by our group[6] and others. In addition, we have integrated as part of this comprehensive approach other genetic data—human genetic data (linkage, copy number variant (CNV) or association) for schizophrenia, as well as relevant mouse model genetic evidence (Figure 1, Table 1 and Figure 2). Animal model data provide sensitivity of detection, and human data provide specificity for the illness. Together, they help to identify and prioritize candidate genes for the illness, using a polyevidence CFG score, resulting in essence in a de facto field-wide integration putting together the

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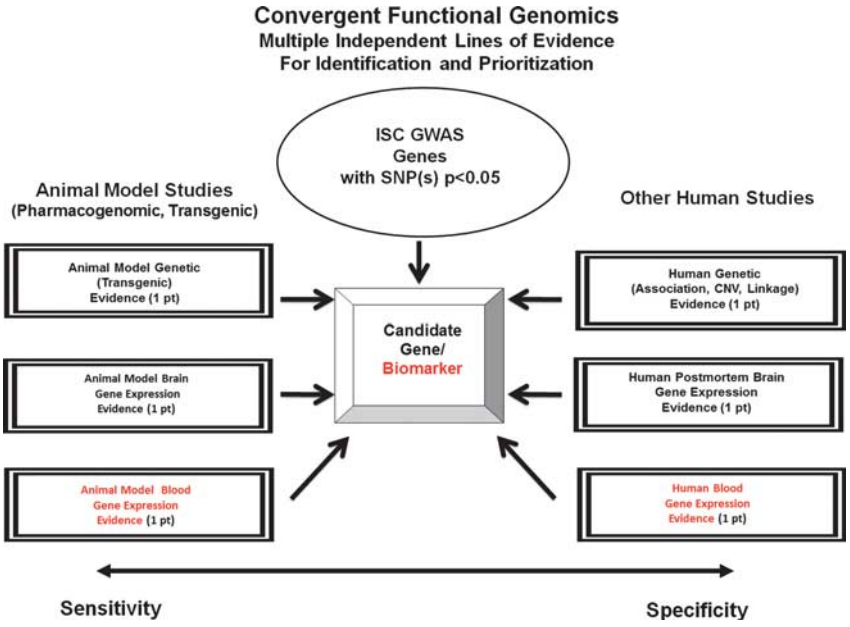


Figure 1. Convergent functional genomics. GWAS, genome-wide association study; ISC, International Schizophrenia Consortium; SNP, single-nucleotide polymorphism.

best available evidence to date. Once that is done, biological pathway analyses can be conducted and mechanistic models can be constructed (Figure 3).

An obvious next step is developing a way of applying that knowledge to genetic testing of individuals to determine risk for the disorder. On the basis of our comprehensive identification of top candidate genes described in this paper, we have chosen the nominally significant single-nucleotide polymorphisms (SNPs) inside those genes in the GWAS data set used for discovery (International Schizophrenia Consortium, ISC), and assembled a genetic risk prediction (GRP) panel out of those SNPs. We then developed a genetic risk prediction score (GRPS) for schizophrenia based on the presence or absence of the alleles of the SNPs associated with the illness in ISC, and tested the GRPS in independent cohorts (GAIN European Americans (EA), GAIN African Americans (AA), nonGAIN EA, nonGAIN AA)[9] for which we had both genotypic and clinical data available, comparing the schizophrenia subjects to normal controls. Our results show that a panel of SNPs in top genes identified and prioritized by CFG analysis can differentiate between schizophrenia subjects and controls at a population level, although at an individual level the margin is minimal. The latter point suggests that, like for bipolar disorder,[11] the contextual cumulative combinatorics of common variants and environment[12] plays a major role in risk for illness. Moreover, the genetic risk component identified by us seems to be stronger for classic age at onset schizophrenia than for early onset and late-onset schizophrenia, suggesting that those subtypes may be different, either in having a larger environmental component or having a different genetic component.

We have also looked at genetic heterogeneity, overlap and reproducibility between independent GWAS for schizophrenia. We show that the overlap is minimal at a nominal *P*-value SNP level, but increases dramatically at a gene level, then at a CFG-prioritized gene level and finally at a pathway level. CFG provides a fit-to-disease prioritization of genes that leads to generalizability in independent cohorts, and counterbalances the fit-to-cohort prioritization inherent in classic SNP level genetic-only approaches, which have been plagued by poor reproducibility across cohorts. Finally, we have looked at overlap with candidate genes for other psychiatric disorders (bipolar disorder, anxiety disorders), as well as with other disorders affecting cognition (autism, Alzheimer disease (AD)), and provide evidence for shared genes.

Overall, this work sheds comprehensive light on the genetic architecture and pathophysiology of schizophrenia, provides mechanistic targets for therapeutic intervention and has implications for genetic testing to assess risk for illness before the illness manifests itself clinically.

MATERIALS AND METHODS

Genome-wide association studies data for schizophrenia

The GWAS data from the ISC was used for the discovery CFG work.[8] This cohort consists of EA subjects (3322 schizophrenics and 3587 controls). SNPs with a nominal allelic *P*-value <0.05 were selected for our analysis. No Bonferroni correction was performed.

Four independent cohorts,[9] two EA (GAIN EA 1170 schizophrenics and 1378 controls; nonGAIN EA 1149 schizophrenics and 1347 controls) and two AA (GAIN AA 915 schizophrenics and 949 controls; nonGAIN AA 78 schizophrenics and 20 controls), were used for testing the results of the discovery analyses. The GWAS GAIN and nonGAIN data used for analyses described in this paper were obtained from the database of Genotype and Phenotype (dbGaP) found at www.ncbi.nlm.nih.gov.

The software package PLINK (http://pngu.mgh.harvard.edu/~purcell) was used to extract individual genotype information for each subject from the GAIN GWAS data files. We analyzed EA, and separately, AA, schizophrenia subjects and controls.

Gene identification

To identify the genes that correspond to the selected SNPs, the lists of SNPs from the GWAS were uploaded to NetAFFX (Affymetrix, Santa Clara, CA, USA; http://www.affymetrix.com/analysis/index.affx). We used the Netaffx na32 Genotyping Annotation build. In the cases where a SNP mapped to multiple genes, we selected all the genes. SNPs for which no gene was identified were not included in our subsequent analyses.

Table 1. Top candidate genes for schizophrenia—CFG analysis of ISC GWAS data

Gene Symbol/name	*ISC GWAS best P-value SNP*	*Animal model genetic evidence (TG)*	*Animal model brain gene expression evidence*	*Animal model blood gene expression evidence*[6]	*Human genetic evidence (association CNV or linkage)*	*Human postmortem brain gene expression evidence*	*Human blood/other peripheral tissue gene expression evidence*	*CFG score*	*GAIN-EA GWAS best P-value SNP*	*GAIN-AA GWAS best P-value SNP*
DISC1, disrupted in schizophrenia 1	0.002934, rs10910616	SZ[18,27,78–85]	(I) Antipsychotic treatment,[86] mouse neurodevelopment[87]		1q42.2 (Assoc) SZ[22,67,88–94]	(I) SZ HIP[25]	(I) SZ lymphoblasts,[25] PMBCs[26]	5.0	0.001562, rs12754490	**0.0001308, rs11122318**
HSPA1B, heat-shock 70-kDa protein 1B	**0.0009003, rs2763979**		(D) PCP HIP; (D) CLZ VT[6]	(D) CLZ	6p21.33 (Assoc) SZ[44]	(I) SZ[45]	(I) SZ, IPS-derived neurons[10]	5.0		
MBP, myelin basic protein	0.01002, rs12959006		(I) PCP and CLZ AMY; (D), PCP PFC,[6] (I), SZ,[95] (D) SZ[96]	(I) PCP and CLZ	18q23 (Assoc) SZ[37]	(D) SZ[38]	(D) SZ peripheral blood[97]	5.0	0.01345, rs9967028	0.03257, rs1629089
TCF4, transcription factor 4	**0.0002902, rs17594665**	SZ[98]	(I) PCP NAC[6]		18q21.2 (Assoc) SZ[32–35]	(I) SZ[36]	(I) SZ, IPS-derived neurons;[10] (D) delusions SZ[7]	5.0	0.01039, rs17594665	0.00126, rs1539951
MOBP, myelin-associated oligodendrocyte basic protein	0.003529, rs1708044		(I), PCP and CLZ AMY; (D), CLZ CP; (I), CLZ NAC; (D), PCP PFC; (D), CLZ VT,[6] (I), Psychosis,[99] (I), Response to antipsychotics,[100] (D), SZ[101]	(I) CLZ	3p22.1 (Linkage) SZ[102]	(D), SZ,[38] (I), SZ and substance abuse[103]	(D), SZ lymphocytes[104]	4.5	0.02583, rs1405798	0.004474, rs1538783
NCAM1, neural cell adhesion molecule 1	0.003917, rs11214441	SZ[105]	(I) SZ[95]		11q23.2 (Assoc) SZ[106]	(I) SZ[106,107]	(D) SZ, IPS-derived neurons[10]	4.5	0.002043, rs1245133	0.001454, rs600964
NDUFV2, NADH dehydrogenase (ubiquinon) flavoprotein 2, 24kDa	0.003243, rs8084822		Response to antipsychotics[108]	(D) PCP and CLZ	18p11.22 (Assoc) SZ[109]	(D), SZ Striatum,[110] (I), SZ parito-occipital cortex[1,10] (I), SZ[111]	(I), SZ lymphocytes[110]	4.5	0.004361, rs1893144	**0.0009294, rs10468792**
NRCAM, neuronal cell adhesion molecule	0.006234, rs10250083	SZ[112]	(I) CLZ VT[6]		7q31.1 (Linkage) SZ[113]	(D) SZ[48]	(D) SZ serum[49]	4.5	0.004773, rs404287	0.002343, rs409797
RAB18, RAB18, member RAS oncogene family	0.03817, rs12261690		(I) PCP AMY; (D), PCP PFC; (D) CLZ VT[6]	(I) PCP	10p12.1 (Linkage) SZ[114–118]	(D) SZ[119]	(D) SZ whole blood[120]	4.5	0.01716, rs7476899	0.01231, rs11015796
ADCYAP1, adenylate cyclase-activating polypeptide 1 (pituitary)	0.002876, rs9954574	SZ[121]	(I) CLZ NAC; (D) CLZ VT [6]		18p11.32 (Assoc) SZ[121,122]	(D) SZ[119]		4.0	0.02558, rs1394890	0.005448, rs16953183
ALDH1A1, aldehyde dehydrogenase 1 family, member A1	0.02526, rs11143438		(I) PCP and CLZ AMY; (D), PCP and CLZ NAC,[6] (I) Psychosis[99]	(I) PCP		(D) SZ,[111,123] (I) SZ[124]	(I) SZ, fibroblasts[125]	4.0	0.01389, rs7028573	0.01285, rs11999628
ANK3, ankyrin 3, node of Ranvier (ankyrin G)	0.001727, rs4948256		(D) PCP AMY; (I), PCP CP;v(D), PCP NAC; (I), CLZ VT[6]		10q21.2 (Assoc) SZ[48,126]	(D) SZ[48]	(I), SZ IPS-derived neurons[10]	4.0	0.006456, rs10509133	0.005837, rs7906905
BDNF, brain-derived neurotrophic factor	0.001666, rs10742178		(I) SZ,[127–129] (I) PCP in rats, [130] (I) MK-801 in rats[131]		11p14.1 (Assoc) SZ[132–135]	(D) SZ[136–138]	(D) SZ serum,[49,139–141] (D) leukocytes psychosis[142]	4.0		0.005507, rs2131060
CD9, CD9 molecule	0.0455, rs3181291		(I) PCP AMY; (D), PCP PFC; (I), PCP VT[6]	(I) PCP and CLZ		(D) SZ[143]	(D) SZ IPS-derived neurons[10]	4.0	0.01167, rs2268014	0.04739, rs7342306
CNR1, cannabinoid receptor 1 (brain)	0.002567, rs1324073	SZ[144]	(D) PCP and CLZ VT,[6] (D) response to antipsychotics[100]		6q15 (Assoc), SZ[50,51]	(D) SZ[52]		4.0	0.001542, rs9451023	0.002128, rs873413
COMT, catechol-O-methyltransferase	0.04098, rs1544325	SZ[145,146]	(I), CLZ VT[6], (D), SZ[147]		22q11.21 (Assoc) SZ[148]	(I), SZ[149]		4.0		0.01457, rs1544325
CPLX2, complexin 2	0.04338, rs10213927	SZ[150]	(D), PCP and CLZ VT,[6] (D), SZ[127]		5q35.2, (Assoc), SZ[151]	(D), SZ[136,152,153]		4.0	0.01658, rs6887620	
DRD2, dopamine receptor D2	0.01151, rs12791990		(D), PCP and CLZ PFC,[6] (D), SZ[154]		11q23.2 (Assoc), SZ[155,156]	(D) SZ[136,157,158]	(D) SZ delusions[7]	4.0	0.007265, rs4938021	0.01096, rs17529477
DTNBP1, dystrobrevin binding protein 1	0.002634, rs12209943	SZ[159–162]			6p22.3 (Assoc) SZ[163–168]	(D), SZ[169–172]	(D) Lymphocytes[173]	4.0	0.009146, rs9477021	**0.0001501, rs16876575**
FABP7, fatty acid–binding protein 7, brain	0.01053, rs9490546	SZ[174]	(I), CLZ NAC; (I), PCP and CLZ PFC[6]		6q22.31 (Assoc), SZ[174]	(I), SZ[174]		4.0		
GABRB3, gamma-aminobutyric acid (GABA) A receptor, β3	0.004635, rs8037461		(I), PCP AMY; (D), PCP HIP; (D), PCP PFC[6]		15q12 (Assoc) SZ[175]	(I) SZ,[176] (D) SZ[177]	(I), SZ serum[178]	4.0	0.01579, rs12904865	**0.0009769, rs4906835**
GAD1, glutamate decarboxylase 1 (brain, 67 kDa)	0.03907, rs16859026		(I), PCP AMY,[6] (D), SZ,[127,128] (I), SZ[176]	(I), CLZ	2q31.1 (Assoc), SZ[179]	(D), SZ,[136,176,177,179–191] (I), SZ[192]		4.0	0.008447, rs10191129	0.01776, rs2883888
GNB1L, guanine nucleotide–binding protein (G-protein), β-polypeptide 1-like	0.03659, rs17745302	Impaired PPI[193]	(I), Chronic haloperidol,[194] (D), SZ[147]		22q11.21 (Assoc), SZ[195]	(D), SZ [194]		4.0		
GRIA1, glutamate receptor, ionotropic, AMPA 1	**0.0008031, rs2962816**	SZ[196]	(D), PCP and CLZ AMY,[6] (I), response to antipsychotics,[100] (D), response to PCP[197]		5q33.2 (Assoc), SZ [198,199]	(D), SZ[200,201], (I), SZ[181,202,203]		4.0	0.00659, rs10044974	0.006037, rs498660

Table 1 (*Continued*)

Gene Symbol/name	*ISC GWAS best P-value SNP*	*Animal model genetic evidence (TG)*	*Animal model brain gene expression evidence*	*Animal model blood gene expression evidence*[6]	*Human genetic evidence (association CNV or linkage)*	*Human postmortem brain gene expression evidence*	*Human blood/other peripheral tissue gene expression evidence*	*CFG score*	*GAIN-EA GWAS best P-value SNP*	*GAIN-AA GWAS best P-value SNP*
GRIA4, glutamate receptor, ionotrophic, AMPA 4	0.02792, rs649098	Cognition (impaired PPI)[204]	(I), PCP and CLZ AMY,[6] (D), SZ[205]		11q22.3 (Assoc), SZ[206]	(D), SZ,[119,207] (I), SZ[202]		4.0	0.001526, rs7116118	0.00343, rs2277280
GRIN2B, glutamate receptor, ionotropic, *N*-methyl D-aspartate 2B	0.001569, rs4363703	SZ [208]	(D), CLZ AMY; (I), CLZ VT,[6] MK-801-treated rats,[209] (D), response to antipsychotics,[100] (D), SZ,[176]		12p13.1 (Assoc), SZ[155,167]	(D), SZ,[201] (I), SZ[210]		4.0	0.001427, rs1072388	0.003102, rs12826365
GRM5, glutamate receptor, metabotropic 5	0.002559, rs992259	SZ[211]	(D), PCP AMY, (D), PCP VT,[6] (D), SZ[129]		11q14.3 (Assoc), SZ[212]	(D), SZ[181]		4.0	0.01842, rs170110	0.001263, rs1846475
GSN, gelsolin	0.04739, rs12376078		(I), PCP AMY, (D), CLZ CP[6]	(I) PCP and CLZ	33.2 (Assoc), SZ[213]	(D), SZ[111,192,143,214]		4.0	0.002313, rs767770	**0.0001564**, **rs4837835**
HINT1, histidine triad nucleotide–binding protein 1	**0.00008672**, **rs11242025**	SZ[215]			5q23.3 (Assoc), SZ, [216,217]	(D), SZ[218]	(I), SZ whole blood[120]	4.0	0.008637, rs7734177	
HTR2A, 5-hydroxytryptamine (serotonin) receptor 2A	0.02014, rs7985155		(I), Response to antipsychotics,[100] (D), SZ[219] (I), SZ[154]		13q14.2 (Assoc), SZ[155,220]	(D), SZ[136,221,222]	(D), SZ lymphocytes[223]	4.0	0.003461, rs17070879	0.002529, rs1886439
KALRN, kalirin, RhoGEF kinase	0.006285, rs3772756		(I), CLZ VT[6]		3q21.1 (Assoc), SZ[224]	(D), SZ[225]	(D), SZ IPS-derived neurons[10]	4.0	0.01015, rs9832419	0.009074, rs1822791
KIF2A, kinesin heavy chain member 2A	0.005374, rs6864793		(D), CLZ VT[6]	(I) PCP and CLZ	5q12.1 (Assoc), SZ[226]	(D), SZ[119]		4.0	0.003396, rs153864	0.005207, rs10069830
NR4A2, nuclear receptor subfamily 4, group A, member 2	**0.0006887**, **rs12465886**	SZ[227]	(I), PCP and CLZ HIP, (I), PCP and CLZ NAC;, (D), PCP PFC, (I), PCP and CLZ VT[6]		2q24.1 (Assoc), SZ,[228]		(I), SZ IPS-derived neurons [10]	4.0	0.001624, rs6743834	0.004081, rs16840214
NRG1, neuregulin 1	0.001731, rs1158001	SZ[229–231]			8p12 (Assoc), SZ[94,220,232–235]	(D), SZ[38,236–238] (I), SZ[239–241]	(I), SZ IPS-derived neurons,[10] (I), SZ, Leucocytes,[242] (I), SZ lymphocyte, [243] (I), SZ delusions[7]	4.0	0.00104, rs2716960	**0.000006564**, **rs6989777**
PDE4B, phosphodiesterase 4B, cAMP-specific	0.003042, rs6588193	SZ[244]	(D), PCP,[6] (I), psychosis,[245] (D), response to antipsychotics[246]		1p31.3 (Assoc) SZ[234,247–250]	(D) SZ[247]		4.0	0.02102, rs11805090	**0.000103, rs17417507**
PRKCA, protein kinase C, alpha	0.007991, rs6504428		(I), CLZ PFC, (D), CLZ VT,[6] (I), response to antipsychotics[251]		17q24.2, (Assoc), SZ[252,253]	(D), SZ[136]	(D), SZ IPS-derived neurons[10]	4.0	0.01166, rs9908814	**0.0004001**, **rs16959057**
RELN, reelin	0.01368, rs2711865	SZ[254]	(I), CLZ PFC;, (D), PCP and CLZ VT,[6] (D), SZ[128,255]		7q22.1 (Assoc), SZ[94,155,233,256–259]	(D), SZ[136,186,187,190,260,261]		4.0	0.007165, rs10227303	0.004365, rs7794418
RGS4, regulator of G-protein signaling 4	0.004835, rs4657235	SZ[262]	(I), PCP and CLZ AMY;, (I), CLZ HIP ;, (D), CLZ PFC;, (I), PCP and CLZ VT,[6] (D), SZ[263,264]		1q23.3 (Assoc), SZ[167,220,265,266]	(D), SZ,[45,210,267–271] (I), SZ[272]		4.0	0.007928, rs12403644	0.007516, rs10917637
SLC1A2, solute carrier family 1 (glial high-affinity glutamate transporter), member 2	0.02565, rs3794086		(D), CLZ AMY, (D), CLZ VT[6]	(I), CLZ	11p13 (Assoc), SZ,[273]	(D), SZ,[153] (I), SZ[274,275]		4.0	0.03109, rs3829280	0.002563, rs12270460
SNAP25, synaptosomal-associated protein, 25 kDa	0.01815, rs6032783	SZ[276]	(I), SZ[127,263]		20p12.2 (Assoc), SZ[277]	(D), SZ,[181,278–281] (I), SZ[181,282,283]		4.0	0.005819, rs362616	0.01192, rs362560
SYN2, synapsin II	0.003144, rs2960421	SZ[284,285]	(D), PCP and CLZ AMY, (D), PCP CP, (D), PCP and CLZ VT,[6] (I), SZ,[205] (D), SZ[127,263]		3p25.2 (Assoc), SZ[151,286,287]	(D), SZ,[45,288,183] (I), SZ antipsychotic, treatment[107]		4.0	0.042, rs2618406	0.02541, rs17671592
TNIK, TRAF2 and NCK interacting kinase	0.001377, rs260769		(I), CLZ VT[6]		3q26.31 (Assoc), SZ[9,89,234,289]	(I), SZ[278]	(D), SZ lymphoblastoid cell lines[290]	4.0	0.006987, rs12639373	**0.00007179**, **rs13065441**

Abbreviations: AA, African American; AMY, amygdala; Assoc, association evidence; CFG, convergent functional genomics; CLZ, clozapine; CP, caudate putamen; D, decreased in expression; EA, European American; GWAS, genome-wide association study; I, increased in expression; IPS, pluripotent stem cell; ISC, International Schizophrenia Consortium; Linkage, linkage evidence; NAC, nucleus accumbens; PCP, phencyclidine; PFC, prefrontal cortex; PMBC, peripheral mononuclear blood cells; SNP, single-nucleotide polymorphism; SZ, schizophrenia; TG, transgenic; VT, ventral tegmentum.
Top genes with a CFG score of 4 and above ($n = 42$) are shown. A more complete list of genes with CFG score of 3 and above ($n = 186$) is available in the Supplementary Information. Gene symbols underlined are blood biomarker candidate genes. Best *P*-value SNP within the gene or flanking regions are depicted. *P*-values in bold are <0.001. The last two columns depict gene-level replication of findings, that is, best *P*-value SNPs in the same gene from two other independent cohorts (GAIN EA and GAIN AA). In total, 37 of our top 42 genes (88.1%) had at least a SNP with $P<0.05$, in both the GAIN-EA cohort and in the GAIN-AA cohort.

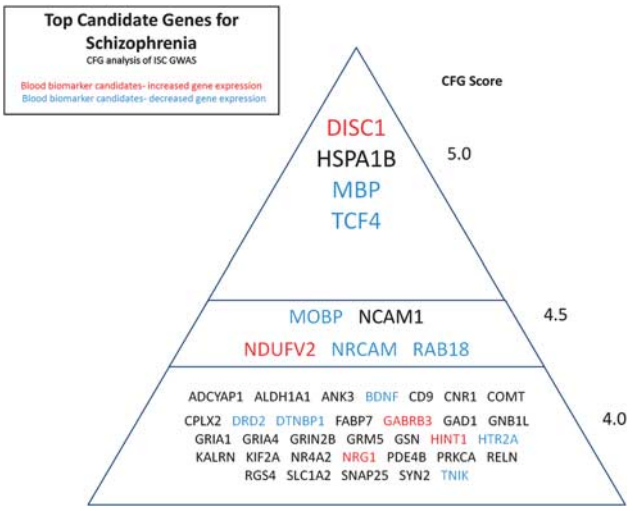


Figure 2. Top candidate genes for schizophrenia. CFG, convergent functional genomics; GWAS, genome-wide association study; ISC, International Schizophrenia Consortium.

CONVERGENT FUNCTIONAL GENOMICS ANALYSES

Databases

We have established in our laboratory (Laboratory of Neurophenomics, Indiana University School of Medicine; www.neurophenomics.info) manually curated databases of all the human gene expression (postmortem brain, blood, cell cultures), human genetic (association, CNVs, linkage) and animal model gene expression and genetic studies published to date on psychiatric disorders.[12] Only the findings deemed significant in the primary publication, by the study authors, using their particular experimental design and thresholds, are included in our databases. Our databases include only primary literature data, and do not include review papers or other secondary data integration analyses, to avoid redundancy and circularity. These large and constantly updated databases have been used in our CFG cross-validation and prioritization (Figure 1).

Human postmortem brain gene expression evidence

Information about genes was obtained and imported in our databases by searching the primary literature with PubMed (http://ncbi.nlm.nih.gov/PubMed), using various combinations of

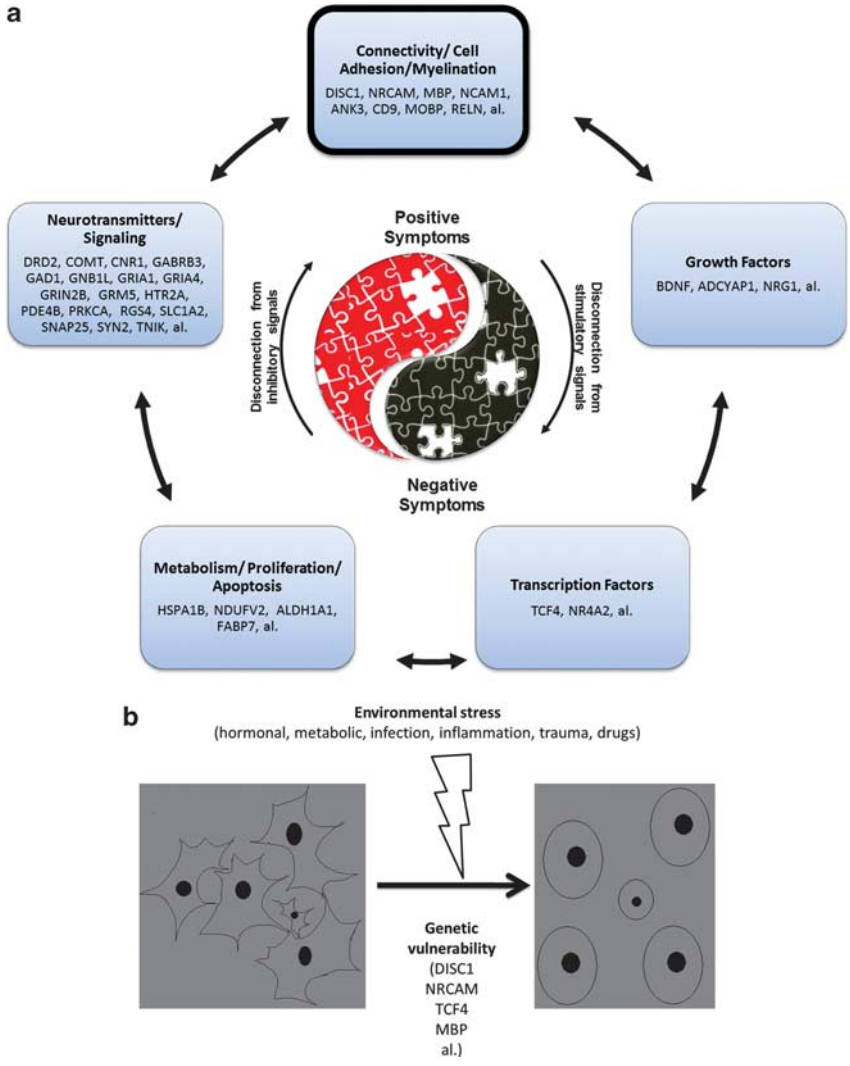


Figure 3. Schizophrenia as a disease of disconnection. (**a**) Biology of schizophrenia, (**b**) gene–environment interplay.

keywords (for this work: schizophrenia, psychosis, human, brain, postmortem). Convergence was deemed to occur for a gene if there were published human postmortem brain data showing changes in expression of that gene in tissue from patients with schizophrenia.

Human blood and other peripheral tissue gene expression data

For human blood gene expression evidence, we have used previously generated data from our group,[7] as well as published data from the literature. We also included recent data generated from induced pluripotent stem cell-derived neurons.[10]

Human genetic evidence (association, CNVs, linkage)

To designate convergence for a particular gene, the gene had to have independent published evidence of association, CNVs or linkage for schizophrenia. We sought to avoid using any association studies that included subjects that were also included in the ISC or GAIN GWAS. For CNVs, all the known genes on a CNV were taken. For linkage, the location of each gene was obtained through GeneCards (http://www.genecards.org), and the sex-averaged cM location of the start of the gene was then obtained through http://compgen.rutgers.edu/old/map-interpolator/. For linkage convergence, per our previously published criteria,[2] the start of the gene had to map within 5 cM of the location of a marker linked to the disorder.

Animal model brain and blood gene expression evidence

For animal model brain and blood gene expression evidence, we have used our own comprehensive pharmacogenomic mouse model (phencyclidine and clozapine) data sets,[6] as well as published reports from the literature curated in our databases.

Animal model genetic evidence (transgenic)

To search for mouse genetic evidence (transgenic) for our candidate genes, we utilized PubMed as well as the Mouse Genome Informatics (http://www.informatics.jax.org; Jackson Laboratory, Bar Harbor, ME, USA) database, and used the search 'Genes and Markers' form to find transgenics for categories 'Schizophrenia' as well as 'abnormal nervous system physiology' (subcategory 'abnormal sensorimotor gating').

Convergent functional genomics analysis scoring

We used a nominal *P*-value threshold for including genes from the ISC GWAS in the CFG analysis: having a SNP with $P<0.05$. All six cross-validating lines of evidence (other human data, animal model data) were weighted equally, receiving a maximum of 1 point each (for human genetic evidence: 0.5 points if it is linkage, 0.75 if it is from CNVs, 1 point if it is association). Thus, the maximum possible CFG score for each gene is 6. We have capped each line of evidence at 1 point, regardless of how many different studies support that line of evidence, to avoid potential 'popularity' biases, where some genes are more studied than others.

The more lines of evidence, that is, the more times a gene shows up as a positive finding across independent studies, platforms, methodologies and species, the higher its CFG score (Figure 1). This is similar conceptually to the Google PageRank algorithm, in which the more links to a page, the higher it comes up on the search prioritization list.[13] Human and animal model data, genetic and gene expression were integrated and tabulated, resulting in a polyevidence CFG score. It has not escaped our attention that other ways of weighing the lines of evidence may give slightly different results in terms of prioritization, if not in terms of the list of genes *per se*. Nevertheless, we feel this simple scoring system provides a good separation of genes, with sensitivity provided by animal model data and specificity provided by human data.

Pathway analyses

IPA 9.0. (Ingenuity Systems, Redwood City, CA, USA) was used to analyze the biological roles, including top canonical pathways, of the candidate genes resulting from our work (Table 2 and Supplementary Table S5), as well as used to identify genes in our data sets that are the target of existing drugs (Supplementary Table S2).

Intra-pathway epistasis testing

As an example,[11] the ISC GWAS data were used to test for epistatic interactions among the best *P*-value SNPs in genes from our data set present in a top canonical biological pathway identified by Ingenuity pathway analysis (Supplementary Table S4). SNP × SNP allelic epistasis was tested for each distinct pair of SNPs between genes, using the PLINK software package.

Genetic risk prediction panel and scoring

As we had previously done for bipolar disorder,[11] we developed a polygenic GRPS for schizophrenia based on the presence or absence of the alleles of the SNPs associated with illness, and tested the GRPS in independent cohorts for which we had both genotypic and clinical data available, comparing the schizophrenia subjects to normal controls. We tested two panels: a smaller one (GRPS-42) containing the single best *P*-value SNP in ISC in each of the top CFG prioritized genes ($n=42$), and a larger one (GRPS-542), containing all the nominally significant SNPs ($n=542$) in ISC in the top CFG prioritized genes ($n=42$; Tables 3, 4, Supplementary Table S3, and Figure 4).

Of note, our SNP panels and choice of affected alleles were based solely on analysis of the ISC GWAS, which is our discovery cohort, completely independently from the test cohorts. Each SNP has two alleles (represented by base letters at that position). One of them is associated with the illness (affected), the other not (non-affected), based on the odds ratios from the discovery ISC GWAS. We assigned the affected allele a score of 1 and the non-affected allele a score of 0. A two-dimensional matrix of

Table 2. Ingenuity pathway analyses of top candidate genes

Top canonical pathways CFG ⩾3	P-*value*	*Ratio*
*ISC (*n = *186 genes)*		
Glutamate receptor signaling	9.25E−13	12/69 (0.174)
G-protein–coupled receptor signaling	9.33E−13	27/530 (0.051)
CREB signaling in neurons	1.76E−12	17/202 (0.084)
cAMP-mediated signaling	3.55E−11	17/219 (0.078)
Neuropathic pain signaling in dorsal horn neurons	3.64E−11	13/112 (0.116)
*GAIN EA (*n = *173 genes)*		
Glutamate receptor signaling	4.57E−16	14/69 (0.203)
CREB signaling in neurons	4.72E−14	18/202 (0.089)
G-protein–coupled receptor signaling	2E−13	27/530 (0.051)
cAMP-mediated signaling	1.2E−12	18/219 (0.082)
Synaptic long-term potentiation	1.58E−12	14/114 (0.123)
*GAIN AA (*n = *201 genes)*		
cAMP-mediated signaling	7.6E-17	23/219 (0.105)
Glutamate receptor signaling	1.09E−16	15/69 (0.217)
Synaptic long-term potentiation	2.24E−15	17/114 (0.149)
G-Protein–coupled receptor signaling	2.43E−14	30/530 (0.057)
CREB signaling in neurons	4.52E−14	19/202 (0.094)

Abbreviations: AA, African American; CFG, convergent functional genomics; EA, European American; ISC, International Schizophrenia Consortium.
Discovery in ISC and reproducibility in two independent cohorts, GAIN EA and GAIN AA.

subjects by GRP panel alleles is generated, with the cells populated by 0 or 1. A SNP in a particular individual subject can have any permutation of 1 and 0 (1 and 1, 0 and 1, 0 and 0). By adding these numbers, the minimum score for a SNP in an individual subject is 0, and the maximum score is 2. By adding the scores for all the alleles in the panel, averaging that, and multiplying by 100, we generate for each subject an average score corresponding to a genetic loading for disease, which we call Genetic Risk Predictive Score (GRPS).

The software package PLINK (http://pngu.mgh.harvard.edu/~purcell) was used to extract individual genotype information for each subject from the GAIN and nonGAIN GWAS data files. We analyzed separately EA and AA schizophrenia subjects and controls, to examine any potential ethnicity variability (Tables 3 and 4, and Supplementary Table S3). To test for significance, a one-tailed *t*-test was performed between the schizophrenia subjects and the control subjects, looking at differences in GRPS.

Table 3. GRPS-42: non-differentiation between schizophrenics and controls in independent cohorts using a panel composed of the single best SNP from ISC in each of the top candidate genes (42 SNPs, in 42 genes)

Description of panel	*GAIN EA*	*GAIN AA*
Single best *P*-value SNPs in each of the top 42 candidate genes from ISC GWAS, $n=42$	$P=0.10308$, 39 out of the 42 ISC SNPs were present in GAIN EA	$P=0.13567$, 37 out of the 42 ISC SNPs were present in GAIN AA

Abbreviations: AA, African American; EA, European American; GRPS, genetic risk prediction score; GWAS, genome-wide association study; ISC, International Schizophrenia Consortium; SNP, single-nucleotide polymorphism.

Table 4. GRPS-542: differentiation between schizophrenics and controls in four independent cohorts using a panel composed of all the nominally significant SNPs from ISC in the top candidate genes (542 SNPs in 42 genes)

GAIN EA	*GAIN AA*
$P=0.03213$, 527 SNPs in 41 genes were present in GAIN EA	$P=0.00847$, 516 SNPs in 42 genes were present in GAIN AA
NonGAIN EA $P=0.00664$, 537 SNPs in 42 genes were present in nonGAIN EA	NonGAIN AA $P=0.03829$, 537 SNPs in 42 genes were present in nonGAIN AA

Abbreviations: AA, African American; EA, European American; GRPS, genetic risk prediction score; ISC, International Schizophrenia Consortium; SNP, single-nucleotide polymorphism.

RESULTS

Top candidate genes

To minimize false negatives, we initially cast a wide net, using as a filter a minimal requirement for a gene to have both some GWAS evidence and some additional independent evidence. We thus generated an initial list of 3194 unique genes with at least a SNP at $P<0.05$ in the discovery GWAS analyzed (ISC),[8] that also had some additional evidence (human or animal model data), implicating them in schizophrenia (CFG score $\geqslant 1$; Table 5). This suggests, using these minimal thresholds and requirements, that the repertoire of genes potentially involved directly or indirectly in cognitive processes and schizophrenia may be quite large, similar to what we have previously seen for bipolar disorder.[11]

To minimize false positives, we then used the CFG analysis integrating multiple lines of evidence to further prioritize this list of genes, and focused our subsequent analyses on only the top CFG scoring candidate genes. Overall, 186 genes had a CFG score of 3 and above ($\geqslant$50% of maximum possible score of 6), and 42 had a CFG score of 4 and above (Tables 1 and 5, and Figure 2).

Our top findings from ISC (Table 1) were over-represented in two independent schizophrenia GWAS cohorts, the GAIN EA and GAIN AA. In total, 37 of the top 42 genes identified by our approach (88.1%) had at least a SNP with a *P*-value of <0.05 in those independent cohorts, an estimated twofold enrichment

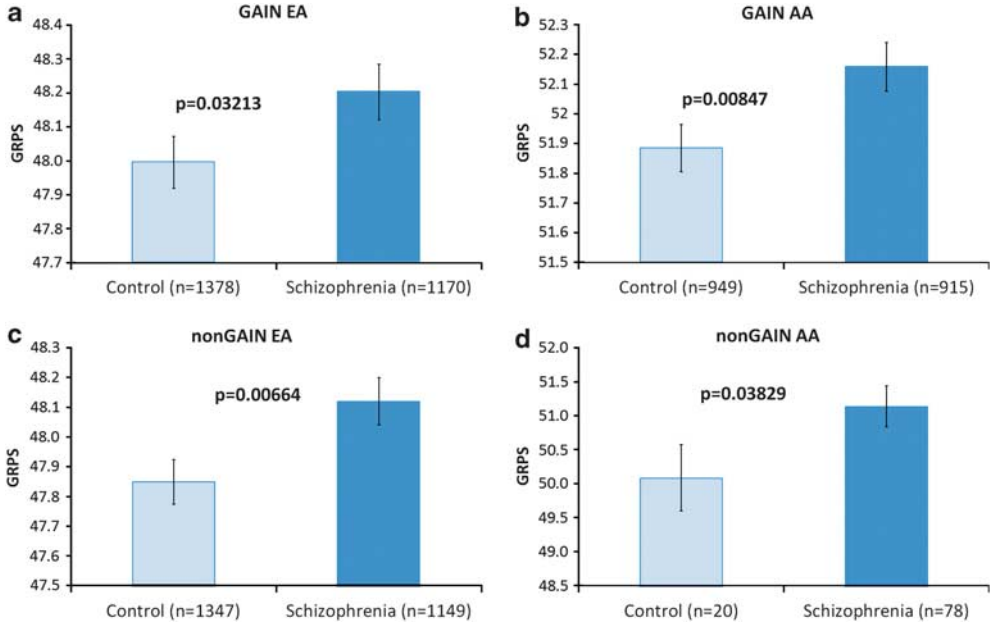


Figure 4. Genetic risk prediction of schizophrenia in four independent cohorts. AA, African American; EA, European American; GRPS, genetic risk prediction score.

Table 5. Reproducibility between independent GWAS

Numbers and overlap across studies	*ISC*	*GAIN EA*	*GAIN AA*	*ISC vs GAIN EA*	*ISC vs GAIN AA*	*GAIN EA vs GAIN AA*	*ISC vs. GAIN-EA vs. GAIN-AA (% of ISC)*
SNPs $P \leqslant 0.05$	45 972	42 336	57 118	2649	2986	2839	163 (0.4%)
Genes	10 180	9002	11 260	6470	7583	6807	5518 (54.2%)
Genes CFG $\geqslant 1$	3194	2913	3524	2243	2564	2384	2012 (63.0%)
Genes CFG $\geqslant 3$	186	173	201	147	160	153	134 (72.0%)
Genes CFG $\geqslant 4$	42	41	45	37	37	38	35 (83.3%)
Pathways for genes with CFG $\geqslant 1$	217	210	205	194	188	180	176 (81.1%)
Pathways for genes with CFG $\geqslant 3$	79	85	108	72	76	81	72 (91.1%)
Pathways for genes with CFG $\geqslant 4$	34	50	75	33	34	48	33 (97.1%)

Abbreviations: AA, African American; CFG, convergent functional genomics; EA, European American; GWAS, genome-wide association study; ISC, International Schizophrenia Consortium; SNP, single-nucleotide polymorphism.
Increasing consistency and overlap observed from nominally significant SNPs (0.4%) to genes, then to CFG prioritized genes, and finally to pathways of CFG prioritized genes (97.1%).

over what would be expected by chance alone at a genetic level (as there were 9002 genes at $P<0.05$ in the GAIN-EA GWAS, and the number of genes in the human genome is estimated at 20 500,[14] the enrichment factor provided by our approach is $(37/42)/(9002/20\,500) \approx 2$). Of note, there was no correlation between CFG prioritization and gene size, thus excluding a gene-size effect for the observed enrichment (Supplementary Figure S1).

Candidate blood biomarkers

Of the top candidate genes from Table 1 (see also Figure 2), 15 out of 42 have prior human blood evidence for change in schizophrenia, implicating them as potential blood biomarkers. The additional evidence provided by GWAS data suggests a genetic rather than purely environmental (medications, stress) basis for their alteration in disease, and their potential utility as trait rather than purely state markers.

Biological pathways

Pathway analyses were carried out on the top genes (Table 2), and on all the candidate genes (Supplementary Table S5). Notably, glutamate receptor signaling, G-protein–coupled receptor signaling and cAMP-mediated signaling were the top canonical pathways over-represented in schizophrenia, which may be informative for new drug discovery efforts by pharmaceutical companies.

Genetic risk prediction

Once the genes involved in a disorder are identified, and prioritized for likelihood of involvement, then an obvious next step is developing a way of applying that knowledge to genetic testing of individuals to determine risk for the disorder. Based on our identification of top candidate genes described above using CFG, we pursued a polygenic panel approach, with digitized binary scoring for presence or absence, similar to the one we have devised and used in the past for biomarkers testing[5] and for genetic testing in bipolar disorder.[11] Somewhat similar approaches but without CFG prioritization, attempted by other groups, have been either unsuccessful[15] or have required very large panels of markers.[8,16]

We first chose the single best *P*-value SNPs in each of our top CFG prioritized genes ($n=42$) in the ISC GWAS data set used for discovery, and assembled a GRP panel out of those SNPs (Table 3). We then developed a GRPS for schizophrenia based on the presence or absence of the alleles of the SNPs associated with the illness, and tested the GRPS in independent cohorts (GAIN EA and GAIN AA), comparing the schizophrenia subjects to normal controls (Table 3). The results were not significant. We concluded that genetic heterogeneity at a SNP level is a possible explanation for these negative results. We then sought to see if we get better separation with a larger panel, containing all the nominally significant SNPs ($n=542$) in the top CFG prioritized genes in ISC ($n=42$), on the premise that a larger panel may reduce the heterogeneity effects, as different SNPs might be more strongly associated with illness in different cohorts. We found that our larger panel of SNPs was indeed able to significantly distinguish schizophrenics from controls in both GAIN EA and GAIN AA, two independent cohorts of different ethnicities. To verify this unexpectedly strong result, we further tested our panel in two other independent cohorts, nonGAIN EA and nonGAIN AA, and obtained similarly significant results (Table 4 and Figure 4).

We also looked at whether our GRPS score distinguishes classic age of onset schizophrenia (defined by us as ages 15 to 30 years) from early onset (before 15 years) and late-onset (after 30 years) illness. Our results show that classic age of onset schizophrenia has a significantly higher GRPS than early or late-onset schizophrenia, in three out of the four independent cohorts of two different ethnicities (Figure 5).

Finally, as we had done previously for bipolar disorder,[11] we developed a prototype of how the GRPS score could be used in testing individuals to establish their category of risk for schizophrenia (Figure 6). The current iteration of the test, using the panel of 542 SNPs, seems to be able to distinguish in independent cohorts who is at lower risk for classic age of onset schizophrenia in two out of three EA subjects, and who is at higher risk for classic age of onset schizophrenia in three out of four AA subjects.

Overlap among studies

We examined the overlap at a nominally significant ($P<0.05$) SNP level between ISC, GAIN EA and GAIN AA, and found that a minority of these SNPs (0.4%) overlap (Table 5 and Figure 7). We then examined the overlap at a gene level, then CFG prioritized genes level and finally biological pathways level, and found increasing evidence of commonality and reproducibility of findings across studies.

DISCUSSION

Our CFG approach helped prioritize genes, such as DISC1 and MBP, with weaker evidence in the GWAS data but with strong independent evidence in terms of gene expression studies and other prior human or animal genetic work. Conversely, some of the top findings from GWAS, such as ZNF804A, have fewer different independent lines of evidence, and thus received a lower CFG prioritization score in our analysis (Supplementary Informa-

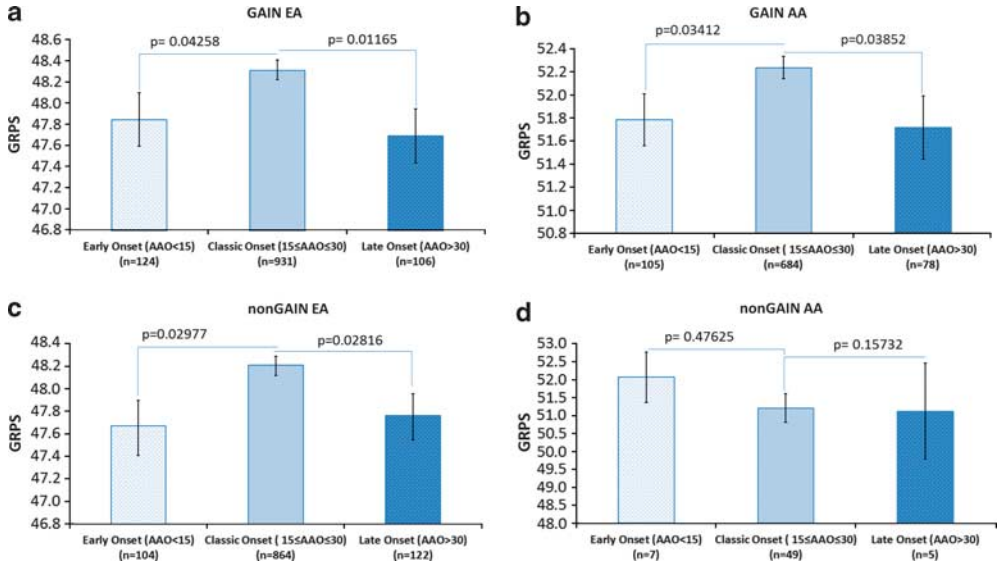


Figure 5. Genetic risk score and age at onset of schizophrenia. AA, African American; AAO, age at onset; EA, European American; GRPS, genetic risk prediction score.

tion-Table S1), although ZNF804A is clearly involved in schizophrenia-related cognitive processes.[17] While we cannot exclude that more recently discovered genes have had less hypothesis-driven work done and thus might score lower on CFG, it is to be noted that the CFG approach integrates predominantly non-hypothesis driven, discovery-type data sets, such as gene expression, GWAS, CNV, linkage and quantitative traits loci. We also cap each line of evidence from an experimental approach (Figure 1) at a maximum score of 1, to minimize any 'popularity' bias, whereas multiple studies of the same kind are conducted on better-established genes. In the end, it is gene-level reproducibility across multiple approaches and platforms that is built into the approach and gets prioritized most by CFG scoring during the discovery process. Our top results subsequently show good reproducibility and predictive ability in independent cohort testing, the litmus test for any such work.

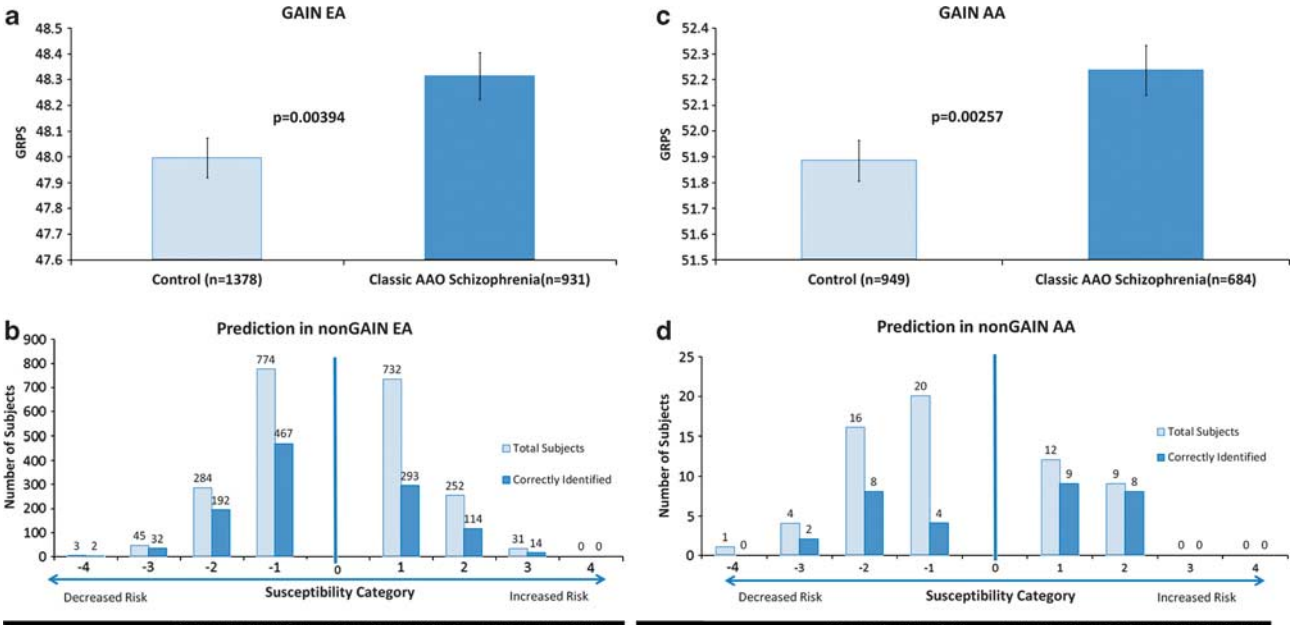
At the very top of our list of candidate genes for schizophrenia, with a CFG score of 5, we have four genes: DISC1, TCF4, MBP and HSPA1B. An additional five genes have a CFG score of 4.5: MOBP, NRCAM, NCAM1, NDUFV2 and RAB18.

DISC1 (Disrupted-in Schizophrenia 1), encodes a scaffold protein that has an impact on neuronal development and function,[18–20] including neuronal connectivity.[21] DISC1 has been identified as a susceptibility gene for major mental disorders by multiple studies.[22–24] DISC1 isoforms are upregulated in expression in blood cells in schizophrenia, thus serving as a potential peripheral biomarker as well.[25,26] Developmental stress interacts with DISC1 expression to produce neuropsychiatric phenotypes in mice.[27] Notably, its interacting partners PDE4B,[28] TNIK,[29] FEZ1 (ref. 30) and DIXDC1 (ref. 31) are also present on our list of prioritized candidate genes, with CFG scores of 4, 4, 3.5 and 2.5, respectively (Table 1 and Supplementary Table S1).

TCF4 (transcription factor 4) encodes a basic helix-turn-helix transcription factor, expressed in immune system as well as neuronal cells. It is required for the differentiation of subsets of neurons in the developing brain. There are multiple alternatively spliced transcripts that encode different proteins, providing for biological diversity and heterogeneity. Defects in this gene are a cause of Pitt-Hopkins syndrome, characterized by mental retardation with or without associated facial dysmorphisms and intermittent hyperventilation. TCF4 has additional genetic evidence for association with schizophrenia-relevant phenotypes.[32–35] It is changed in expression in postmortem brain,[36] induced pluripotent stem cell-derived neurons[10] and blood from schizophrenia patients.[7] Notably, it is a candidate blood biomarker for level of delusional symptoms (decreased in high delusional states) based on our previous work.[7]

MBP (myelin basic protein) is a major constituent of the myelin sheath of oligodendrocytes and Schwann cells in the nervous system. MBP-related transcripts are also present in the bone marrow and the immune system. MBP has additional genetic evidence for association with schizophrenia.[37] It is decreased in expression in postmortem brain[38] and blood[39] from schizophrenia patients. MBP is also changed in expression in the brain and blood of a pharmacogenomics mouse model of schizophrenia, based on our previous work.[6] It was also decreased in expression in a stress-reactive genetic mouse model of bipolar disorder,[40] and treatment with the omega-3 fatty acid docosahexaenoic acid led to an increase in expression. Notably, MBP is a candidate blood biomarker for level of mood symptoms (increased in high mood states in bipolar subjects), based on our previous work.[5] Overall, the data indicate that MBP and other myelin-related genes[41,42] may be involved in the effects of stress on psychosis and mood. Demyelinating disorders such as multiple sclerosis tend to be precipitated and exacerbated by stress, and have co-morbid psychiatric symptoms.[43] Of note, other myelin-related genes are also present on our list of prioritized candidate genes: MOBP and MOG, with CFG scores of 4.5 and 3, respectively (Table 1 and Supplementary Table S1).

HSPA1B (heat-shock 70-kDa protein 1B), a chaperone involved in stress response, stabilizes existing proteins against aggregation and mediates the folding of newly translated proteins. HSPA1B has additional genetic evidence for association with schizophrenia.[44] It is changed in expression in postmortem brain[45] and induced pluripotent stem cell-derived neurons[10] from schizophrenia patients. HSPA1B is also increased in expression in the brain and blood of a pharmacogenomics mouse model of schizophrenia, based on our previous work.[6] It was also co-directionally changed in the brain and blood in a phramacogenomic mouse model of anxiety disorders, we have recently described,[46] as well as in a stress-reactive genetic mouse model.[40] Treatment with the omega-3 fatty acid docosahexaenoic acid reversed the increase in expression of HSPA1B in this stress-reactive genetic mouse model.[47] Another closely related molecule,



Category	Total Subjects	Correctly Identified Controls	Correctly Identified SZ	Positive Predictive Value
-4	3	2		66.67%
-3	45	32		71.11%
-2	284	192		67.61%
-1	774	467		60.34%
0	90			
1	732		293	40.03%
2	252		114	45.24%
3	31		14	45.16%
4	0		0	0.00%

Category	Total Subjects	Correctly Identified Control	Correctly Identified SZ	Positive Predictive Value
-4	1	0		0.00%
-3	4	2		50.00%
-2	16	8		50.00%
-1	20	4		20.00%
0	7			
1	12		9	75.00%
2	9		8	88.89%
3	0		0	0.00%
4	0		0	0.00%

Figure 6. Prototype of how genetic risk prediction score (GRPS) testing could be used at an individual rather than population level, to aid diagnostic and personalized medicine approaches. We used the average values and standard deviation values for GRPS from the GAIN samples from each ethnicity (European American (EA) and African American (AA)) as thresholds for predictive testing in the independent nonGAIN EA and nonGAIN AA cohorts. The average GRPS score for schizophrenics in the GAIN cohort is used as a cut-off for schizophrenics in the test cohort (that is, being above that threshold), and the average GRPS score for controls in the GAIN cohort is used as a cut-off for controls in the test nonGAIN cohort (that is, being below that threshold). The subjects who are in between these two thresholds are called undetermined. Furthermore, to stratify risk, we categorized subjects into risk categories (in red, increased risk; in blue, decreased risk): Category 1 if they fall within one standard deviation above the schizophrenics' threshold, and category −1 if they fall within one standard deviation below the controls threshold. Category 2 and −2, subjects are between one and two standard deviations from the thresholds, category 3 and −3, subjects are between two and three standard deviations, and category 4 and −4, subjects are those who fall beyond three standard deviations of the thresholds. The positive predictive value (PPV) of the tests increases in the higher categories, and the test is somewhat better at distinguishing controls in EA (that is, in a practical application, individuals that are lower risk of developing the illness), and schizophrenics in AA (that is, in a practical application, individuals that are higher risk of developing the illness).

HSPA1A (heat-shock 70-kDa protein 1A), is also present on our list of prioritized candidate genes, with a CFG score of 3.5 (Supplementary Table S1). Heat-shock proteins may be involved in the biological and clinical overlap and interdependence between response to stress, anxiety and psychosis.

NRCAM (neuronal cell adhesion molecule) encodes a neuronal cell adhesion molecule. This ankyrin-binding protein is involved in neuron–neuron adhesion and promotes directional signaling during axonal cone growth. NRCAM is also expressed in non-neural tissues and may have a general role in cell–cell communication via signaling from its intracellular domain to the actin cytoskeleton during directional cell migration. It is decreased in expression in postmortem brain[48] and peripherally in serum[49] from schizophrenia patients. NRCAM is also changed in expression in the brain of a pharmacogenomics mouse model of schizophrenia, based on our previous work.[6] It was also increased in the amygdala in a stress-reactive genetic mouse model studied by our group.[40] Another closely related molecule, NCAM1 (neural cell adhesion molecule 1), is among our top candidate genes as well. These data support a central role for cell connectivity and cell adhesion in schizophrenia.

Another top candidate gene is CNR1 (cannabinoid receptor 1, brain). CNR1 is a member of the guanine-nucleotide-binding protein (G-protein) coupled receptor family, which inhibits adenylate cyclase activity in a dose-dependent manner. CNR1 has additional genetic evidence for association with schizophrenia.[50,51] It is decreased in expression in postmortem brain from schizophrenics.[52] The other main cannabinoid receptor, CNR2 (cannabinoid receptor 2), is among our top candidate genes too (Supplementary Table S1), and is decreased in expression in postmortem brain from schizophrenics as well. These data support a role for the cannabinoid system in schizophrenia, perhaps through a deficiency of the endogenous cannabinoid signaling that leads to vulnerability to psychotogenic stress,[53] and is accompanied by increased compensatory exogenous cannabinoid consumption that may have additional deleterious consequences.[54]

A number of glutamate receptor genes are present among our top candidate genes for schizophrenia (GRIA1, GRIA4, GRIN2B and GRM5), as well as GAD1, an enzyme involved in glutamate metabolism, and SLC1A2, a glutamate transporter (Table 1). Other genes involved in glutamate signaling present in our data, with a lower scores, are GRIN2A, SLC1A3, GRIA3, GRIK4, GRM1, GRM4 and GRM7 (Supplementary Table S1). Glutamate receptor signaling is

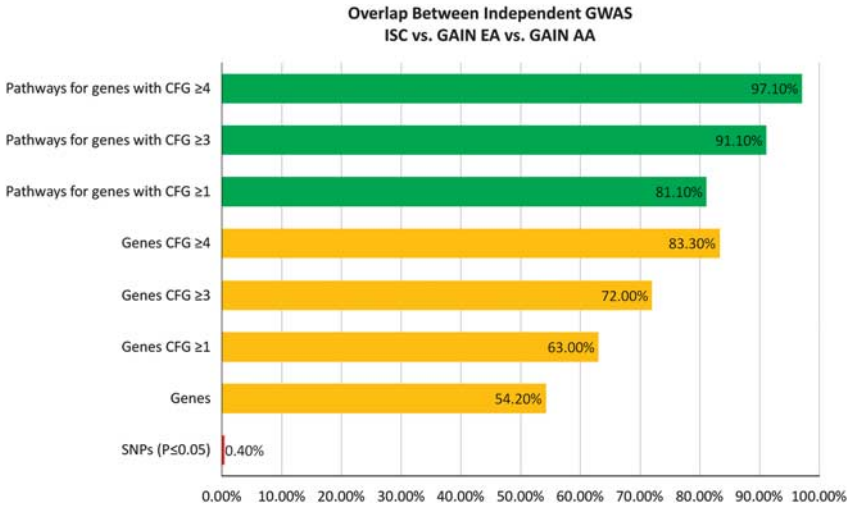


Figure 7. Overlap between independent genome-wide association study (GWAS). AA, African American; EA, European American; CFG, convergent functional genomics; ISC, International Schizophrenia Consortium; SNP, single-nucleotide polymorphism.

one of the top canonical pathways over-represented in our analyses (Table 2), and that finding is reproduced in independent GWA data sets (Table 2). One has to be circumspect with interpreting such results, as glutamate signaling is quasi-ubiquitous in the brain, and a lot of prior hypothesis-driven work has focused on this area, potentially biasing the available evidence. Nevertheless, our results are striking, and contribute to the growing body of evidence that has emerged over the last few years implicating glutamate signaling as a point of convergence for findings in schizophrenia,[55] as well as for autism[56] and AD.[57] Glutamate signaling is the target of active drug development efforts,[58] which may be informed and encouraged by our current findings.

Our analysis also provides evidence for other genes that have long been of interest in schizophrenia, but have had previous variable evidence from genetic-only studies: BDNF, COMT, DRD2, DTNBP1 (dystrobrevin binding protein1/dysbindin; Table 1). In addition, our analysis provides evidence for genes that had previously not been widely implicated in schizophrenia, but do have relevant biological roles, demonstrating the value of empirical discovery-based approaches such as CFG (Table 1): ANK3,[48] ALDH1A1 and ADCYAP1, which is a ligand for schizophrenia candidate gene VIPR2,[59,60] also present in our data set, albeit with a lower CFG score of 2. Other genes of interest in our full data set (Supplementary Table S1) include ADRBK2 (GRK3), first described by us as a candidate gene for psychosis,[1] CHRNA7,[61] and PDE10A,[62] which are targets for drug development efforts.

Pathways and mechanisms

Our pathway analyses results are consistent with the accumulating evidence about the role of synaptic connections and glutamate signaling in schizophrenia, most recently from CNV studies[63] (Table 2, Supplementary Table S5, Figure 3). Very importantly, the same top pathways were consistent across independent GWA studies we analyzed (Tables 2, 5, and Supplementary Table S5). We also did a manual curation of the top candidate genes and their grouping into biological roles examining them one by one using PubMed and GeneCards, to come up with a heuristic model of schizophrenia (Figure 3). Overall, while multiple mechanistic entry points may contribute to schizophrenia pathogenesis (Figure 3a), it is likely at its core a disease of decreased cellular connectivity precipitated by environmental stress during brain development, on a background of genetic vulnerability (Figure 3b).

Genetic risk prediction

Of note, our SNP panels and choice of affected alleles were based solely on analysis of the discovery ISC GWAS, completely independently from the test GAIN EA, GAIN AA, nonGAIN EA and nonGAIN AA GWAS. Our results show that a relatively limited and well-defined panel of SNPs identified based on our CFG analysis could differentiate between schizophrenia subjects and controls in four independent cohorts of two different ethnicities, EA and AA. Moreover, the genetic risk component identified by us seems to be stronger for classic age of onset schizophrenia than for early or late-onset illness, suggesting that the latter two may be more environmentally driven or have a somewhat different genetic architecture. It is likely that such genetic testing will have to be optimized for different cohorts if done at a SNP level. Interestingly, at a gene and pathway level, the differences between studies seem much less pronounced than at a SNP level, if at all present (Table 5), suggesting that gene-level and pathway-level tests may have more universal applicability. In the end, such genetic data, combined with family history and other clinical information (phenomics),[64] as well as with blood biomarker testing,[5] may provide a comprehensive picture of risk of illness.[65,66]

Reproducibility among studies

Our work provides striking evidence for the advantages, reproducibility and consistency of gene-level analyses of data, as opposed to SNP level analyses, pointing to the fundamental issue of genetic heterogeneity at a SNP level (Table 5 and Figure 7). In fact, it may be that the more biologically important a gene is for higher mental functions, the more heterogenity it has at a SNP level[67] and the more evolutionary divergence,[68] for adaptive reasons. On top of that, CFG provides a way to prioritize genes based on disease relevance, not study-specific effects (that is, fit-to-disease as opposed to fit-to-cohort). Reproducibility of findings across different studies, experimental paradigms and technical platforms is deemed more important (and scored as such by CFG) than the strength of finding in an individual study (for example, *P*-value in a GWAS). The CFG prioritized genes show even more reproducibility among independent GWAS cohorts (ISC, GAIN EA, GAIN AA) than the full list of unprioritized genes with nominal significant SNPs. The increasing overlap and reproducibility between studies of genes with a higher average CFG score points out to their biological relevance to disease architecture. Finally, at a pathway level, there is even more

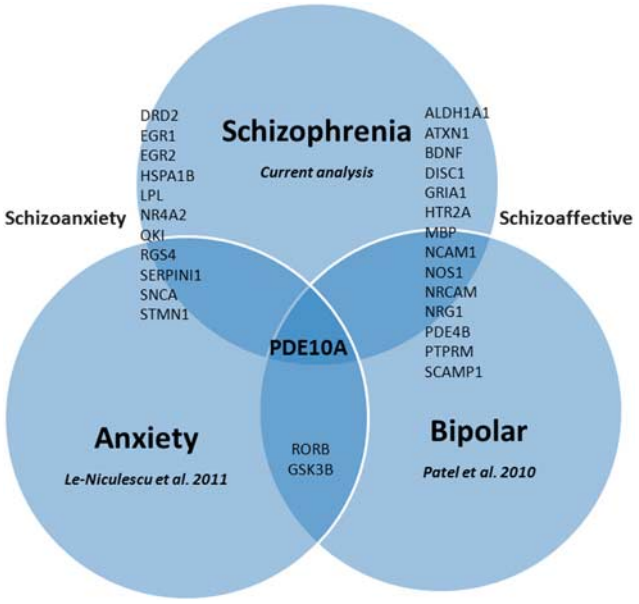


Figure 8. Genetic overlap among psychiatric disorders.

consistency across studies. Again, the pathways derived from the top CFG scoring genes show more consistency than the pathways derived from the lower CFG scoring genes. Overall, using our approach, we go from a reproducibilty between independent studies of 0.4% at the level of nominally significant SNPs to a reproducibility of 97.1% at the level of pathways derived from top CFG scoring genes.

Overlap with other psychiatric disorders

Despite using lines of evidence for our CFG approach that have to do only with schizophrenia, the list of genes identified has a notable overlap with other psychiatric disorders (Figure 8, Supplementary Table S1). This is a topic of major interest and debate in the field.[12,69] We demonstrate an overlap between top candidate genes for schizophrenia and candidate genes for anxiety and bipolar disorder, previously identified by us through CFG (Figure 8), thus providing a possible molecular basis for the frequently observed clinical co-morbidity and interdependence between schizophrenia and those other major psychiatric disorders, as well as cross-utility of pharmacological agents. In particular, PDE10A is at the overlap of all three major psychiatric domains, and may be of major interest for drug development.[62] The overlap between schizophrenia and bipolar may have to do primarily with neurotrophicity and brain infrastructure (underlined by genes such as DISC1, NRG1, BDNF, MBP, NCAM1, NRCAM, PTPRM). The overlap between schizophrenia and anxiety may have to do primarily to do with reactivity and stress response (underlined by genes such as NR4A2, QKI, RGS4, HSPA1B, SNCA, STMN1, LPL). Notably, the overlap between schizophrenia and anxiety is of the same magnitude as the previously better appreciated overlap between schizophrenia and bipolar disorder,[6,70] supporting the consideration of a nosological domain of schizoanxiety disorder,[46] by analogy to schizoaffective disorder. Clinically, while there are some reports of co-morbidity between schizophrenia and anxiety,[71] it is an area that has possibly been under-appreciated and understudied. 'Schizoanxiety disorder' may have heuristic value and pragmatic clinical utility.

We also looked at the overlap with candidate genes for autism and AD from the literature (Supplementary Table S1), to elucidate whether schizophrenia, autism and AD might be on a spectrum, that is, whether autism might be a form of 'schizophrenia praecox', similar to schizophrenia being referred to as 'dementia praecox' (Kraepelin). We see significant overlap between the three disorders among the top genes with a CFG score of 4: a third of the genes overlap between schizophrenia and autism, and a quarter between schizophrenia and AD. Additional key genes of interest are lower on the list as well, with a CFG score of 3: CNTNAP2 for autism, MAPT and SNCA for AD (Supplementary Table S1).

Conclusions and future directions

First, in spite of its limitations, our analysis is arguably the most comprehensive integration of genetics and functional genomics to date in the field of schizophrenia, yielding a comprehensive view of genes, blood biomarkers, pathways and mechanisms that may underlie the disorder. From a pragmatic standpoint, we would like to suggest that our work provides new and/or more comprehensive insights on genes and biological pathways to target for new drug development by pharmaceutical companies, as well as potential new uses in schizophrenia for existing drugs, including omega-3 fatty acids (Supplementary Table S2).

Second, our current work and body of work over the years provides proof how a combined approach, integrating functional and genotypic data, can be used for complex disorders-psychiatric and non-psychiatric, as has been attempted by others as well.[72,73] What we are seeing across GWAS of complex disorders are not necessarily the same SNPs showing the strongest signal, but rather consistency at the level of genes and biological pathways. The distance from genotype to phenotype may be a bridge too far for genetic-only approaches, given genetic heterogeneity and the intervening complex layers of epigenetics and gene expression regulation.[74] Consistency is much higher at a gene expression level (Table 5),[75] and then at a biological pathway level. Using GWAS data in conjunction with gene expression data as part of CFG or integrative genomics[76] approaches, followed by pathway-level analysis of the prioritized candidate genes, can lead to the unraveling of the genetic code of complex disorders such as schizophrenia.

Third, our work provides additional integrated evidence focusing attention and prioritizing a number of genes as candidate blood biomarkers for schizophrenia, with an inherited genetic basis (Table 1 and Figure 2). While prior evidence existed as to alterations in gene expression levels of those genes in whole-blood samples or lymphoblastoid cell lines from schizophrenia patients, it was unclear prior to our analysis whether those alterations were truly related to the disorder or were instead related only to medication effects and environmental factors.

Fourth, we have put together a panel of SNPs, based on the top candidate genes we identified. We developed a GRPS based on our panel, and demonstrate how in four independent cohorts of two different ethnicities, the GRPS differentiates between subjects with schizophrenia and normal controls. From a personalized medicine standpoint, genetic testing with highly prioritized panels of best SNP markers may have, upon further development (Figure 6) and calibration by ethnicity and gender, a role in informing decisions regarding early intervention and prevention efforts; for example, for classic age of onset schizophrenia before the illness fully manifests itself clinically, in young offspring from high-risk families. After the illness manifests itself, gene expression biomarkers and phenomic testing approaches, including clinical data, may have higher yield than genetic testing. A multi-modal integration of testing modalities would be the best approach to assess and track patients, as individual markers are likely to not be specific for a single disorder. The continuing re-evaluation in psychiatric nosology[66,77] brought about by recent advances will have to be taken into account as well for final interpretation of any such testing. The complexity, heterogeneity, overlap and inter-

dependence of major psychiatric disorders as currently defined by DSM suggests that the development of tests for dimensional disease manifestations (psychosis, mood and anxiety)[66] will ultimately be more useful and precise than developing tests for existing DSM diagnostic categories.

Finally, while we cannot exclude that rare genetic variants with major effects may exist in some individuals and families, we suggest a contextual cumulative combinatorics of common variants genetic model best explains our findings, and accounts for the thin genetic load margin between clinically ill subjects and normal controls, which leaves a major role to be played by gene expression (including epigenetic changes) and the environment. This is similar to our conclusions when studying bipolar disorder,[11] and may hold true in general for complex medical disorders, psychiatric and non-psychiatric. Full-blown illness occurs when genetic and environmental factors converge, usually in young adulthood for schizophrenia. When they diverge, a stressful/hostile environment may lead to mild or transient illness even in normal genetic load individuals, whereas a favorable environment may lead to supra-normative functioning in certain life areas (such as creative endeavors) for individuals who carry a higher genetic load. The flexible interplay between genetic load, environment and phenotype may permit evolution to engender diversity, select and conserve alleles, and ultimately shape populations. Our emerging mechanistic understanding of psychosis as disconnectivity, mood as activity[11] and anxiety as reactivity[46] may guide such testing and understanding of population distribution as being on a multi-dimensional spectrum, from supra-normative to normal to clinical illness.

CONFLICT OF INTEREST

ABN is a founder of Mindscape Diagnostics. NJS is a founder of Cypher Genomics.

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REFERENCES

1 Niculescu 3rd AB, Segal DS, Kuczenski R, Barrett T, Hauger RL, Kelsoe JR. Identifying a series of candidate genes for mania and psychosis: a convergent functional genomics approach. *Physiol Genomics* 2000; **4**: 83–91.
2 Ogden CA, Rich ME, Schork NJ, Paulus MP, Geyer MA, Lohr JB *et al.* Candidate genes, pathways and mechanisms for bipolar (manic-depressive) and related disorders: an expanded convergent functional genomics approach. *Mol Psychiatry* 2004; **9**: 1007–1029.
3 Bertsch B, Ogden CA, Sidhu K, Le-Niculescu H, Kuczenski R, Niculescu AB. Convergent functional genomics: a Bayesian candidate gene identification approach for complex disorders. *Methods* 2005; **37**: 274–279.
4 Rodd ZA, Bertsch BA, Strother WN, Le-Niculescu H, Balaraman Y, Hayden E *et al.* Candidate genes, pathways and mechanisms for alcoholism: an expanded convergent functional genomics approach. *Pharmacogenomics J* 2007; **7**: 222–256.
5 Le-Niculescu H, Kurian SM, Yehyawi N, Dike C, Patel SD, Edenberg HJ *et al.* Identifying blood biomarkers for mood disorders using convergent functional genomics. *Mol Psychiatry* 2009; **14**: 156–174.
6 Le-Niculescu H, Balaraman Y, Patel S, Tan J, Sidhu K, Jerome RE *et al.* Towards understanding the schizophrenia code: an expanded convergent functional genomics approach. *Am J Med Genet B Neuropsychiatr Genet* 2007; **144**: 129–158.
7 Kurian SM, Le-Niculescu H, Patel SD, Bertram D, Davis J, Dike C *et al.* Identification of blood biomarkers for psychosis using convergent functional genomics. *Mol Psychiatry* 2011; **16**: 37–58.
8 Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF *et al.* Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* 2009; **460**: 748–752.
9 Shi J, Levinson DF, Duan J, Sanders AR, Zheng Y, Pe'er I *et al.* Common variants on chromosome 6p22.1 are associated with schizophrenia. *Nature* 2009; **460**: 753–757.
10 Brennand KJ, Simone A, Jou J, Gelboin-Burkhart C, Tran N, Sangar S *et al.* Modelling schizophrenia using human induced pluripotent stem cells. *Nature* 2011; **473**: 221–225.
11 Patel SD, Le-Niculescu H, Koller DL, Green SD, Lahiri DK, McMahon FJ *et al.* Coming to grips with complex disorders: genetic risk prediction in bipolar disorder using panels of genes identified through convergent functional genomics. *Am J Med Genet B Neuropsychiatr Genet* 2010; **153B**: 850–877.
12 Niculescu AB, Le-Niculescu H. Convergent Functional Genomics: what we have learned and can learn about genes, pathways, and mechanisms. *Neuropsychopharmacology* 2010; **35**: 355–356.
13 Le-Niculescu H, Patel SD, Niculescu AB. Convergent integration of animal model and human studies of bipolar disorder (manic-depressive illness). *Curr Opin Pharmacol* 2010; **10**: 594–600.
14 Clamp M, Fry B, Kamal M, Xie X, Cuff J, Lin MF *et al.* Distinguishing protein-coding and noncoding genes in the human genome. *Proc Natl Acad Sci USA* 2007; **104**: 19428–19433.
15 Tsutsumi A, Glatt SJ, Kanazawa T, Kawashige S, Uenishi H, Hokyo A *et al.* The genetic validation of heterogeneity in schizophrenia. *Behav Brain Funct* 2011; **7**: 43.
16 Ikeda M, Aleksic B, Kinoshita Y, Okochi T, Kawashima K, Kushima I *et al.* Genome-wide association study of schizophrenia in a Japanese population. *Biol Psychiatry* 2011; **69**: 472–478.
17 Rasetti R, Sambataro F, Chen Q, Callicott JH, Mattay VS, Weinberger DR. Altered cortical network dynamics: a potential intermediate phenotype for schizophrenia and association with ZNF804A. *Arch Gen Psychiatry* 2011; **68**: 1207–1217.
18 Ishizuka K, Kamiya A, Oh EC, Kanki H, Seshadri S, Robinson JF *et al.* DISC1-dependent switch from progenitor proliferation to migration in the developing cortex. *Nature* 2011; **473**: 92–96.
19 Brandon NJ, Sawa A. Linking neurodevelopmental and synaptic theories of mental illness through DISC1. *Nat Rev Neurosci* 2011; **12**: 707–722.
20 Porteous DJ, Millar JK, Brandon NJ, Sawa A. DISC1 at 10: connecting psychiatric genetics and neuroscience. *Trends Mol Med* 2011; **17**: 699–706.
21 Hattori T, Shimizu S, Koyama Y, Yamada K, Kuwahara R, Kumamoto N *et al.* DISC1 regulates cell-cell adhesion, cell-matrix adhesion and neurite outgrowth. *Mol Psychiatry* 2010; **15**: 778, 98–809.
22 Callicott JH, Straub RE, Pezawas L, Egan MF, Mattay VS, Hariri AR *et al.* Variation in DISC1 affects hippocampal structure and function and increases risk for schizophrenia. *Proc Natl Acad Sci USA* 2005; **102**: 8627–8632.
23 Carless MA, Glahn DC, Johnson MP, Curran JE, Bozaoglu K, Dyer TD *et al.* Impact of DISC1 variation on neuroanatomical and neurocognitive phenotypes. *Mol Psychiatry* 2011; **16**: 1096–1104.
24 Singh KK, De Rienzo G, Drane L, Mao Y, Flood Z, Madison J *et al.* Common DISC1 polymorphisms disrupt Wnt/GSK3beta signaling and brain development. *Neuron* 2011; **72**: 545–558.
25 Nakata K, Lipska BK, Hyde TM, Ye T, Newburn EN, Morita Y *et al.* DISC1 splice variants are upregulated in schizophrenia and associated with risk polymorphisms. *Proc Natl Acad Sci USA* 2009; **106**: 15873–15878.
26 Olincy A, House R, Gao B, Recksiek P, Phang TL, Sullivan B *et al.* Elevated DISC1 transcript levels in PBMCs during acute psychosis in patients with schizophrenia. *Transl Biomed* 2011; **2**: pii: 183.
27 Ayhan Y, Abazyan B, Nomura J, Kim R, Ladenheim B, Krasnova IN *et al.* Differential effects of prenatal and postnatal expressions of mutant human DISC1 on neurobehavioral phenotypes in transgenic mice: evidence for neurodevelopmental origin of major psychiatric disorders. *Mol Psychiatry* 2011; **16**: 293–306.
28 Millar JK, Mackie S, Clapcote SJ, Murdoch H, Pickard BS, Christie S *et al.* Disrupted in schizophrenia 1 and phosphodiesterase 4B: towards an understanding of psychiatric illness. *J Physiol* 2007; **584**(Part 2): 401–405.
29 Wang Q, Charych EI, Pulito VL, Lee JB, Graziane NM, Crozier RA *et al.* The psychiatric disease risk factors DISC1 and TNIK interact to regulate synapse composition and function. *Mol Psychiatry* 2011; **16**: 1006–1023.
30 Kang E, Burdick KE, Kim JY, Duan X, Guo JU, Sailor KA *et al.* Interaction between FEZ1 and DISC1 in regulation of neuronal development and risk for schizophrenia. *Neuron* 2011; **72**: 559–571.

31 Singh KK, Ge X, Mao Y, Drane L, Meletis K, Samuels BA *et al.* Dixdc1 is a critical regulator of DISC1 and embryonic cortical development. *Neuron* 2010; **67**: 33–48.
32 Lennertz L, Rujescu D, Wagner M, Frommann I, Schulze-Rauschenbach S, Schuhmacher A *et al.* Novel schizophrenia risk gene TCF4 influences verbal learning and memory functioning in schizophrenia patients. *Neuropsychobiology* 2011; **63**: 131–136.
33 Li T, Li Z, Chen P, Zhao Q, Wang T, Huang K *et al.* Common variants in major histocompatibility complex region and TCF4 gene are significantly associated with schizophrenia in Han Chinese. *Biol Psychiatry* 2010; **68**: 671–673.
34 Quednow BB, Ettinger U, Mossner R, Rujescu D, Giegling I, Collier DA *et al.* The schizophrenia risk allele C of the TCF4 rs9960767 polymorphism disrupts sensorimotor gating in schizophrenia spectrum and healthy volunteers. *J Neurosci* 2011; **31**: 6684–6691.
35 Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D *et al.* Common variants conferring risk of schizophrenia. *Nature* 2009; **460**: 744–747.
36 Mudge J, Miller NA, Khrebtukova I, Lindquist IE, May GD, Huntley JJ *et al.* Genomic convergence analysis of schizophrenia: mRNA sequencing reveals altered synaptic vesicular transport in post-mortem cerebellum. *PLoS One* 2008; **3**: e3625.
37 Baruch K, Silberberg G, Aviv A, Shamir E, Bening-Abu-Shach U, Baruch Y *et al.* Association between golli-MBP and schizophrenia in the Jewish Ashkenazi population: are regulatory regions involved? *Int J Neuropsychopharmacol* 2009; **12**: 885–894.
38 Tkachev D, Mimmack ML, Ryan MM, Wayland M, Freeman T, Jones PB *et al.* Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. *Lancet* 2003; **362**: 798–805.
39 Glatt SJ, Stone WS, Nossova N, Liew CC, Seidman LJ, Tsuang MT. Similarities and differences in peripheral blood gene-expression signatures of individuals with schizophrenia and their first-degree biological relatives. *Am J Med Genet B Neuropsychiatr Genet* 2011; **156B**: 869–887.
40 Le-Niculescu H, McFarland MJ, Ogden CA, Balaraman Y, Patel S, Tan J *et al.* Phenomic, convergent functional genomic, and biomarker studies in a stress-reactive genetic animal model of bipolar disorder and co-morbid alcoholism. *Am J Med Genet B Neuropsychiatr Genet* 2008; **147B**: 134–166.
41 Haroutunian V, Davis KL. Introduction to the special section: myelin and oligodendrocyte abnormalities in schizophrenia. *Int J Neuropsychopharmacol* 2007; **10**: 499–502.
42 Takahashi N, Sakurai T, Davis KL, Buxbaum JD. Linking oligodendrocyte and myelin dysfunction to neurocircuitry abnormalities in schizophrenia. *Prog Neurobiol* 2011; **93**: 13–24.
43 Konradi C, Sillivan SE, Clay HB. Mitochondria, oligodendrocytes and inflammation in bipolar disorder: evidence from transcriptome studies points to intriguing parallels with multiple sclerosis. *Neurobiol Dis* 2012; **45**: 37–47.
44 Pae CU, Drago A, Kim JJ, Mandelli L, De Ronchi D, Serretti A. The impact of heat shock protein 70 gene variations on clinical presentation and outcome in schizophrenic inpatients. *Neuropsychobiology* 2009; **59**: 135–141.
45 Arion D, Unger T, Lewis DA, Levitt P, Mirnics K. Molecular evidence for increased expression of genes related to immune and chaperone function in the prefrontal cortex in schizophrenia. *Biol Psychiatry* 2007; **62**: 711–721.
46 Le-Niculescu H, Balaraman Y, Patel SD, Ayalew M, Gupta J, Kuczenski R *et al.* Convergent functional genomics of anxiety disorders: translational identification of genes, biomarkers, pathways and mechanisms. *Translational Psychiatry* 2011; **1**: e9; doi:10.1038/tp.2011.9.
47 Le-Niculescu H, Case NJ, Hulvershorn L, Patel SD, Bowker D, Gupta J *et al.* Convergent functional genomic studies of omega-3 fatty acids in stress reactivity, bipolar disorder and alcoholism. *Translational Psychiatry* 2011; **1**: e4; doi:10.1038/tp.2011.1.
48 Roussos P, Katsel P, Davis KL, Bitsios P, Giakoumaki SG, Jogia J *et al.* Molecular and genetic evidence for abnormalities in the nodes of ranvier in schizophrenia. *Arch Gen Psychiatry* 2012; **69**: 7–15.
49 Schwarz E, Guest PC, Rahmoune H, Harris LW, Wang L, Leweke FM *et al.* Identification of a biological signature for schizophrenia in serum. *Mol Psychiatry* advance online publication, 12 April 2011 (e-pub ahead of print).
50 Ujike H, Takaki M, Nakata K, Tanaka Y, Takeda T, Kodama M *et al.* CNR1, central cannabinoid receptor gene, associated with susceptibility to hebephrenic schizophrenia. *Mol Psychiatry* 2002; **7**: 515–518.
51 Xu B, Woodroffe A, Rodriguez-Murillo L, Roos JL, van Rensburg EJ, Abecasis GR *et al.* Elucidating the genetic architecture of familial schizophrenia using rare copy number variant and linkage scans. *Proc Natl Acad Sci USA* 2009; **106**: 16746–16751.
52 Eggan SM, Hashimoto T, Lewis DA. Reduced cortical cannabinoid 1 receptor messenger RNA and protein expression in schizophrenia. *Arch Gen Psychiatry* 2008; **65**: 772–784.
53 Newsom RJ, Osterlund C, Masini CV, Day HE, Spencer RL, Campeau S. Cannabinoid receptor type 1 antagonism significantly modulates basal and loud noise induced neural and hypothalamic-pituitary-adrenal axis responses in male Sprague-Dawley rats. *Neuroscience* 2012; **204**: 64–73.
54 Murray RM, Morrison PD, Henquet C, Di Forti M. Cannabis, the mind and society: the hash realities. *Nat Rev Neurosci* 2007; **8**: 885–895.
55 Moghaddam B, Javitt D. From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment. *Neuropsychopharmacology* 2012; **37**: 4–15.
56 Auerbach BD, Osterweil EK, Bear MF. Mutations causing syndromic autism define an axis of synaptic pathophysiology. *Nature* 2011; **480**: 63–68.
57 Cisse M, Halabisky B, Harris J, Devidze N, Dubal DB, Sun B *et al.* Reversing EphB2 depletion rescues cognitive functions in Alzheimer model. *Nature* 2011; **469**: 47–52.
58 Javitt DC, Schoepp D, Kalivas PW, Volkow ND, Zarate C, Merchant K *et al.* Translating glutamate: from pathophysiology to treatment. *Sci Transl Med* 2011; **3**: 102mr2.
59 Levinson DF, Duan J, Oh S, Wang K, Sanders AR, Shi J *et al.* Copy number variants in schizophrenia: confirmation of five previous findings and new evidence for 3q29 microdeletions and VIPR2 duplications. *Am J psychiatry* 2011; **168**: 302–316.
60 Vacic V, McCarthy S, Malhotra D, Murray F, Chou HH, Peoples A *et al.* Duplications of the neuropeptide receptor gene VIPR2 confer significant risk for schizophrenia. *Nature* 2011; **471**: 499–503.
61 Tregellas JR, Tanabe J, Rojas DC, Shatti S, Olincy A, Johnson L *et al.* Effects of an alpha 7-nicotinic agonist on default network activity in schizophrenia. *Biol psychiatry* 2011; **69**: 7–11.
62 Charych EI, Jiang LX, Lo F, Sullivan K, Brandon NJ. Interplay of palmitoylation and phosphorylation in the trafficking and localization of phosphodiesterase 10A: implications for the treatment of schizophrenia. *J Neurosci* 2010; **30**: 9027–9037.
63 Kirov G, Pocklington AJ, Holmans P, Ivanov D, Ikeda M, Ruderfer D *et al. De novo* CNV analysis implicates specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia. *Mol Psychiatry* 2012; **17**: 142–153.
64 Niculescu AB, Lulow LL, Ogden CA, Le-Niculescu H, Salomon DR, Schork NJ *et al.* PhenoChipping of psychotic disorders: a novel approach for deconstructing and quantitating psychiatric phenotypes. *Am J Med Genet B Neuropsychiatr Genet* 2006; **141B**: 653–662.
65 Niculescu 3rd AB. Polypharmacy in oligopopulations: what psychiatric genetics can teach biological psychiatry. *Psychiatr Genet* 2006; **16**: 241–244.
66 Niculescu 3rd AB, Schork NJ, Salomon DR. Mindscape: A convergent perspective on life, mind, consciousness and happiness. *J Affect Disord* 2010; **123**: 1–8.
67 Hennah W, Thomson P, McQuillin A, Bass N, Loukola A, Anjorin A *et al.* DISC1 association, heterogeneity and interplay in schizophrenia and bipolar disorder. *Mol Psychiatry* 2009; **14**: 865–873.
68 Bord L, Wheeler J, Paek M, Saleh M, Lyons-Warren A, Ross CA *et al.* Primate disrupted-in-schizophrenia-1 (DISC1): high divergence of a gene for major mental illnesses in recent evolutionary history. *Neurosci Res* 2006; **56**: 286–293.
69 Craddock N, Owen MJ. The Kraepelinian dichotomy—going, going... but still not gone. *Br J Psychiatry* 2010; **196**: 92–95.
70 Williams HJ, Craddock N, Russo G, Hamshere ML, Moskvina V, Dwyer S *et al.* Most genome-wide significant susceptibility loci for schizophrenia and bipolar disorder reported to date cross-traditional diagnostic boundaries. *Hum Mol Genet* 2011; **20**: 387–391.
71 Buckley PF, Miller BJ, Lehrer DS, Castle DJ. Psychiatric comorbidities and schizophrenia. *Schizophr Bull* 2009; **35**: 383–402.
72 Allen NC, Bagade S, McQueen MB, Ioannidis JP, Kavvoura FK, Khoury MJ *et al.* Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database. *Nat Genet* 2008; **40**: 827–834.
73 Jia P, Sun J, Guo AY, Zhao Z. SZGR: a comprehensive schizophrenia gene resource. *Mol Psychiatry* 2010; **15**: 453–462.
74 Tan HY, Callicott JH, Weinberger DR. Intermediate phenotypes in schizophrenia genetics redux: is it a no brainer? *Mol psychiatry* 2008; **13**: 233–238.
75 Colantuoni C, Lipska BK, Ye T, Hyde TM, Tao R, Leek JT *et al.* Temporal dynamics and genetic control of transcription in the human prefrontal cortex. *Nature* 2011; **478**: 519–523.
76 Degnan JH, Lasky-Su J, Raby BA, Xu M, Molony C, Schadt EE *et al.* Genomics and genome-wide association studies: an integrative approach to expression QTL mapping. *Genomics* 2008; **92**: 129–133.
77 O'Donovan MC, Craddock NJ, Owen MJ. Genetics of psychosis; insights from views across the genome. *Hum Genet* 2009; **126**: 3–12.
78 Clapcote SJ, Lipina TV, Millar JK, Mackie S, Christie S, Ogawa F *et al.* Behavioral phenotypes of Disc1 missense mutations in mice. *Neuron* 2007; **54**: 387–402.

79 Hikida T, Jaaro-Peled H, Seshadri S, Oishi K, Hookway C, Kong S *et al.* Dominant-negative DISC1 transgenic mice display schizophrenia-associated phenotypes detected by measures translatable to humans. *Proc Natl Acad Sci USA* 2007; **104**: 14501–14506.
80 Duan X, Chang JH, Ge S, Faulkner RL, Kim JY, Kitabatake Y *et al.* Disrupted-In-Schizophrenia 1 regulates integration of newly generated neurons in the adult brain. *Cell* 2007; **130**: 1146–1158.
81 Koike H, Arguello PA, Kvajo M, Karayiorgou M, Gogos JA. Disc1 is mutated in the 129S6/SvEv strain and modulates working memory in mice. *Proc Natl Acad Sci USA* 2006; **103**: 3693–3697.
82 Kvajo M, McKellar H, Arguello PA, Drew LJ, Moore H, MacDermott AB *et al.* A mutation in mouse Disc1 that models a schizophrenia risk allele leads to specific alterations in neuronal architecture and cognition. *Proc Natl Acad Sci USA* 2008; **105**: 7076–7081.
83 Shen S, Lang B, Nakamoto C, Zhang F, Pu J, Kuan SL *et al.* Schizophrenia-related neural and behavioral phenotypes in transgenic mice expressing truncated Disc1. *J Neurosci* 2008; **28**: 10893–10904.
84 Pletnikov MV, Ayhan Y, Xu Y, Nikolskaia O, Ovanesov M, Huang H *et al.* Enlargement of the lateral ventricles in mutant DISC1 transgenic mice. *Mol Psychiatry* 2008; **13**: 115.
85 Pletnikov MV, Ayhan Y, Nikolskaia O, Xu Y, Ovanesov MV, Huang H *et al.* Inducible expression of mutant human DISC1 in mice is associated with brain and behavioral abnormalities reminiscent of schizophrenia. *Mol Psychiatry* 2008; **13**: 173–186, 15.
86 Chiba S, Hashimoto R, Hattori S, Yohda M, Lipska B, Weinberger DR *et al.* Effect of antipsychotic drugs on DISC1 and dysbindin expression in mouse frontal cortex and hippocampus. *J Neural Transm* 2006; **113**: 1337–1346.
87 Schurov IL, Handford EJ, Brandon NJ, Whiting PJ. Expression of disrupted in schizophrenia 1 (DISC1) protein in the adult and developing mouse brain indicates its role in neurodevelopment. *Mol Psychiatry* 2004; **9**: 1100–1110.
88 Palo OM, Antila M, Silander K, Hennah W, Kilpinen H, Soronen P *et al.* Association of distinct allelic haplotypes of DISC1 with psychotic and bipolar spectrum disorders and with underlying cognitive impairments. *Hum Mol Genet* 2007; **16**: 2517–2528.
89 Potkin SG, Macciardi F, Guffanti G, Fallon JH, Wang Q, Turner JA *et al.* Identifying gene regulatory networks in schizophrenia. *Neuroimage* 2010; **53**: 839–847.
90 Schumacher J, Laje G, Abou Jamra R, Becker T, Muhleisen TW, Vasilescu C *et al.* The DISC locus and schizophrenia: evidence from an association study in a central European sample and from a meta-analysis across different European populations. *Hum Mol Genet* 2009; **18**: 2719–2727.
91 Glessner JT, Reilly MP, Kim CE, Takahashi N, Albano A, Hou C *et al.* Strong synaptic transmission impact by copy number variations in schizophrenia. *Proc Natl Acad Sci USA* 2010; **107**: 10584–10589.
92 Green EK, Grozeva D, Sims R, Raybould R, Forty L, Gordon-Smith K *et al.* DISC1 exon 11 rare variants found more commonly in schizoaffective spectrum cases than controls. *Am J Med Genet B Neuropsychiatr Genet* 2011; **156B**: 490–492.
93 Liu YL, Fann CS, Liu CM, Chen WJ, Wu JY, Hung SI *et al.* A single nucleotide polymorphism fine mapping study of chromosome 1q42.1 reveals the vulnerability genes for schizophrenia, GNPAT and DISC1: association with impairment of sustained attention. *Biol Psychiatry* 2006; **60**: 554–562.
94 Greenwood TA, Lazzeroni LC, Murray SS, Cadenhead KS, Calkins ME, Dobie DJ *et al.* Analysis of 94 candidate genes and 12 endophenotypes for schizophrenia from the Consortium on the Genetics of Schizophrenia. *Am J Psychiatry* 2011; **168**: 930–946.
95 Ouchi Y, Kubota Y, Kuramasu A, Watanabe T, Ito C. Gene expression profiling in whole cerebral cortices of phencyclidine- or methamphetamine-treated rats. *Brain Res Mol Brain Res* 2005; **140**: 142–149.
96 Fatemi SH, Pearce DA, Brooks AI, Sidwell RW. Prenatal viral infection in mouse causes differential expression of genes in brains of mouse progeny: a potential animal model for schizophrenia and autism. *Synapse* 2005; **57**: 91–99.
97 Glatt SJ, Stone WS, Nossova N, Liew CC, Seidman LJ, Tsuang MT. Similarities and differences in peripheral blood gene-expression signatures of individuals with schizophrenia and their first-degree biological relatives. *American journal of medical genetics Part B, Neuropsychiatric genetics: the official publication of the International Society of Psychiatric Genetics* 2011; **156B**: 869–887.
98 Brzozka MM, Radyushkin K, Wichert SP, Ehrenreich H, Rossner MJ. Cognitive and sensorimotor gating impairments in transgenic mice overexpressing the schizophrenia susceptibility gene Tcf4 in the brain. *Biol Psychiatry* 2010; **68**: 33–40.
99 Lowe XR, Lu X, Marchetti F, Wyrobek AJ. The expression of Troponin T1 gene is induced by ketamine in adult mouse brain. *Brain Res* 2007; **1174**: 7–17.
100 Takahashi Y, Kumanishi T, Hayashi S. Using a DNA microarray method to examine gene expression in brain from clozapine-injected mice. *Ann N Y Acad Sci* 2004; **1025**: 561–569.
101 Matsuoka T, Tsunoda M, Sumiyoshi T, Takasaki I, Tabuchi Y, Seo T *et al.* Effect of MK-801 on gene expressions in the amygdala of rats. *Synapse* 2008; **62**: 1–7.
102 Lewis CM, Levinson DF, Wise LH, DeLisi LE, Straub RE, Hovatta I *et al.* Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: Schizophrenia. *Am J Hum Genet* 2003; **73**: 34–48.
103 Mitkus SN, Hyde TM, Vakkalanka R, Kolachana B, Weinberger DR, Kleinman JE *et al.* Expression of oligodendrocyte-associated genes in dorsolateral prefrontal cortex of patients with schizophrenia. *Schizophr Res* 2008; **98**: 129–138.
104 Bowden NA, Weidenhofer J, Scott RJ, Schall U, Todd J, Michie PT *et al.* Preliminary investigation of gene expression profiles in peripheral blood lymphocytes in schizophrenia. *Schizophr Res* 2006; **82**: 175–183.
105 Wood GK, Tomasiewicz H, Rutishauser U, Magnuson T, Quirion R, Rochford J *et al.* NCAM-180 knockout mice display increased lateral ventricle size and reduced prepulse inhibition of startle. *Neuroreport* 1998; **9**: 461–466.
106 Atz ME, Rollins B, Vawter MP. NCAM1 association study of bipolar disorder and schizophrenia: polymorphisms and alternatively spliced isoforms lead to similarities and differences. *Psychiatr Genet* 2007; **17**: 55–67.
107 Chan MK, Tsang TM, Harris LW, Guest PC, Holmes E, Bahn S. Evidence for disease and antipsychotic medication effects in post-mortem brain from schizophrenia patients. *Mol Psychiatry* 2011; **16**: 1189–1202.
108 Ji B, La Y, Gao L, Zhu H, Tian N, Zhang M *et al.* A comparative proteomics analysis of rat mitochondria from the cerebral cortex and hippocampus in response to antipsychotic medications. *J Proteome Res* 2009; **8**: 3633–3641.
109 Washizuka S, Kametani M, Sasaki T, Tochigi M, Umekage T, Kohda K *et al.* Association of mitochondrial complex I subunit gene NDUFV2 at 18p11 with schizophrenia in the Japanese population. *Am J Med Genet B Neuropsychiatr Genet* 2006; **141B**: 301–304.
110 Ben-Shachar D, Karry R. Sp1 expression is disrupted in schizophrenia; a possible mechanism for the abnormal expression of mitochondrial complex I genes, NDUFV1 and NDUFV2. *PLoS One* 2007; **2**: e817.
111 Prabakaran S, Swatton JE, Ryan MM, Huffaker SJ, Huang JT, Griffin JL *et al.* Mitochondrial dysfunction in schizophrenia: evidence for compromised brain metabolism and oxidative stress. *Mol Psychiatry* 2004; **9**: 684–697, 43.
112 Moy SS, Nonneman RJ, Young NB, Demyanenko GP, Maness PF. Impaired sociability and cognitive function in Nrcam-null mice. *Behav Brain Res* 2009; **205**: 123–131.
113 Ekelund J, Lichtermann D, Hovatta I, Ellonen P, Suvisaari J, Terwilliger JD *et al.* Genome-wide scan for schizophrenia in the Finnish population: evidence for a locus on chromosome 7q22. *Hum Mol Genet* 2000; **9**: 1049–1057.
114 Maziade M, Roy MA, Chagnon YC, Cliche D, Fournier JP, Montgrain N *et al.* Shared and specific susceptibility loci for schizophrenia and bipolar disorder: a dense genome scan in Eastern Quebec families. *Mol Psychiatry* 2005; **10**: 486–499.
115 Faraone SV, Matise T, Svrakic D, Pepple J, Malaspina D, Suarez B *et al.* Genome scan of European-American schizophrenia pedigrees: results of the NIMH Genetics Initiative and Millennium Consortium. *Am J Med Genet* 1998; **81**: 290–295.
116 Takahashi S, Faraone SV, Lasky-Su J, Tsuang MT. Genome-wide scan of homogeneous subtypes of NIMH genetics initiative schizophrenia families. *Psychiatry Res* 2005; **133**: 111–122.
117 Freedman R, Leonard S, Olincy A, Kaufmann CA, Malaspina D, Cloninger CR *et al.* Evidence for the multigenic inheritance of schizophrenia. *Am J Med Genet* 2001; **105**: 794–800.
118 Straub RE, MacLean CJ, Ma Y, Webb BT, Myakishev MV, Harris-Kerr C *et al.* Genome-wide scans of three independent sets of 90 Irish multiplex schizophrenia families and follow-up of selected regions in all families provides evidence for multiple susceptibility genes. *Mol Psychiatry* 2002; **7**: 542–559.
119 Chu TT, Liu Y, Kemether E. Thalamic transcriptome screening in three psychiatric states. *J Hum Genet* 2009; **54**: 665–675.
120 Kuzman MR, Medved V, Terzic J, Krainc D. Genome-wide expression analysis of peripheral blood identifies candidate biomarkers for schizophrenia. *J Psychiatr Res* 2009; **43**: 1073–1077.
121 Hashimoto R, Hashimoto H, Shintani N, Chiba S, Hattori S, Okada T *et al.* Pituitary adenylate cyclase-activating polypeptide is associated with schizophrenia. *Mol Psychiatry* 2007; **12**: 1026–1032.
122 Koga M, Ishiguro H, Horiuchi Y, Inada T, Ujike H, Itokawa M *et al.* Replication study of association between ADCYAP1 gene polymorphisms and schizophrenia. *Psychiatr Genet* 2010; **20**: 123–125.
123 Galter D, Buervenich S, Carmine A, Anvret M, Olson L. ALDH1 mRNA: presence in human dopamine neurons and decreases in substantia nigra in Parkinson's

disease and in the ventral tegmental area in schizophrenia. *Neurobiol Dis* 2003; **14**: 637–647.
124 Barley K, Dracheva S, Byne W. Subcortical oligodendrocyte- and astrocyte-associated gene expression in subjects with schizophrenia, major depression and bipolar disorder. *Schizophr Res* 2009; **112**: 54–64.
125 Wang L, Lockstone HE, Guest PC, Levin Y, Palotas A, Pietsch S *et al.* Expression profiling of fibroblasts identifies cell cycle abnormalities in schizophrenia. *J Proteome Res* 2010; **9**: 521–527.
126 Athanasiu L, Mattingsdal M, Kahler AK, Brown A, Gustafsson O, Agartz I *et al.* Gene variants associated with schizophrenia in a Norwegian genome-wide study are replicated in a large European cohort. *J Psychiatr Res* 2010; **44**: 748–753.
127 Sommer JU, Schmitt A, Heck M, Schaeffer EL, Fendt M, Zink M *et al.* Differential expression of presynaptic genes in a rat model of postnatal hypoxia: relevance to schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2010; **260** (Suppl 2): S81–S89.
128 Pillai A, Mahadik SP. Increased truncated TrkB receptor expression and decreased BDNF/TrkB signaling in the frontal cortex of reeler mouse model of schizophrenia. *Schizophr Res* 2008; **100**: 325–333.
129 Grottick AJ, Bagnol D, Phillips S, McDonald J, Behan DP, Chalmers DT *et al.* Neurotransmission- and cellular stress-related gene expression associated with prepulse inhibition in mice. *Brain Res Mol Brain Res* 2005; **139**: 153–162.
130 Kaiser S, Foltz LA, George CA, Kirkwood SC, Bemis KG, Lin X *et al.* Phencyclidine-induced changes in rat cortical gene expression identified by microarray analysis: implications for schizophrenia. *Neurobiol Dis* 2004; **16**: 220–235.
131 Guo C, Yang Y, Su Y, Si T. Postnatal BDNF expression profiles in prefrontal cortex and hippocampus of a rat schizophrenia model induced by MK-801 administration. *J Biomed Biotechnol* 2010; **2010**: 783297.
132 Chao HM, Kao HT, Porton B. BDNF Val66Met variant and age of onset in schizophrenia. *Am J Med Genet B Neuropsychiatr Genet* 2008; **147B**: 505–506.
133 Gratacos M, Gonzalez JR, Mercader JM, de Cid R, Urretavizcaya M, Estivill X. Brain-derived neurotrophic factor Val66Met and psychiatric disorders: meta-analysis of case-control studies confirm association to substance-related disorders, eating disorders, and schizophrenia. *Biol Psychiatry* 2007; **61**: 911–922.
134 Suchanek R, Owczarek A, Kowalski J. Association Study between BDNF C-281A polymorphism and paranoid schizophrenia in Polish population. *J Mol Neurosci* 2012; **46**: 217–222.
135 Decoster J, van Os J, Kenis G, Henquet C, Peuskens J, De Hert M *et al.* Age at onset of psychotic disorder: cannabis, BDNF Val66Met, and sex-specific models of gene-environment interaction. *Am J Med Genet B Neuropsychiatr Genet* 2011; **156B**: 363–369.
136 Torrey EF, Barci BM, Webster MJ, Bartko JJ, Meador-Woodruff JH, Knable MB. Neurochemical markers for schizophrenia, bipolar disorder, and major depression in postmortem brains. *Biol Psychiatry* 2005; **57**: 252–260.
137 Pillai A. Decreased expression of Sprouty2 in the dorsolateral prefrontal cortex in schizophrenia and bipolar disorder: a correlation with BDNF expression. *PLoS One* 2008; **3**: e1784.
138 Weickert CS, Hyde TM, Lipska BK, Herman MM, Weinberger DR, Kleinman JE. Reduced brain-derived neurotrophic factor in prefrontal cortex of patients with schizophrenia. *Mol Psychiatry* 2003; **8**: 592–610.
139 Rizos EN, Papathanasiou M, Michalopoulou PG, Mazioti A, Douzenis A, Kastania A *et al.* Association of serum BDNF levels with hippocampal volumes in first psychotic episode drug-naive schizophrenic patients. *Schizophr Res* 2011; **129**: 201–204.
140 Grillo RW, Ottoni GL, Leke R, Souza DO, Portela LV, Lara DR. Reduced serum BDNF levels in schizophrenic patients on clozapine or typical antipsychotics. *J Psychiatr Res* 2007; **41**: 31–35.
141 Miodownik C, Maayan R, Ratner Y, Lerner V, Pintov L, Mar M *et al.* Serum levels of brain-derived neurotrophic factor and cortisol to sulfate of dehydroepiandrosterone molar ratio associated with clinical response to l-theanine as augmentation of antipsychotic therapy in schizophrenia and schizoaffective disorder patients. *Clin Neuropharmacol* 2011; **34**: 155–160.
142 Mondelli V, Cattaneo A, Murri MB, Di Forti M, Handley R, Hepgul N *et al.* Stress and inflammation reduce brain-derived neurotrophic factor expression in first-episode psychosis: a pathway to smaller hippocampal volume. *J Clin Psychiatry* 2011; **72**: 1677–1684.
143 Katsel P, Davis KL, Haroutunian V. Variations in myelin and oligodendrocyte-related gene expression across multiple brain regions in schizophrenia: a gene ontology study. *Schizophr Res* 2005; **79**: 157–173.
144 Haller J, Szirmai M, Varga B, Ledent C, Freund TF. Cannabinoid CB1 receptor dependent effects of the NMDA antagonist phencyclidine in the social withdrawal model of schizophrenia. *Behav Pharmacol* 2005; **16**: 415–422.
145 Babovic D, O'Tuathaigh CM, O'Connor AM, O'Sullivan GJ, Tighe O, Croke DT *et al.* Phenotypic characterization of cognition and social behavior in mice with heterozygous versus homozygous deletion of catechol-O-methyltransferase. *Neuroscience* 2008; **155**: 1021–1029.
146 Huotari M, Garcia-Horsman JA, Karayiorgou M, Gogos JA, Mannisto PT. D-amphetamine responses in catechol-O-methyltransferase (COMT) disrupted mice. *Psychopharmacology (Berl)* 2004; **172**: 1–10.
147 Jurata LW, Gallagher P, Lemire AL, Charles V, Brockman JA, Illingworth EL *et al.* Altered expression of hippocampal dentate granule neuron genes in a mouse model of human 22q11 deletion syndrome. *Schizophr Res* 2006; **88**: 251–259.
148 Shifman S, Bronstein M, Sternfeld M, Pisante-Shalom A, Lev-Lehman E, Weizman A *et al.* A highly significant association between a COMT haplotype and schizophrenia. *Am J Hum Genet* 2002; **71**: 1296–1302.
149 Abdolmaleky HM, Cheng KH, Faraone SV, Wilcox M, Glatt SJ, Gao F *et al.* Hypomethylation of MB-COMT promoter is a major risk factor for schizophrenia and bipolar disorder. *Hum Mol Genet* 2006; **15**: 3132–3145.
150 Yamauchi Y, Qin LH, Nishihara M, Sawada K, Kato K, Inoue S. Vulnerability of synaptic plasticity in the complexin II knockout mouse to maternal deprivation stress. *Brain Res* 2005; **1056**: 59–67.
151 Lee HJ, Song JY, Kim JW, Jin SY, Hong MS, Park JK *et al.* Association study of polymorphisms in synaptic vesicle-associated genes, SYN2 and CPLX2, with schizophrenia. *Behav Brain Funct* 2005; **1**: 15.
152 Eastwood SL, Harrison PJ. Decreased expression of vesicular glutamate transporter 1 and complexin II mRNAs in schizophrenia: further evidence for a synaptic pathology affecting glutamate neurons. *Schizophr Res* 2005; **73**: 159–172.
153 Weidenhofer J, Bowden NA, Scott RJ, Tooney PA. Altered gene expression in the amygdala in schizophrenia: up-regulation of genes located in the cytomatrix active zone. *Mol Cell Neurosci* 2006; **31**: 243–250.
154 Ortega-Alvaro A, Aracil-Fernandez A, Garcia-Gutierrez MS, Navarrete F, Manzanares J. Deletion of CB2 cannabinoid receptor induces schizophrenia-related behaviors in mice. *Neuropsychopharmacology* 2011; **36**: 1489–1504.
155 Liu W, Downing AC, Munsie LM, Chen P, Reed MR, Ruble CL *et al.* Pharmacogenetic analysis of the mGlu2/3 agonist LY2140023 monohydrate in the treatment of schizophrenia. *Pharmacogenomics J* advance online publication, 21 December 2010 (e-pub ahead of print).
156 McClay JL, Adkins DE, Aberg K, Bukszar J, Khachane AN, Keefe RS *et al.* Genome-wide pharmacogenomic study of neurocognition as an indicator of antipsychotic treatment response in schizophrenia. *Neuropsychopharmacology* 2011; **36**: 616–626.
157 Zhan L, Kerr JR, Lafuente MJ, Maclean A, Chibalina MV, Liu B *et al.* Altered expression and coregulation of dopamine signalling genes in schizophrenia and bipolar disorder. *Neuropathol Appl Neurobiol* 2011; **37**: 206–219.
158 Dean B, Pavey G, Scarr E, Goeringer K, Copolov DL. Measurement of dopamine D2-like receptors in postmortem CNS and pituitary: differential regional changes in schizophrenia. *Life Sci* 2004; **74**: 3115–3131.
159 Chen XW, Feng YQ, Hao CJ, Guo XL, He X, Zhou ZY *et al.* DTNBP1, a schizophrenia susceptibility gene, affects kinetics of transmitter release. *J Cell Biol* 2008; **181**: 791–801.
160 Feng YQ, Zhou ZY, He X, Wang H, Guo XL, Hao CJ *et al.* Dysbindin deficiency in sandy mice causes reduction of snapin and displays behaviors related to schizophrenia. *Schizophr Res* 2008; **106**: 218–228.
161 Hattori S, Murotani T, Matsuzaki S, Ishizuka T, Kumamoto N, Takeda M *et al.* Behavioral abnormalities and dopamine reductions in sdy mutant mice with a deletion in Dtnbp1, a susceptibility gene for schizophrenia. *Biochem Biophys Res Commun* 2008; **373**: 298–302.
162 Takao K, Toyama K, Nakanishi K, Hattori S, Takamura H, Takeda M *et al.* Impaired long-term memory retention and working memory in sdy mutant mice with a deletion in Dtnbp1, a susceptibility gene for schizophrenia. *Mol Brain* 2008; **1**: 11.
163 Voisey J, Swagell CD, Hughes IP, Lawford BR, Young RM, Morris CP. Analysis of HapMap tag-SNPs in dysbindin (DTNBP1) reveals evidence of consistent association with schizophrenia. *Eur Psychiatry* 2010; **25**: 314–319.
164 Rethelyi JM, Bakker SC, Polgar P, Czobor P, Strengman E, Pasztor PI *et al.* Association study of NRG1, DTNBP1, RGS4, G72/G30, and PIP5K2A with schizophrenia and symptom severity in a Hungarian sample. *Am J Med Genet B Neuropsychiatr Genet* 2010; **153B**: 792–801.
165 Schwab SG, Knapp M, Mondabon S, Hallmayer J, Borrmann-Hassenbach M, Albus M *et al.* Support for association of schizophrenia with genetic variation in the 6p22.3 gene, dysbindin, in sib-pair families with linkage and in an additional sample of triad families. *Am J Hum Genet* 2003; **72**: 185–190.
166 Fatjo-Vilas M, Papiol S, Estrada G, Bombin I, Peralta V, Rosa A *et al.* Dysbindin-1 gene contributes differentially to early- and adult-onset forms of functional psychosis. *Am J Med Genet B Neuropsychiatr Genet* 2011; **156B**: 322–333.
167 Fallin MD, Lasseter VK, Avramopoulos D, Nicodemus KK, Wolyniec PS, McGrath JA *et al.* Bipolar I disorder and schizophrenia: a 440-single-nucleotide polymorphism screen of 64 candidate genes among Ashkenazi Jewish case-parent trios. *Am J Hum Genet* 2005; **77**: 918–936.
168 Kirov G, Ivanov D, Williams NM, Preece A, Nikolov I, Milev R *et al.* Strong evidence for association between the dystrobrevin binding protein 1 gene (DTNBP1) and

schizophrenia in 488 parent-offspring trios from Bulgaria. *Biol Psychiatry* 2004; **55**: 971–975.
169 Weickert CS, Straub RE, McClintock BW, Matsumoto M, Hashimoto R, Hyde TM *et al.* Human dysbindin (DTNBP1) gene expression in normal brain and in schizophrenic prefrontal cortex and midbrain. *Arch Gen Psychiatry* 2004; **61**: 544–555.
170 Talbot K, Eidem WL, Tinsley CL, Benson MA, Thompson EW, Smith RJ *et al.* Dysbindin-1 is reduced in intrinsic, glutamatergic terminals of the hippocampal formation in schizophrenia. *J Clin Invest* 2004; **113**: 1353–1363.
171 Weickert CS, Rothmond DA, Hyde TM, Kleinman JE, Straub RE. Reduced DTNBP1 (dysbindin-1) mRNA in the hippocampal formation of schizophrenia patients. *Schizophr Res* 2008; **98**: 105–110.
172 Talbot K, Louneva N, Cohen JW, Kazi H, Blake DJ, Arnold SE. Synaptic dysbindin-1 reductions in schizophrenia occur in an isoform-specific manner indicating their subsynaptic location. *PLoS One* 2011; **6**: e16886.
173 Chagnon YC, Roy MA, Bureau A, Merette C, Maziade M. Differential RNA expression between schizophrenic patients and controls of the dystrobrevin binding protein 1 and neuregulin 1 genes in immortalized lymphocytes. *Schizophr Res* 2008; **100**: 281–290.
174 Watanabe A, Toyota T, Owada Y, Hayashi T, Iwayama Y, Matsumata M *et al.* Fabp7 maps to a quantitative trait locus for a schizophrenia endophenotype. *PLoS Biol* 2007; **5**: e297.
175 Bergen SE, Fanous AH, Walsh D, O'Neill FA, Kendler KS. Polymorphisms in SLC6A4, PAH, GABRB3, and MAOB and modification of psychotic disorder features. *Schizophr Res* 2009; **109**: 94–97.
176 Bullock WM, Cardon K, Bustillo J, Roberts RC, Perrone-Bizzozero NI. Altered expression of genes involved in GABAergic transmission and neuromodulation of granule cell activity in the cerebellum of schizophrenia patients. *Am J Psychiatry* 2008; **165**: 1594–1603.
177 Hashimoto T, Arion D, Unger T, Maldonado-Aviles JG, Morris HM, Volk DW *et al.* Alterations in GABA-related transcriptome in the dorsolateral prefrontal cortex of subjects with schizophrenia. *Mol Psychiatry* 2008; **13**: 147–161.
178 Silver H, Susser E, Danovich L, Bilker W, Youdim M, Goldin V *et al.* SSRI augmentation of antipsychotic alters expression of GABA(A) receptor and related genes in PMC of schizophrenia patients. *Int J Neuropsychopharmacol* 2011; **14**: 573–584.
179 Straub RE, Lipska BK, Egan MF, Goldberg TE, Callicott JH, Mayhew MB *et al.* Allelic variation in GAD1 (GAD67) is associated with schizophrenia and influences cortical function and gene expression. *Mol Psychiatry* 2007; **12**: 854–869.
180 Hashimoto T, Bazmi HH, Mirnics K, Wu Q, Sampson AR, Lewis DA. Conserved regional patterns of GABA-related transcript expression in the neocortex of subjects with schizophrenia. *Am J Psychiatry* 2008; **165**: 479–489.
181 Benes FM, Lim B, Matzilevich D, Subburaju S, Walsh JP. Circuitry-based gene expression profiles in GABA cells of the trisynaptic pathway in schizophrenics versus bipolars. *Proc Natl Acad Sci USA* 2008; **105**: 20935–20940.
182 Hashimoto T, Volk DW, Eggan SM, Mirnics K, Pierri JN, Sun Z *et al.* Gene expression deficits in a subclass of GABA neurons in the prefrontal cortex of subjects with schizophrenia. *J Neurosci* 2003; **23**: 6315–6326.
183 Mirnics K, Middleton FA, Marquez A, Lewis DA, Levitt P. Molecular characterization of schizophrenia viewed by microarray analysis of gene expression in prefrontal cortex. *Neuron* 2000; **28**: 53–67.
184 Akbarian S, Huang HS. Molecular and cellular mechanisms of altered GAD1/GAD67 expression in schizophrenia and related disorders. *Brain Res Rev* 2006; **52**: 293–304.
185 Heckers S, Stone D, Walsh J, Shick J, Koul P, Benes FM. Differential hippocampal expression of glutamic acid decarboxylase 65 and 67 messenger RNA in bipolar disorder and schizophrenia. *Arch Gen Psychiatry* 2002; **59**: 521–529.
186 Guidotti A, Auta J, Davis JM, Di-Giorgi-Gerevini V, Dwivedi Y, Grayson DR *et al.* Decrease in reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: a postmortem brain study. *Arch Gen Psychiatry* 2000; **57**: 1061–1069.
187 Impagnatiello F, Guidotti AR, Pesold C, Dwivedi Y, Caruncho H, Pisu MG *et al.* A decrease of reelin expression as a putative vulnerability factor in schizophrenia. *Proc Natl Acad Sci USA* 1998; **95**: 15718–15723.
188 Costa E, Davis J, Grayson DR, Guidotti A, Pappas GD, Pesold C. Dendritic spine hypoplasticity and downregulation of reelin and GABAergic tone in schizophrenia vulnerability. *Neurobiol Dis* 2001; **8**: 723–742.
189 Woo TU, Walsh JP, Benes FM. Density of glutamic acid decarboxylase 67 messenger RNA-containing neurons that express the *N*-methyl-D-aspartate receptor subunit NR2A in the anterior cingulate cortex in schizophrenia and bipolar disorder. *Arch Gen Psychiatry* 2004; **61**: 649–657.
190 Veldic M, Caruncho HJ, Liu WS, Davis J, Satta R, Grayson DR *et al.* DNA-methyltransferase 1 mRNA is selectively overexpressed in telencephalic GABAergic interneurons of schizophrenia brains. *Proc Natl Acad Sci USA* 2004; **101**: 348–353.
191 Veldic M, Guidotti A, Maloku E, Davis JM, Costa E. In psychosis, cortical interneurons overexpress DNA-methyltransferase 1. *Proc Natl Acad Sci USA* 2005; **102**: 2152–2157.
192 Hakak Y, Walker JR, Li C, Wong WH, Davis KL, Buxbaum JD *et al.* Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. *Proc Natl Acad Sci USA* 2001; **98**: 4746–4751.
193 Paylor R, Glaser B, Mupo A, Ataliotis P, Spencer C, Sobotka A *et al.* Tbx1 haploinsufficiency is linked to behavioral disorders in mice and humans: implications for 22q11 deletion syndrome. *Proc Natl Acad Sci USA* 2006; **103**: 7729–7734.
194 Ishiguro H, Koga M, Horiuchi Y, Noguchi E, Morikawa M, Suzuki Y *et al.* Supportive evidence for reduced expression of GNB1L in schizophrenia. *Schizophr Bull* 2010; **36**: 756–765.
195 Williams NM, Glaser B, Norton N, Williams H, Pierce T, Moskvina V *et al.* Strong evidence that GNB1L is associated with schizophrenia. *Hum Mol Genet* 2008; **17**: 555–566.
196 Wiedholz LM, Owens WA, Horton RE, Feyder M, Karlsson RM, Hefner K *et al.* Mice lacking the AMPA GluR1 receptor exhibit striatal hyperdopaminergia and 'schizophrenia-related' behaviors. *Mol Psychiatry* 2008; **13**: 631–640.
197 Toyooka K, Usui M, Washiyama K, Kumanishi T, Takahashi Y. Gene expression profiles in the brain from phencyclidine-treated mouse by using DNA microarray. *Ann N Y Acad Sci* 2002; **965**: 10–20.
198 Magri C, Gardella R, Barlati SD, Podavini D, Iatropoulos P, Bonomi S *et al.* Glutamate AMPA receptor subunit 1 gene (GRIA1) and DSM-IV-TR schizophrenia: a pilot case-control association study in an Italian sample. *Am J Med Genet B Neuropsychiatr Genet* 2006; **141B**: 287–293.
199 Leon CA, Schumacher J, Kluck N, Herold C, Schulze TG, Propping P *et al.* Association study of the GRIA1 and CLINT1 (Epsin 4) genes in a German schizophrenia sample. *Psychiatr Genet* 2011; **21**: 114.
200 Sokolov BP. Expression of NMDAR1, GluR1, GluR7, and KA1 glutamate receptor mRNAs is decreased in frontal cortex of "neuroleptic-free" schizophrenics: evidence on reversible up-regulation by typical neuroleptics. *J Neurochem* 1998; **71**: 2454–2464.
201 Ibrahim HM, Hogg Jr AJ, Healy DJ, Haroutunian V, Davis KL, Meador-Woodruff JH. Ionotropic glutamate receptor binding and subunit mRNA expression in thalamic nuclei in schizophrenia. *Am J Psychiatry* 2000; **157**: 1811–1823.
202 Dracheva S, McGurk SR, Haroutunian V. mRNA expression of AMPA receptors and AMPA receptor binding proteins in the cerebral cortex of elderly schizophrenics. *J Neurosci Res* 2005; **79**: 868–878.
203 Stadler F, Kolb G, Rubusch L, Baker SP, Jones EG, Akbarian S. Histone methylation at gene promoters is associated with developmental regulation and region-specific expression of ionotropic and metabotropic glutamate receptors in human brain. *J Neurochem* 2005; **94**: 324–336.
204 Sagata N, Iwaki A, Aramaki T, Takao K, Kura S, Tsuzuki T *et al.* Comprehensive behavioural study of GluR4 knockout mice: implication in cognitive function. *Genes Brain Behav* 2010; **9**: 899–909.
205 Chong VZ, Young LT, Mishra RK. cDNA array reveals differential gene expression following chronic neuroleptic administration: implications of synapsin II in haloperidol treatment. *J Neurochem* 2002; **82**: 1533–1539.
206 Makino C, Fujii Y, Kikuta R, Hirata N, Tani A, Shibata A *et al.* Positive association of the AMPA receptor subunit GluR4 gene (GRIA4) haplotype with schizophrenia: linkage disequilibrium mapping using SNPs evenly distributed across the gene region. *Am J Med Genet B Neuropsychiatr Genet* 2003; **116B**: 17–22.
207 Beneyto M, Meador-Woodruff JH. Lamina-specific abnormalities of NMDA receptor-associated postsynaptic protein transcripts in the prefrontal cortex in schizophrenia and bipolar disorder. *Neuropsychopharmacology* 2008; **33**: 2175–2186.
208 Kochlamazashvili G, Senkov O, Grebenyuk S, Robinson C, Xiao MF, Stummeyer K *et al.* Neural cell adhesion molecule-associated polysialic acid regulates synaptic plasticity and learning by restraining the signaling through GluN2B-containing NMDA receptors. *J Neurosci* 2010; **30**: 4171–4183.
209 Marvanova M, Lakso M, Wong G. Identification of genes regulated by memantine and MK-801 in adult rat brain by cDNA microarray analysis. *Neuropsychopharmacology* 2004; **29**: 1070–1079.
210 Bowden NA, Scott RJ, Tooney PA. Altered gene expression in the superior temporal gyrus in schizophrenia. *BMC Genomics* 2008; **9**: 199.
211 Kinney GG, Burno M, Campbell UC, Hernandez LM, Rodriguez D, Bristow LJ *et al.* Metabotropic glutamate subtype 5 receptors modulate locomotor activity and sensorimotor gating in rodents. *J Pharmacol Exp Ther* 2003; **306**: 116–123.
212 Devon RS, Anderson S, Teague PW, Muir WJ, Murray V, Pelosi AJ *et al.* The genomic organisation of the metabotropic glutamate receptor subtype 5 gene, and its association with schizophrenia. *Mol Psychiatry* 2001; **6**: 311–314.

213 Xi ZR, Qin W, Yang YF, He G, Gao SH, Ren MS *et al.* Transmission disequilibrium analysis of the GSN gene in a cohort of family trios with schizophrenia. *Neurosci Lett* 2004; **372**: 200–203.
214 Davis KL, Haroutunian V. Global expression-profiling studies and oligodendrocyte dysfunction in schizophrenia and bipolar disorder. *Lancet* 2003; **362**: 758.
215 Barbier E, Zapata A, Oh E, Liu Q, Zhu F, Undie A *et al.* Supersensitivity to amphetamine in protein kinase-C interacting protein/HINT1 knockout mice. *Neuropsychopharmacology* 2007; **32**: 1774–1782.
216 Chen Q, Wang X, O'Neill FA, Walsh D, Kendler KS, Chen X. Is the histidine triad nucleotide-binding protein 1 (HINT1) gene a candidate for schizophrenia? *Schizophr Res* 2008; **106**: 200–207.
217 Kurotaki N, Tasaki S, Mishima H, Ono S, Imamura A, Kikuchi T *et al.* Identification of novel schizophrenia loci by homozygosity mapping using DNA microarray analysis. *PLoS One* 2011; **6**: e20589.
218 Vawter MP, Crook JM, Hyde TM, Kleinman JE, Weinberger DR, Becker KG *et al.* Microarray analysis of gene expression in the prefrontal cortex in schizophrenia: a preliminary study. *Schizophr Res* 2002; **58**: 11–20.
219 Steward LJ, Kennedy MD, Morris BJ, Pratt JA. The atypical antipsychotic drug clozapine enhances chronic PCP-induced regulation of prefrontal cortex 5-HT2A receptors. *Neuropharmacology* 2004; **47**: 527–537.
220 McClay JL, Adkins DE, Aberg K, Stroup S, Perkins DO, Vladimirov VI *et al.* Genome-wide pharmacogenomic analysis of response to treatment with antipsychotics. *Mol Psychiatry* 2011; **16**: 76–85.
221 Polesskaya OO, Sokolov BP. Differential expression of the "C" and "T" alleles of the 5-HT2A receptor gene in the temporal cortex of normal individuals and schizophrenics. *J Neurosci Res* 2002; **67**: 812–822.
222 Garbett K, Gal-Chis R, Gaszner G, Lewis DA, Mirnics K. Transcriptome alterations in the prefrontal cortex of subjects with schizophrenia who committed suicide. *Neuropsychopharmacol Hung* 2008; **10**: 9–14.
223 Fukuda Y, Koga M, Arai M, Noguchi E, Ohtsuki T, Horiuchi Y *et al.* Monoallelic and unequal allelic expression of the HTR2A gene in human brain and peripheral lymphocytes. *Biol Psychiatry* 2006; **60**: 1331–1335.
224 Kushima I, Nakamura Y, Aleksic B, Ikeda M, Ito Y, Shiino T *et al.* Resequencing and association analysis of the KALRN and EPHB1 genes and their contribution to schizophrenia susceptibility. *Schizophr Bull* advance online publication, 1 November 2010 (e-pub ahead of print).
225 Hill JJ, Hashimoto T, Lewis DA. Molecular mechanisms contributing to dendritic spine alterations in the prefrontal cortex of subjects with schizophrenia. *Mol Psychiatry* 2006; **11**: 557–566.
226 Li C, Zheng Y, Qin W, Tao R, Pan Y, Xu Y *et al.* A family-based association study of kinesin heavy chain member 2 gene (KIF2) and schizophrenia. *Neurosci Lett* 2006; **407**: 151–155.
227 Rojas P, Joodmardi E, Hong Y, Perlmann T, Ogren SO. Adult mice with reduced Nurr1 expression: an animal model for schizophrenia. *Mol Psychiatry* 2007; **12**: 756–766.
228 Huang J, Perlis RH, Lee PH, Rush AJ, Fava M, Sachs GS *et al.* Cross-disorder genomewide analysis of schizophrenia, bipolar disorder, and depression. *Am J Psychiatry* 2010; **167**: 1254–1263.
229 O'Tuathaigh CM, Babovic D, O'Sullivan GJ, Clifford JJ, Tighe O, Croke DT *et al.* Phenotypic characterization of spatial cognition and social behavior in mice with 'knockout' of the schizophrenia risk gene neuregulin 1. *Neuroscience* 2007; **147**: 18–27.
230 Stefansson H, Sigurdsson E, Steinthorsdottir V, Bjornsdottir S, Sigmundsson T, Ghosh S *et al.* Neuregulin 1 and susceptibility to schizophrenia. *Am J Hum Genet* 2002; **71**: 877–892.
231 Chen YJ, Johnson MA, Lieberman MD, Goodchild RE, Schobel S, Lewandowski N *et al.* Type III neuregulin-1 is required for normal sensorimotor gating, memory-related behaviors, and corticostriatal circuit components. *J Neurosci* 2008; **28**: 6872–6883.
232 Walker RM, Christoforou A, Thomson PA, McGhee KA, Maclean A, Muhleisen TW *et al.* Association analysis of Neuregulin 1 candidate regions in schizophrenia and bipolar disorder. *Neurosci Lett* 2010; **478**: 9–13.
233 van Schijndel JE, van Loo KM, van Zweeden M, Djurovic S, Andreassen OA, Hansen T *et al.* Three-cohort targeted gene screening reveals a non-synonymous TRKA polymorphism associated with schizophrenia. *J Psychiatr Res* 2009; **43**: 1195–1199.
234 Mozhui XW, Chen J, Mulligan MK, Li Z, Ingles J, Chen X *et al.* Genetic regulation of Nrxn1 expression: an integrative cross-species analysis of schizophrenia candidate genes. *Translational Psychiatry* 2011; **1**: e38.
235 Stefansson H, Sarginson J, Kong A, Yates P, Steinthorsdottir V, Gudfinnsson E *et al.* Association of neuregulin 1 with schizophrenia confirmed in a Scottish population. *Am J Hum Genet* 2003; **72**: 83–87.
236 Harris LW, Lockstone HE, Khaitovich P, Weickert CS, Webster MJ, Bahn S. Gene expression in the prefrontal cortex during adolescence: implications for the onset of schizophrenia. *BMC Med Genomics* 2009; **2**: 28.
237 Colantuoni C, Hyde TM, Mitkus S, Joseph A, Sartorius L, Aguirre C *et al.* Age-related changes in the expression of schizophrenia susceptibility genes in the human prefrontal cortex. *Brain Struct Funct* 2008; **213**: 255–271.
238 Law AJ, Shannon Weickert C, Hyde TM, Kleinman JE, Harrison PJ. Neuregulin-1 (NRG-1) mRNA and protein in the adult human brain. *Neuroscience* 2004; **127**: 125–136.
239 Hahn CG, Wang HY, Cho DS, Talbot K, Gur RE, Berrettini WH *et al.* Altered neuregulin 1-erbB4 signaling contributes to NMDA receptor hypofunction in schizophrenia. *Nat Med* 2006; **12**: 824–828.
240 Law AJ, Lipska BK, Weickert CS, Hyde TM, Straub RE, Hashimoto R *et al.* Neuregulin 1 transcripts are differentially expressed in schizophrenia and regulated by 5′ SNPs associated with the disease. *Proc Natl Acad Sci USA* 2006; **103**: 6747–6752.
241 Hashimoto R, Straub RE, Weickert CS, Hyde TM, Kleinman JE, Weinberger DR. Expression analysis of neuregulin-1 in the dorsolateral prefrontal cortex in schizophrenia. *Mol Psychiatry* 2004; **9**: 299–307.
242 Petryshen TL, Middleton FA, Kirby A, Aldinger KA, Purcell S, Tahl AR *et al.* Support for involvement of neuregulin 1 in schizophrenia pathophysiology. *Mol Psychiatry* 2005; **10**: 366–374, 28.
243 Middleton FA, Pato CN, Gentile KL, McGann L, Brown AM, Trauzzi M *et al.* Gene expression analysis of peripheral blood leukocytes from discordant sib-pairs with schizophrenia and bipolar disorder reveals points of convergence between genetic and functional genomic approaches. *Am J Med Genet B Neuropsychiatr Genet* 2005; **136**: 12–25.
244 Siuciak JA, McCarthy SA, Chapin DS, Martin AN. Behavioral and neurochemical characterization of mice deficient in the phosphodiesterase-4B (PDE4B) enzyme. *Psychopharmacology (Berl)* 2008; **197**: 115–126.
245 Dlaboga D, Hajjhussein H, O'Donnell JM. Chronic haloperidol and clozapine produce different patterns of effects on phosphodiesterase-1B, -4B, and -10A expression in rat striatum. *Neuropharmacology* 2008; **54**: 745–754.
246 Fatemi SH, Folsom TD, Reutiman TJ, Braun NN, Lavergne LG. Levels of phosphodiesterase 4A and 4B are altered by chronic treatment with psychotropic medications in rat frontal cortex. *Synapse* 2010; **64**: 550–555.
247 Fatemi SH, King DP, Reutiman TJ, Folsom TD, Laurence JA, Lee S *et al.* PDE4B polymorphisms and decreased PDE4B expression are associated with schizophrenia. *Schizophr Res* 2008; **101**: 36–49.
248 Kahler AK, Otnaess MK, Wirgenes KV, Hansen T, Jonsson EG, Agartz I *et al.* Association study of PDE4B gene variants in Scandinavian schizophrenia and bipolar disorder multicenter case-control samples. *Am J Med Genet B Neuropsychiatr Genet* 2010; **153B**: 86–96.
249 Pickard BS, Thomson PA, Christoforou A, Evans KL, Morris SW, Porteous DJ *et al.* The PDE4B gene confers sex-specific protection against schizophrenia. *Psychiatr Genet* 2007; **17**: 129–133.
250 Tomppo L, Hennah W, Lahermo P, Loukola A, Tuulio-Henriksson A, Suvisaari J *et al.* Association between genes of disrupted in schizophrenia 1 (DISC1) interactors and schizophrenia supports the role of the DISC1 pathway in the etiology of major mental illnesses. *Biol Psychiatry* 2009; **65**: 1055–1062.
251 Chen ML, Chen CH. Microarray analysis of differentially expressed genes in rat frontal cortex under chronic risperidone treatment. *Neuropsychopharmacology* 2005; **30**: 268–277.
252 Carroll LS, Williams NM, Moskvina V, Russell E, Norton N, Williams HJ *et al.* Evidence for rare and common genetic risk variants for schizophrenia at protein kinase C, alpha. *Mol Psychiatry* 2010; **15**: 1101–1111.
253 Jablensky A, Morar B, Wiltshire S, Carter K, Dragovic M, Badcock JC *et al.* Polymorphisms associated with normal memory variation also affect memory impairment in schizophrenia. *Genes Brain Behav* 2011; **10**: 410–417.
254 Ballmaier M, Zoli M, Leo G, Agnati LF, Spano P. Preferential alterations in the mesolimbic dopamine pathway of heterozygous reeler mice: an emerging animal-based model of schizophrenia. *Eur J Neurosci* 2002; **15**: 1197–1205.
255 Fatemi SH, Reutiman TJ, Folsom TD. Chronic psychotropic drug treatment causes differential expression of Reelin signaling system in frontal cortex of rats. *Schizophr Res* 2009; **111**: 138–152.
256 Alkelai A, Lupoli S, Greenbaum L, Kohn Y, Kanyas-Sarner K, Ben-Asher E *et al.* DOCK4 and CEACAM21 as novel schizophrenia candidate genes in the Jewish population. *Int J Neuropsychopharmacol* 2011; 20:1–2011.
257 Kahler AK, Djurovic S, Kulle B, Jonsson EG, Agartz I, Hall H *et al.* Association analysis of schizophrenia on 18 genes involved in neuronal migration: MDGA1 as a new susceptibility gene. *Am J Med Genet B Neuropsychiatr Genet* 2008; **147B**: 1089–1100.
258 Ovadia G, Shifman S. The genetic variation of RELN expression in schizophrenia and bipolar disorder. *PLoS One* 2011; **6**: e19955.
259 Shifman S, Johannesson M, Bronstein M, Chen SX, Collier DA, Craddock NJ *et al.* Genome-wide association identifies a common variant in the reelin gene that increases the risk of schizophrenia only in women. *PLoS Genet* 2008; **4**: e28.

260 Knable MB, Barci BM, Webster MJ, Meador-Woodruff J, Torrey EF. Molecular abnormalities of the hippocampus in severe psychiatric illness: postmortem findings from the Stanley Neuropathology Consortium. *Mol Psychiatry* 2004; **9**: 609–620, 544.
261 Grayson DR, Jia X, Chen Y, Sharma RP, Mitchell CP, Guidotti A *et al.* Reelin promoter hypermethylation in schizophrenia. *Proc Natl Acad Sci USA* 2005; **102**: 9341–9346.
262 Grillet N, Pattyn A, Contet C, Kieffer BL, Goridis C, Brunet JF. Generation and characterization of Rgs4 mutant mice. *Mol Cell Biol* 2005; **25**: 4221–4228.
263 MacDonald ML, Eaton ME, Dudman JT, Konradi C. Antipsychotic drugs elevate mRNA levels of presynaptic proteins in the frontal cortex of the rat. *Biol Psychiatry* 2005; **57**: 1041–1051.
264 McOmish CE, Burrows EL, Howard M, Hannan AJ. PLC-beta1 knockout mice as a model of disrupted cortical development and plasticity: behavioral endophenotypes and dysregulation of RGS4 gene expression. *Hippocampus* 2008; **18**: 824–834.
265 So HC, Chen RY, Chen EY, Cheung EF, Li T, Sham PC. An association study of RGS4 polymorphisms with clinical phenotypes of schizophrenia in a Chinese population. *Am J Med Genet B Neuropsychiatr Genet* 2008; **147B**: 77–85.
266 Prasad KM, Almasy L, Gur RC, Gur RE, Pogue-Geile M, Chowdari KV *et al.* RGS4 polymorphisms associated with variability of cognitive performance in a family-based schizophrenia sample. *Schizophr Bull* 2010; **36**: 983–990.
267 Bowden NA, Scott RJ, Tooney PA. Altered expression of regulator of G-protein signalling 4 (RGS4) mRNA in the superior temporal gyrus in schizophrenia. *Schizophr Res* 2007; **89**: 165–168.
268 Lipska BK, Mitkus S, Caruso M, Hyde TM, Chen J, Vakkalanka R *et al.* RGS4 mRNA expression in postmortem human cortex is associated with COMT Val158Met genotype and COMT enzyme activity. *Hum Mol Genet* 2006; **15**: 2804–2812.
269 Mirnics K, Middleton FA, Stanwood GD, Lewis DA, Levitt P. Disease-specific changes in regulator of G-protein signaling 4 (RGS4) expression in schizophrenia. *Mol Psychiatry* 2001; **6**: 293–301.
270 Prasad KM, Chowdari KV, Nimgaonkar VL, Talkowski ME, Lewis DA, Keshavan MS. Genetic polymorphisms of the RGS4 and dorsolateral prefrontal cortex morphometry among first episode schizophrenia patients. *Mol Psychiatry* 2005; **10**: 213–219.
271 Erdely HA, Tamminga CA, Roberts RC, Vogel MW. Regional alterations in RGS4 protein in schizophrenia. *Synapse* 2006; **59**: 472–479.
272 Volk DW, Eggan SM, Lewis DA. Alterations in metabotropic glutamate receptor 1alpha and regulator of G protein signaling 4 in the prefrontal cortex in schizophrenia. *Am J Psychiatry* 2010; **167**: 1489–1498.
273 Deng X, Shibata H, Ninomiya H, Tashiro N, Iwata N, Ozaki N *et al.* Association study of polymorphisms in the excitatory amino acid transporter 2 gene (SLC1A2) with schizophrenia. *BMC Psychiatry* 2004; **4**: 21.
274 Shao L, Vawter MP. Shared gene expression alterations in schizophrenia and bipolar disorder. *Biol Psychiatry* 2008; **64**: 89–97.
275 Matute C, Melone M, Vallejo-Illarramendi A, Conti F. Increased expression of the astrocytic glutamate transporter GLT-1 in the prefrontal cortex of schizophrenics. *Glia* 2005; **49**: 451–455.
276 Jeans AF, Oliver PL, Johnson R, Capogna M, Vikman J, Molnar Z *et al.* A dominant mutation in Snap25 causes impaired vesicle trafficking, sensorimotor gating, and ataxia in the blind-drunk mouse. *Proc Natl Acad Sci USA* 2007; **104**: 2431–2436.
277 Fanous AH, Zhao Z, van den Oord EJ, Maher BS, Thiselton DL, Bergen SE *et al.* Association study of SNAP25 and schizophrenia in Irish family and case-control samples. *Am J Med Genet B Neuropsychiatr Genet* 2010; **153B**: 663–674.
278 Glatt SJ, Everall IP, Kremen WS, Corbeil J, Sasik R, Khanlou N *et al.* Comparative gene expression analysis of blood and brain provides concurrent validation of SELENBP1 up-regulation in schizophrenia. *Proc Natl Acad Sci USA* 2005; **102**: 15533–15538.
279 Thompson PM, Egbufoama S, Vawter MP. SNAP-25 reduction in the hippocampus of patients with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2003; **27**: 411–417.
280 Karson CN, Mrak RE, Schluterman KO, Sturner WQ, Sheng JG, Griffin WS. Alterations in synaptic proteins and their encoding mRNAs in prefrontal cortex in schizophrenia: a possible neurochemical basis for 'hypofrontality'. *Mol Psychiatry* 1999; **4**: 39–45.
281 Hemby SE, Ginsberg SD, Brunk B, Arnold SE, Trojanowski JQ, Eberwine JH. Gene expression profile for schizophrenia: discrete neuron transcription patterns in the entorhinal cortex. *Arch Gen Psychiatry* 2002; **59**: 631–640.
282 Gabriel SM, Haroutunian V, Powchik P, Honer WG, Davidson M, Davies P *et al.* Increased concentrations of presynaptic proteins in the cingulate cortex of subjects with schizophrenia. *Arch Gen Psychiatry* 1997; **54**: 559–566.
283 Clark D, Dedova I, Cordwell S, Matsumoto I. A proteome analysis of the anterior cingulate cortex gray matter in schizophrenia. *Mol Psychiatry* 2006; **11**: 459–470, 23.
284 Dyck BA, Skoblenick KJ, Castellano JM, Ki K, Thomas N, Mishra RK. Synapsin II knockout mice show sensorimotor gating and behavioural abnormalities similar to those in the phencyclidine-induced preclinical animal model of schizophrenia. *Schizophr Res* 2007; **97**: 292–293.
285 Dyck BA, Skoblenick KJ, Castellano JM, Ki K, Thomas N, Mishra RK. Behavioral abnormalities in synapsin II knockout mice implicate a causal factor in schizophrenia. *Synapse* 2009; **63**: 662–672.
286 Chen Q, He G, Qin W, Chen QY, Zhao XZ, Duan SW *et al.* Family-based association study of synapsin II and schizophrenia. *Am J Hum Genet* 2004; **75**: 873–877.
287 Saviouk V, Moreau MP, Tereshchenko IV, Brzustowicz LM. Association of synapsin 2 with schizophrenia in families of Northern European ancestry. *Schizophr Res* 2007; **96**: 100–111.
288 Vawter MP, Thatcher L, Usen N, Hyde TM, Kleinman JE, Freed WJ. Reduction of synapsin in the hippocampus of patients with bipolar disorder and schizophrenia. *Mol Psychiatry* 2002; **7**: 571–578.
289 Potkin SG, Turner JA, Guffanti G, Lakatos A, Fallon JH, Nguyen DD *et al.* A genome-wide association study of schizophrenia using brain activation as a quantitative phenotype. *Schizophr Bull* 2009; **35**: 96–108.
290 Martin MV, Rollins B, Sequeira PA, Mesen A, Byerley W, Stein R *et al.* Exon expression in lymphoblastoid cell lines from subjects with schizophrenia before and after glucose deprivation. *BMC Med Genomics* 2009; **2**: 62.

Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)

Supplementary Information

Figure S1. Lack of gene size effect bias with our CFG approach.

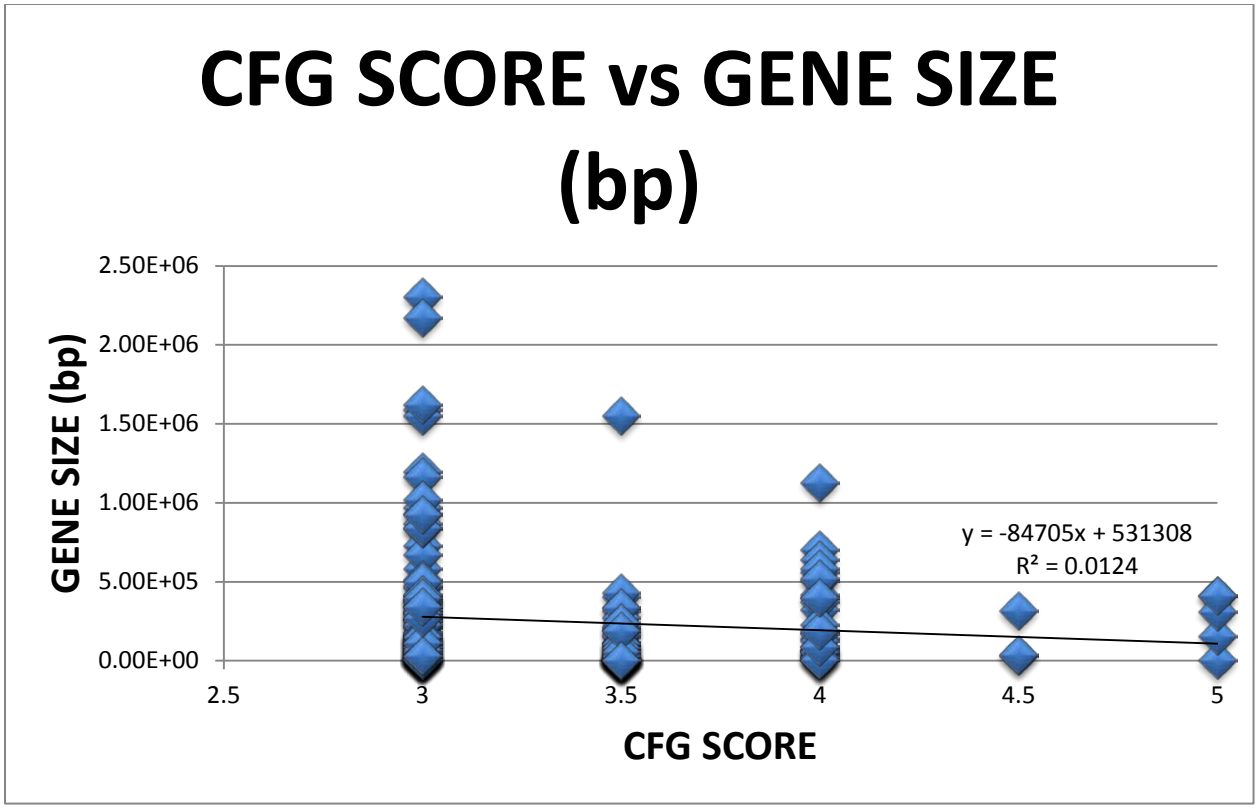

Table S1.Top candidate genes for schziophrenia- extended list. CFG analysis of ISC GWAS data. Genes with a CFG score of 3 and above. For top genes with CFG score of 4 and above, we also list wether there is any evidence for involvement in autism and/or Alzheimer Disease (AD). 15 of 42 had evidence of involvement in autism and 10 out 42 had evidence of involvement in AD.

Gene Symbol/Name	CFG Score	Autism Evidence	Alzheimer Evidence
DISC1 disrupted in schizophrenia 1	5.0	Yes Kilpinen et al. 2008	Yes Young-Pearse 2011
HSPA1B heat shock 70kDa protein 1B	5.0		
MBP myelin basic protein	5.0		Yes Desai 2009
TCF4 transcription factor 4	5.0		
MOBP myelin-associated oligodendrocyte basic protein	4.0		
NCAM1 neural cell adhesion molecule 1	4.5		
NDUFV2 NADH dehydrogenase (ubiquinone) flavoprotein 2, 24kDa	4.5		
NRCAM neuronal cell adhesion molecule	4.5	Yes Marui et al. 2009	
RAB18 RAB18, member RAS oncogene family	4.5		
ADCYAP1 adenylate cyclase activating polypeptide 1 (pituitary)	4.0		
ALDH1A1 aldehyde dehydrogenase 1 family, member A1	4.0		
ANK3 ankyrin 3, node of Ranvier (ankyrin G)	4.0		
BDNF brain-derived neurotrophic factor	4.0	Yes Correia et al. 2010	Yes Nagahara et al. 2009
CD9 CD9 molecule	4.0		
CNR1 cannabinoid receptor 1 (brain)	4.0	Yes Chakrabarti et al. 2011	
COMT catechol-O-methyltransferase	4.0		
CPLX2 complexin 2	4.0	Yes Voineagu et al. 2011	
DRD2 dopamine receptor D2	4.0		
DTNBP1 dystrobrevin binding protein 1	4.0		
FABP7 fatty acid binding protein 7, brain	4.0		
GABRB3 gamma-aminobutyric acid (GABA) A receptor, beta 3	4.0	Yes Buxbaum et al. 2002	Yes Simpson et al. 2011
GAD1 glutamate decarboxylase 1 (brain, 67kDa)	4.0		
GNB1L guanine nucleotide binding protein (G protein), beta polypeptide 1-like	4.0	Yes Chen et al. 2011	
GRIA1 glutamate receptor, ionotropic, AMPA 1	4.0		
GRIA4 glutamate receptor, ionotrophic, AMPA 4	4.0		Yes Jacob CP et al. 2007
GRIN2B glutamate receptor, ionotropic, N-methyl D-aspartate 2B	4.0	Yes O'Roak et al. 2011	Yes Stein JL et al. 2010
GRM5 glutamate receptor, metabotropic 5	4.0	Yes Dolen et al. 2007	
GSN gelsolin	4.0		
HINT1 histidine triad nucleotide binding protein 1	4.0		
HTR2A	4.0		

5-hydroxytryptamine (serotonin) receptor 2A			
KALRN kalirin, RhoGEF kinase	4.0	Yes Ben-David et al. 2011 Hussman et al. 2011	Yes Youn H et. 2007
KIF2A kinesin heavy chain member 2A	4.0	Yes Voineagu et al. 2011	
NR4A2 nuclear receptor subfamily 4, group A, member 2	4.0		
NRG1 neuregulin 1	4.0		
PDE4B phosphodiesterase 4B, cAMP-specific	4.0	Yes Braun et al. 2007	
PRKCA protein kinase C, alpha	4.0	Yes Hussman et al. 2011	
RELN reelin	4.0	Yes Ashley-Koch et al., 2007; Perisco et al., 2002	Yes Kramer PL et al. 2011
RGS4 regulator of G-protein signaling 4	4.0		Yes Emilsson L et al. 2006
SLC1A2 solute carrier family 1 (glial high affinity glutamate transporter), member 2	4.0		
SNAP25 synaptosomal-associated protein, 25kDa	4.0		Yes Adlard PA et al. 2010
SYN2 synapsin II	4.0		
TNIK TRAF2 and NCK interacting kinase	4.0		

ACBD3 acyl-CoA binding domain containing 3	3.5
ARID5A AT rich interactive domain 5A (MRF1-like)	3.5
ASAH1 N-acylsphingosine amidohydrolase (acid ceramidase) 1	3.5
B2M beta-2-microglobulin	3.5
C1QB complement component 1, q subcomponent, B chain	3.5
CALB1 calbindin 1, 28kDa	3.5
CASP3 caspase 3, apoptosis-related cysteine peptidase	3.5
CCND3 cyclin D3	3.5
CD47 CD47 molecule	3.5
CNR2 cannabinoid receptor 2 (macrophage)	3.5
DNAJA4 DnaJ (Hsp40) homolog, subfamily A, member 4	3.5
DUSP1 dual specificity phosphatase 1	3.5
EBF1 early B-cell factor 1	3.5
EGR1 early growth response 1	3.5
FUT8 fucosyltransferase 8 (alpha (1,6) fucosyltransferase)	3.5
FYN FYN oncogene related to SRC, FGR, YES	3.5
GAP43	3.5

growth associated protein 43	
GNPDA1 glucosamine-6-phosphate deaminase 1	3.5
GRIN2A glutamate receptor, ionotropic, N-methyl D-aspartate 2A	3.5
HSPA1A heat shock 70kDa protein 1A	3.5
IGF1R insulin-like growth factor 1 receptor	3.5
LPL lipoprotein lipase	3.5
MAL mal, T-cell differentiation protein	3.5
MAP6 microtubule-associated protein 6	3.5
MFHAS1 malignant fibrous histiocytoma amplified sequence 1	3.5
MMD monocyte to macrophage differentiation-associated	3.5
MYLK myosin light chain kinase	3.5
NEFL neurofilament, light polypeptide	3.5
NEFM neurofilament, medium polypeptide	3.5
NFKBIA nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha	3.5
NTSR2 neurotensin receptor 2	3.5
PDE10A phosphodiesterase 10A	3.5
PDE4D phosphodiesterase 4D, cAMP-specific	3.5
PKM2 pyruvate kinase, muscle	3.5
PRKAR2B protein kinase, cAMP-dependent, regulatory, type II, beta	3.5
PRNP prion protein	3.5
RAB2A RAB2A, member RAS oncogene family	3.5
RAP2A RAP2A, member of RAS oncogene family	3.5
RIMS3 regulating synaptic membrane exocytosis 3	3.5
SH3GL2 SH3-domain GRB2-like 2	3.5
SLC1A3 solute carrier family 1 (glial high affinity glutamate transporter), member 3	3.5
SLC6A9 solute carrier family 6 (neurotransmitter transporter, glycine), member 9	3.5
SOD1 superoxide dismutase 1, soluble	3.5
STXBP6 syntaxin binding protein 6 (amisyn)	3.5
VDAC1 voltage-dependent anion channel 1	3.5
YWHAE tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide	3.5
ZBTB16 zinc finger and BTB domain containing 16	3.5
ABCA1 ATP-binding cassette, sub-family A (ABC1), member 1	3.0
ADCY1 adenylate cyclase 1 (brain)	3.0

ADRBK2 (GRK3) adrenergic, beta, receptor kinase 2	3.0
APC adenomatous polyposis coli	3.0
ARHGAP18 Rho GTPase activating protein 18	3.0
ATXN1 ataxin 1	3.0
AZIN1 antizyme inhibitor 1	3.0
CACNG2 calcium channel, voltage-dependent, gamma subunit 2	3.0
CHRNA7 cholinergic receptor, nicotinic, alpha 7	3.0
CLU clusterin	3.0
CMIP c-Maf inducing protein	3.0
CNTNAP2 contactin associated protein-like 2	3.0
CPD carboxypeptidase D	3.0
DDR1 discoidin domain receptor tyrosine kinase 1	3.0
DLG2 discs, large homolog 2 (Drosophila)	3.0
DSC3 desmocollin 3	3.0
DUSP6 dual specificity phosphatase 6	3.0
EGF epidermal growth factor	3.0
EGR2 early growth response 2	3.0
EML1 echinoderm microtubule associated protein like 1	3.0
ERBB4 v-erb-a erythroblastic leukemia viral oncogene homolog 4 (avian)	3.0
FEZ1 fasciculation and elongation protein zeta 1 (zygin I)	3.0
FGFR3 fibroblast growth factor receptor 3	3.0
FZD3 frizzled family receptor 3	3.0
GABRB2 gamma-aminobutyric acid (GABA) A receptor, beta 2	3.0
GNAL guanine nucleotide binding protein (G protein), alpha activating activity polypeptide, olfactory type	3.0
GNAO1 guanine nucleotide binding protein (G protein), alpha activating activity polypeptide O	3.0
GPM6A glycoprotein M6A	3.0
GPM6B glycoprotein M6B	3.0
GPR137B G protein-coupled receptor 137B	3.0
GRIA3 glutamate receptor, ionotrophic, AMPA 3	3.0
GRIK4 glutamate receptor, ionotropic, kainate 4	3.0
GRM1 glutamate receptor, metabotropic 1	3.0
GRM4	3.0

glutamate receptor, metabotropic 4	
GRM7 glutamate receptor, metabotropic 7	3.0
GULP1 GULP, engulfment adaptor PTB domain containing 1	3.0
HTR7 5-hydroxytryptamine (serotonin) receptor 7 (adenylate cyclase-coupled)	
IFITM3 interferon induced transmembrane protein 3	3.0
KCNB1 potassium voltage-gated channel, Shab-related subfamily, member 1	3.0
KIAA0513	3.0
KLF5 Kruppel-like factor 5 (intestinal)	3.0
KMO kynurenine 3-monooxygenase (kynurenine 3-hydroxylase)	3.0
LMO3 LIM domain only 3 (rhombotin-like 2)	3.0
MAPT microtubule-associated protein tau	3.0
MCF2 MCF.2 cell line derived transforming sequence	3.0
MCTP2 multiple C2 domains, transmembrane 2	3.0
MEGF10 multiple EGF-like-domains 10	3.0
MOG myelin oligodendrocyte glycoprotein	3.0
NCOA2 nuclear receptor coactivator 2	3.0
NMT1 N-myristoyltransferase 1	
NOS1 nitric oxide synthase 1 (neuronal)	3.0
NPAS2 neuronal PAS domain protein 2	3.0
NPY neuropeptide Y	3.0
NR4A3 nuclear receptor subfamily 4, group A, member 3	3.0
NRGN neurogranin (protein kinase C substrate, RC3)	3.0
NTF3 neurotrophin 3	3.0
NTNG1 netrin G1	3.0
PCLO piccolo (presynaptic cytomatrix protein)	3.0
PCM1 pericentriolar material 1	3.0
PDE7B phosphodiesterase 7B	3.0
PDYN prodynorphin	3.0
PLLP plasmolipin	3.0
PLXNA2 plexin A2	3.0
PNPLA8 patatin-like phospholipase domain containing 8	3.0
PPM1A protein phosphatase, Mg2+/Mn2+ dependent, 1A	3.0
PRKAG2 protein kinase, AMP-activated, gamma 2 non-catalytic subunit	3.0
PSAP prosaposin	3.0

PTPRM protein tyrosine phosphatase, receptor type, M	3.0
PTPRZ1 protein tyrosine phosphatase, receptor-type, Z polypeptide 1	3.0
QKI quaking homolog, KH domain RNA binding (mouse)	3.0
QPCT glutaminyl-peptide cyclotransferase	3.0
RAB31 RAB31, member RAS oncogene family	3.0
RHOBTB3 Rho-related BTB domain containing 3	3.0
RIMS3 regulating synaptic membrane exocytosis 3	3.0
S100A10 (p11) S100 calcium binding protein A10	3.0
SCAMP1 secretory carrier membrane protein 1	3.0
SERPINI1 serpin peptidase inhibitor, clade I (neuroserpin), member 1	3.0
SLC2A3 solute carrier family 2 (facilitated glucose transporter), member 3	3.0
SLC44A1 solute carrier family 44, member 1	3.0
SLC4A4 solute carrier family 4, sodium bicarbonate cotransporter, member 4	3.0
SLC6A3 solute carrier family 6 (neurotransmitter transporter, dopamine), member 3	3.0
SLC6A5 solute carrier family 6 (neurotransmitter transporter, glycine), member 5	3.0
SNCA synuclein, alpha (non A4 component of amyloid precursor)	3.0
SPOCK3 sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican) 3	3.0
SPON1 spondin 1, extracellular matrix protein	3.0
STMN1 stathmin 1	3.0
TAGLN3 transgelin 3	3.0
TAL1 T-cell acute lymphocytic leukemia 1	3.0
TMEM106B transmembrane protein 106B	3.0
USP2 ubiquitin specific peptidase 2	3.0
USP7 ubiquitin specific peptidase 7 (herpes virus-associated)	3.0
USP9X ubiquitin specific peptidase 9, X-linked	3.0
VLDLR very low density lipoprotein receptor	3.0
VSNL1 visinin-like 1	3.0
YWHAZ tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide	3.0
ZCCHC12 zinc finger, CCHC domain containing 12	3.0
ZFHX3 zinc finger homeobox 3	3.0
ZNF804A zinc finger protein 804A	3.0

Table S2. Top candidate genes for schizophrenia from Table 1 that are targets of existing drugs.

Gene	Location	Drug(s)	CFG Score	DHA (Le-Niculescu et al. 2011) Brain region (Direction of change)
ALDH1A1 aldehyde dehydrogenase 1 family, member A1	Cytoplasm	disulfiram, chlorpropamide, DHA	4.0	AMY (I)
CNR1 cannabinoid receptor 1 (brain)	Plasma Membrane	trans-(±)-nabilone,SLV 319,rimonabant,BAY 38-7271,delta-8-tetrahydrocannabinol,delta-9-tetrahydrocannabinol	4.0	
COMT catechol-O-methyltransferase	Cytoplasm	BIA-3-202,tolcapone,entacapone	4.0	
DRD2 dopamine receptor D2	Plasma Membrane	antipsychotics	4.0	AMY (I)
GABRB3 gamma-aminobutyric acid (GABA) A receptor, beta 3	Plasma Membrane	benzodiazepines	4.0	HIP (D)
GRIA1 glutamate receptor, ionotropic, AMPA 1	Plasma Membrane	talampanel,Org 24448,LY451395,tezampanel	4.0	
GRIA4 glutamate receptor, ionotrophic, AMPA 4	Plasma Membrane	talampanel,Org 24448,LY451395,tezampanel	4.0	
GRIN2B glutamate receptor, ionotropic, N-methyl D-aspartate 2B	Plasma Membrane	dextromethorphan,neramexane,bicifadine,delucemine,CR 2249,besonprodil,UK-240455, ,ketamine,felbamate,memantine,orphenadrine,cycloserine,N-(2-indanyl)glycinamide,dextromethorphan,brompheniramine/dextromethorphan/pseudoephedrine,chlorpheniramine/dextromethorphan/phenylephrine,carbinoxamine/dextromethorphan/pseudoephedrine,dextromethorphan/promethazine,1-aminocyclopropane-1-carboxylic acid	4.0	
GRM5 glutamate receptor, metabotropic 5	Plasma Membrane	fasoracetam	4.0	
HTR2A 5-hydroxytryptamine (serotonin) receptor 2A	Plasma Membrane	atypical antipsychotics dihydroergotamine,apomorphine,ergotamine,azatadine	4.0	
NCAM1 neural cell adhesion molecule 1	Plasma Membrane	BB-10901	4.5	
PDE4B phosphodiesterase 4B, cAMP-specific	Cytoplasm	dyphylline,nitroglycerin,arofylline,tetomilast,L 869298,aminophylline,anagrelide,cilomilast,milrinone,rolipram,dipyridamole,L-826,141,roflumilast,tolbutamide,theophylline,pentoxifylline,caffeine	4.0	
PRKCA protein kinase C, alpha	Cytoplasm	L-threo-safingol	4.0	BLOOD (D)
SLC1A2 solute carrier family 1 (glial high affinity glutamate transporter), member 2	Plasma Membrane	riluzole	4.0	BLOOD (D)
SNAP25 synaptosomal-associated protein, 25kDa	Plasma Membrane	botulinum toxin type A	4.0	BLOOD (D)

Table S3. GRPS-542: Panel of SNPs used for genetic risk prediction of schziophrenia. Panel contains all the nominally significant SNPs in the top 42 candidate genes from Table 1 identified by CFG in the ISC GWAS. In the rightmost columns are the alleles, p-values and OR in the independent test cohorts GAIN EA and GAIN AA. Assignment of disease alleles to be tested is based on OR from the ISC, independent of any information from the test cohorts.

	DATA FROM ISC GWAS							DATA FROM GAIN GWAS							
Gene Symbol/Gene Name	SNP	Probe Set ID	A1(ISC)	A2(ISC)	P(ISC)	OR(ISC)		A1(GAIN EA)	A2(GAIN EA)	P(GAIN EA)	OR(GAIN EA)		A1(GAIN AA)	A2(GAIN AA)	P(GAIN AA)	OR(GAIN AA)
ADCYAP1 (adenylate cyclase activating polypeptide 1 (pituitary))	rs9954574	SNP_A-4226637	C	T	0.002876	0.8765		G	A	0.5837	1.039		A	G	0.8128	0.9843
	rs810930	SNP_A-1784156	G	A	0.003912	0.877		G	A	0.8854	1.01		A	G	0.2401	0.9253
	rs809311	SNP_A-2089995	G	A	0.006875	0.8817		C	T	0.7968	1.019		C	T	0.5002	1.048
	rs881897	SNP_A-4256541	A	C	0.009104	0.6855		T	G	0.7172	1.056		T	G	0.02647	1.178
	rs8091765	SNP_A-8628659	C	A	0.01477	0.8759		C	A	0.5493	0.9643		NA	NA	NA	NA
	rs11665625	SNP_A-8485536	A	G	0.01547	1.129		T	C	0.7129	0.9794		C	T	0.9275	0.9938
	rs789042	SNP_A-8289025	G	A	0.01838	0.8587		C	T	0.9609	1.003		T	C	0.6207	0.9672
	rs16954588	SNP_A-1847219	T	C	0.02644	0.8588		A	G	0.6115	0.948		A	G	0.3851	1.081
	rs812573	SNP_A-8482771	A	G	0.02747	0.8537		T	C	0.7775	1.02		C	T	0.4547	0.9523
	rs789038	SNP_A-2032470	G	C	0.03263	0.8637		C	G	0.6115	0.948		C	G	0.4704	1.069
	rs789046	SNP_A-8304674	G	A	0.04408	0.8226		C	T	0.7828	0.9738		C	T	0.3921	1.085
ALDH1A1 (aldehyde dehydrogenase 1 family, member A1)	rs11143438	SNP_A-8364915	G	A	0.02526	1.258		C	T	0.1211	0.8501		C	T	0.042554	0.7837
	rs7040007	SNP_A-8524880	C	T	0.04929	0.8962		G	A	0.03881	1.141		G	A	0.611	0.9673
ANK3 (ankyrin 3, node of Ranvier (ankyrin G))	rs4948256	SNP_A-2235753	A	C	0.001727	1.154		T	G	0.826	1.015		T	G	0.1263	0.8085
	rs7922622	SNP_A-2253626	A	G	0.006055	0.8941		T	C	0.03914	0.8731		T	C	0.386	0.9417

	rs7087489	SNP_A-1914825	G	A	0.009135	0.904		C	T	0.1151	0.9057		C	T	0.5653	0.9529
	rs10761507	SNP_A-2310229	A	C	0.01056	0.9009		T	G	0.09753	0.8969		T	G	0.2538	0.9187
	rs10740035	SNP_A-2001630	G	T	0.01288	0.907		C	A	0.123	0.9068		C	A	0.6022	1.035
	rs11813307	SNP_A-8414824	A	G	0.01678	0.8867		A	G	0.361	0.9497		G	A	0.008764	0.8325
	rs16915157	SNP_A-2277948	T	C	0.01902	1.106		T	C	0.008096	1.204		T	C	0.8286	0.9782
	rs883591	SNP_A-1795629	C	G	0.01985	0.9124		G	C	0.3343	0.9405		G	C	0.8656	1.012
	rs10761432	SNP_A-4288836	A	T	0.02086	0.8412		T	A	0.4198	0.9344		T	A	0.1955	0.9154
	rs10509133	SNP_A-4214095	T	C	0.02156	1.116		T	C	0.006456	1.212		T	C	0.4894	0.9309
	rs7072678	SNP_A-1839057	A	G	0.02473	0.9084		T	C	0.1419	0.9111		T	C	0.6757	0.9728
	rs12767186	SNP_A-1947918	A	G	0.02545	0.9138		T	C	0.9831	1.001		T	C	0.3879	1.066
	rs4948422	SNP_A-2221589	C	T	0.02715	1.088		G	A	0.01226	1.166		G	A	0.2971	1.075
	rs1938526	SNP_A-2265152	G	A	0.02872	1.169		G	A	0.008869	1.351		G	A	0.6747	0.9077
	rs1442540	SNP_A-2029804	A	G	0.02953	0.9134		T	C	0.6587	0.973		T	C	0.7574	1.021
	rs10994257	SNP_A-8450700	T	C	0.03642	1.118		T	C	0.8932	1.008		T	C	0.6601	0.9564
	rs10994322	SNP_A-2278263	T	C	0.03753	1.168		A	G	0.02354	1.32		A	G	0.6103	0.9411
	rs16915156	SNP_A-2200186	C	T	0.0378	1.102		G	A	0.00974	1.198		G	A	0.8598	0.982
	rs1348281	SNP_A-2081611	T	C	0.04408	0.8923		T	C	0.1301	0.9079		T	C	0.8361	0.9864
	rs10994364	SNP_A-21689	T	C	0.04667	1.104		A	G	0.1174	1.124		A	G	0.1536	1.122

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BDNF (brain-derived neurotrophic factor)	rs10742178	SNP_A-1866962	A	G	0.001666	0.8772		A	G	0.745	1.022		A	G	0.8097	0.984
	rs10501087	SNP_A-2009074	C	T	0.001966	0.8724		C	T	0.7737	1.02		C	T	0.8128	1.031
	rs2101467	SNP_A-1903016	A	G	0.002081	0.8693		T	C	0.5147	1.044		T	C	0.5106	0.9565
	rs1114029	SNP_A-2009068	T	C	0.002397	0.8716		A	G	0.6661	1.029		A	G	0.9104	0.9925
	rs4922788	SNP_A-4279338	A	G	0.002602	0.8724		T	C	0.644	1.031		T	C	0.8403	0.9866
	rs4923460	SNP_A-2313824	T	G	0.002746	0.8763		A	C	0.6062	1.038		A	C	0.0243	0.8116
	rs6265	SNP_A-2038925	T	C	0.003375	0.8751		T	C	0.8989	0.9907		T	C	0.7794	0.9544
	rs11030104	SNP_A-1908663	G	A	0.003435	0.8788		C	T	0.8276	1.015		C	T	0.7602	1.05
	rs1013442	SNP_A-2009067	T	A	0.005552	0.8896		T	A	0.8711	1.011		T	A	0.3522	0.8743
	rs11030119	SNP_A-2140952	A	G	0.01266	1.101		T	C	0.5626	1.036		T	C	0.9957	0.9996
	rs988712	SNP_A-4206225	T	G	0.0312	0.8798		A	C	0.9227	1.007		A	C	0.657	0.9356
	rs11030179	SNP_A-2300936	T	C	0.04084	0.9032		T	C	0.4952	0.947		T	C	0.4036	0.9158
	rs10501090	SNP_A-8334867	T	C	0.04287	1.349		T	C	0.6591	1.072		T	C	0.2573	1.158
	rs11030182	SNP_A-2157621	C	T	0.04547	0.9049		G	A	0.5053	0.9479		G	A	0.3932	0.9133
	rs7105410	SNP_A-4275677	T	A	0.04628	0.9069		T	A	0.9336	0.9933		T	A	0.8672	0.9863
	rs11030066	SNP_A-2158242	T	C	0.04836	1.108		T	C	0.9851	1.002		T	C	0.12	0.738
	rs11030175	SNP_A-1879775	T	C	0.04939	0.8991		T	C	0.3108	1.092		T	C	0.7901	0.9574

CD9 (CD9 molecule)	rs3181291	SNP_A-8296074	G	A	0.0455	0.904		C	T	0.3027	0.9434		C	T	0.8878	1.01
CNR1 (cannabinoid receptor 1 (brain))	rs1324073	SNP_A-1986783	G	C	0.002567	0.8806		G	C	0.02821	1.159		G	C	0.6394	0.9514
	rs9362473	SNP_A-8388806	T	C	0.00716	1.228		T	C	0.5655	1.051		T	C	0.05974	0.6979
	rs8180650	SNP_A-8690835	A	G	0.04697	0.8869		T	C	0.8567	0.9877		T	C	0.5646	1.04
COMT (catechol-O-methyltransferase)	rs1544325	SNP_A-8661036	A	G	0.04098	1.11		A	G	0.8614	0.9901		A	G	0.01457	1.193
CPLX2 (complexin 2)	rs10213927	SNP_A-8431092	C	T	0.04338	1.109		G	A	0.3765	1.052		G	A	0.5497	0.9571
DISC1 (disrupted in schizophrenia 1)	rs10910616	SNP_A-8434384	T	C	0.002934	0.7363		T	C	0.06856	1.232		T	C	0.1061	1.442
	rs12076286	SNP_A-8490013	C	T	0.01049	1.181		G	A	0.02855	1.168		G	A	0.1678	1.109
	rs9728261	SNP_A-8609286	T	C	0.02596	1.124		A	G	0.6427	1.028		A	G	0.9908	1.001
	rs4560987	SNP_A-8392987	A	T	0.02697	1.119		T	A	0.5383	0.9656		A	T	0.1507	0.8793
	rs9782927	SNP_A-4286443	G	A	0.02746	1.145		G	A	0.6566	1.031		G	A	0.796	1.04
	rs12087592	SNP_A-1890845	T	C	0.02936	0.8313		T	C	0.3358	0.8814		T	C	0.1181	1.114
	rs12065101	SNP_A-8536682	C	A	0.02953	0.748		C	A	0.4245	1.107		C	A	0.5649	1.04
	rs12058117	SNP_A-8677173	G	A	0.0375	1.504		G	A	0.09143	1.563		G	A	0.8389	0.9815
	rs868584	SNP_A-8380440	T	C	0.03798	0.859		T	C	0.8064	0.983		T	C	0.2386	1.09
	rs789368	SNP_A-8425651	C	A	0.04055	1.123		C	A	0.8222	1.014		C	A	0.5653	0.9462
	rs4642829	SNP_A-8517780	T	C	0.04464	0.8248		T	C	0.4952	0.9303		T	C	0.001159	0.5157
	rs9700757	SNP_A-84139	T	C	0.046	0.7797		A	G	0.3592	0.8842		A	G	0.1879	1.126

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	rs593935	SNP_A-4290632	A	T	0.04956	0.8944		A	T	0.5082	1.045		A	T	0.203	0.8157
DRD2 (dopamine receptor D2)	rs12791990	SNP_A-8464558	C	T	0.01151	1.19		C	T	0.1362	1.124		C	T	0.1193	1.144
	rs4534613	SNP_A-8420069	C	A	0.01765	0.8865		C	A	0.07533	0.9036		C	A	0.9196	0.9934
	rs4309187	SNP_A-8468800	A	C	0.01907	0.8801		A	C	0.1505	0.9159		A	C	0.4215	0.9273
	rs12805897	SNP_A-8329007	A	G	0.02965	1.226		A	G	0.4333	1.085		A	G	0.09759	0.7119
	rs4075412	SNP_A-8607796	A	T	0.03616	1.198		T	A	0.06602	1.187		T	A	0.07925	1.176
	rs4648318	SNP_A-8568798	C	T	0.04038	1.126		C	T	0.6966	1.026		C	T	0.0628	1.13
	rs4254099	SNP_A-8427210	T	C	0.04074	1.207		A	G	0.8531	1.019		A	G	0.2983	0.819
DTNBP1 (dystrobrevin binding protein 1)	rs12209943	SNP_A-2174290	C	T	0.002634	0.8965		G	A	0.1498	1.087		G	A	0.7802	1.033
	rs7751000	SNP_A-2133532	A	C	0.002912	0.8975		A	C	0.1655	1.083		A	C	0.8959	0.9895
	rs1539422	SNP_A-8668086	C	T	0.005126	0.8486		G	A	0.2966	1.061		G	A	0.08649	1.164
	rs2619545	SNP_A-8527969	C	T	0.009163	0.8509		G	A	0.2974	0.9301		G	A	0.2484	0.9256
	rs2743862	SNP_A-8561379	G	C	0.01241	0.854		C	G	0.1802	0.9102		C	G	0.253	0.9263
	rs12201450	SNP_A-8419804	C	G	0.01576	1.29		C	G	0.206	0.8607		C	G	0.9028	0.9696
	rs10949329	SNP_A-8707535	T	G	0.01626	0.8675		A	C	0.06483	1.111		A	C	0.6728	1.049
	rs1935784	SNP_A-2267550	A	G	0.01778	1.095		A	G	0.9803	1.001		G	A	0.6846	0.9738
	rs4716034	SNP_A-1985199	A	C	0.01854	1.095		T	G	0.5055	1.038		G	T	0.7948	0.9826

	rs17620480	SNP_A-1933024	T	C	0.03465	1.084		A	G	0.9678	1.002		G	A	0.8176	0.9849
	rs9477044	SNP_A-8463350	T	C	0.03838	1.197		A	G	0.7909	1.027		A	G	0.03092	1.445
	rs2619552	SNP_A-2135315	G	A	0.04573	0.8824		G	A	0.4631	0.9286		G	A	0.1959	0.9133
	rs11759609	SNP_A-1818933	A	G	0.04853	0.8837		A	G	0.5216	0.9373		A	G	0.1518	0.9036
FABP7 (fatty acid binding protein 7, brain)	rs9490546	SNP_A-2252809	G	A	0.01053	1.108		C	T	0.6009	0.9665		C	T	0.51	1.066
GABRB3 (gamma-aminobutyric acid (GABA) A receptor, beta 3)	rs8037461	SNP_A-8363344	C	T	0.004635	1.164		G	A	0.8976	0.9923		G	A	0.2313	0.9199
	rs8027455	SNP_A-4196271	A	C	0.005299	1.111		T	G	0.5207	1.039		G	T	0.4473	0.9514
	rs8031730	SNP_A-8495092	T	C	0.006932	1.156		A	G	0.5625	1.035		G	A	0.3869	0.9446
	rs1435831	SNP_A-1926078	T	C	0.009322	0.9116		T	C	0.1611	0.923		T	C	0.6444	0.9465
	rs8025575	SNP_A-2027117	C	G	0.00944	0.9123		C	G	0.8209	1.013		G	C	0.8643	1.011
	rs11161309	SNP_A-1931382	T	C	0.0115	0.9093		A	G	0.5986	0.969		A	G	0.4669	1.054
	rs11854349	SNP_A-8631633	A	G	0.01641	0.8436		A	G	0.6549	0.9658		A	G	0.7989	0.9547
	rs4523899	SNP_A-8693032	C	T	0.02013	0.8891		C	T	0.5663	1.033		C	T	0.2138	0.9219
	rs7179684	SNP_A-1929746	G	A	0.03466	1.325		G	A	0.8919	1.023		G	A	0.734	1.033
	rs17669037	SNP_A-2083384	G	A	0.03729	1.166		C	T	0.9597	0.9941		C	T	0.3895	1.11
	rs504441	SNP_A-1782888	G	C	0.03776	1.166		G	C	0.9597	0.9941		G	C	0.2848	1.125
	rs11853743	SNP_A-8693033	C	T	0.03798	0.9007		NA	NA	NA	NA		C	T	0.5088	0.9536

	rs2715574	SNP_A-8325161	G	A	0.04372	0.888		G	A	0.3571	1.061		G	A	0.5435	0.9581
	rs4906680	SNP_A-1957719	A	C	0.04475	0.9261		A	C	0.537	1.035		A	C	0.1758	0.8967
	rs500951	SNP_A-4246924	T	C	0.04553	1.159		T	C	0.9597	0.9941		T	C	0.02716	1.446
GAD1 (glutamate decarboxylase 1 (brain, 67kDa))	rs16859026	SNP_A-2031354	C	G	0.03907	0.7331		C	G	0.0169	1.67		C	G	0.4056	1.265
GNB1L (guanine nucleotide binding protein (G protein), beta polypeptide 1-like)	rs17745302	SNP_A-8528094	T	C	0.03659	1.226		A	G	0.842	1.024		A	G	0.7925	0.9585
	rs6518585	SNP_A-2160938	T	C	0.0372	1.105		T	C	0.8068	1.019		C	T	0.5807	1.038
	rs13057910	SNP_A-8644510	T	C	0.04106	1.219		A	G	0.988	1.002		A	G	0.6693	0.9316
	rs9618705	SNP_A-2270171	A	G	0.04513	1.073		A	G	0.2615	1.066		G	A	0.7091	1.026
GRIA1 (glutamate receptor, ionotropic, AMPA 1)	rs2962816	SNP_A-2054009	A	G	0.0008031	1.283		A	G	0.6909	1.046		A	G	0.6766	1.029
	rs17115481	SNP_A-2097202	A	G	0.001177	1.147		T	C	0.8049	1.016		T	C	0.4127	1.058
	rs4354102	SNP_A-2223459	T	G	0.001498	1.121		T	G	0.3129	1.06		T	G	0.1322	1.104
	rs378267	SNP_A-1893103	G	A	0.002122	1.117		G	A	0.4094	1.049		A	G	0.3423	0.9397
	rs375232	SNP_A-4199980	A	G	0.002771	1.115		T	C	0.3887	1.052		T	C	0.3611	1.063
	rs159971	SNP_A-1796936	G	A	0.003416	1.153		G	A	0.9868	1.001		A	G	0.2516	0.9199
	rs386841	SNP_A-2213609	T	C	0.00425	1.109		T	C	0.503	1.04		T	C	0.6532	1.031
	rs919222	SNP_A-2278557	A	G	0.004479	1.143		A	G	0.9736	0.9974		A	G	0.2822	1.079
	rs893523	SNP_A-4223827	C	T	0.004484	0.893		C	T	0.5548	1.035		C	T	0.6714	0.9704

rs390299	SNP_A-1879538	G	A	0.005409	1.116		G	A	0.5498	1.035		G	A	0.6118	1.035
rs17448815	SNP_A-4302304	C	T	0.005602	0.881		C	T	0.2305	0.9168		C	T	0.5129	0.8939
rs4958687	SNP_A-1811390	G	A	0.006494	0.8976		C	T	0.4618	1.044		C	T	0.7315	0.976
rs1461240	SNP_A-1984109	A	G	0.006938	1.137		T	C	0.8186	0.9837		T	C	0.5249	1.045
rs2615178	SNP_A-4244124	C	T	0.007306	1.192		C	T	0.7458	1.034		C	T	0.9619	1.003
rs17491606	SNP_A-8659666	A	G	0.007334	1.346		T	C	0.5263	1.082		NA	NA	NA	NA
rs2962826	SNP_A-2120789	A	C	0.007641	1.202		T	G	0.7465	1.037		T	G	0.954	1.004
rs1461237	SNP_A-1984102	T	C	0.00804	0.8833		A	G	0.8621	1.013		A	G	0.3927	0.9416
rs2546331	SNP_A-2313741	C	T	0.008405	1.226		G	A	0.6098	0.9376		G	A	0.8751	1.011
rs4285285	SNP_A-2070131	G	A	0.008827	0.9047		C	T	0.9759	1.002		C	T	0.2287	0.9042
rs1462113	SNP_A-2261865	A	G	0.009475	1.186		A	G	0.8162	1.024		A	G	0.8908	0.9907
rs300328	SNP_A-2186284	T	C	0.009612	1.185		T	C	0.8204	1.024		T	C	0.9974	1
rs10515671	SNP_A-4211353	G	A	0.00973	0.8889		C	T	0.3501	0.935		C	T	0.5608	0.9022
rs7717108	SNP_A-2314108	T	C	0.01111	1.123		T	C	0.4099	0.9404		T	C	0.3423	1.075
rs17546335	SNP_A-2202964	G	C	0.01116	0.8899		NA	NA	NA	NA		C	G	0.9495	0.9888
rs10477042	SNP_A-8565425	A	C	0.01124	1.159		A	C	0.2767	1.073		A	C	0.5295	1.048
rs6882589	SNP_A-2011352	T	A	0.01142	0.8076		A	T	0.08675	1.271		A	T	0.9391	0.9945
rs17113771	SNP_A-22500	T	C	0.01156	0.9051		T	C	0.7819	1.017		T	C	0.1044	0.896

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rs498660	SNP_A-4259391	T	C	0.01179	1.267		A	G	0.7231	1.05		A	G	0.006037	1.199
rs3101130	SNP_A-2103390	G	C	0.01204	1.179		C	G	0.7775	1.03		C	G	0.6188	0.9669
rs3112530	SNP_A-2081190	A	G	0.01253	1.174		T	C	0.6559	1.046		C	T	0.5969	0.9655
rs2199123	SNP_A-2062869	A	G	0.01385	1.171		A	G	0.6902	1.041		G	A	0.6887	0.9737
rs12656429	SNP_A-8583028	T	C	0.01416	0.8564		A	G	0.04536	1.162		A	G	0.1538	0.7491
rs1037892	SNP_A-8523871	A	G	0.01426	0.8665		A	G	0.6462	1.03		G	A	0.8518	1.012
rs12655396	SNP_A-1796236	C	T	0.01436	1.174		G	A	0.7835	1.029		G	A	0.9829	0.9985
rs2964003	SNP_A-4222822	G	A	0.01557	0.8931		C	T	0.6526	1.035		C	T	0.3025	0.9278
rs4958549	SNP_A-2039635	A	C	0.01561	0.8871		T	G	0.2034	0.9128		T	G	0.6243	0.9179
rs160163	SNP_A-2167854	T	C	0.01564	1.171		T	C	0.7468	1.034		T	C	0.9216	1.007
rs17113267	SNP_A-8441560	A	G	0.01584	1.16		T	C	0.5309	1.044		T	C	0.8966	1.012
rs4958561	SNP_A-2272453	G	A	0.01638	0.9086		G	A	0.6682	0.9734		G	A	0.07845	0.7675
rs13180912	SNP_A-1804203	T	C	0.01658	1.144		A	G	0.8071	0.9793		A	G	0.57	1.065
rs6579996	SNP_A-8478405	G	A	0.01679	1.177		C	T	0.5791	0.9588		C	T	0.2997	1.072
rs1035396	SNP_A-1887755	A	T	0.01709	0.889		A	T	0.172	0.9069		A	T	0.468	0.8818
rs10515677	SNP_A-8663866	C	T	0.01746	1.319		G	A	0.9902	1.002		NA	NA	NA	NA
rs2973138	SNP_A-2301441	T	C	0.01834	1.201		T	C	0.6503	0.9443		T	C	0.07516	1.244

rs2926862	SNP_A-2024899	T	G	0.01844	0.896		A	C	0.919	1.008		A	C	0.3746	0.9378
rs17452991	SNP_A-2045275	C	G	0.01882	0.9103		C	G	0.7031	0.9763		C	G	0.05031	0.7463
rs6877008	SNP_A-4215103	T	C	0.01923	0.8216		T	C	0.05102	1.311		T	C	0.951	1.005
rs731117	SNP_A-1819179	C	T	0.01972	0.8996		C	T	0.1759	0.9074		C	T	0.6193	0.923
rs1422341	SNP_A-1807380	A	G	0.01985	0.8995		T	C	0.2034	0.9128		T	C	0.5064	0.8902
rs2973151	SNP_A-2033269	T	C	0.01987	1.166		A	G	0.7923	1.028		A	G	0.9732	0.9977
rs1493383	SNP_A-8663886	T	C	0.02091	1.158		A	G	0.8318	0.9846		A	G	0.3553	0.8959
rs10039253	SNP_A-8309065	T	C	0.02127	0.8584		T	C	0.1995	0.9125		T	C	0.5481	0.9421
rs2963940	SNP_A-4276968	G	T	0.02176	1.149		NA	NA	NA	NA		NA	NA	NA	NA
rs1946224	SNP_A-2076705	T	C	0.02349	0.9014		T	C	0.1993	0.9114		T	C	0.5857	0.9251
rs17115298	SNP_A-1984101	G	T	0.02429	1.12		G	T	0.5341	0.9489		G	T	0.1176	1.159
rs1025260	SNP_A-2051203	T	A	0.02569	1.102		T	A	0.7588	0.9782		T	A	0.6112	1.036
rs17566146	SNP_A-4234397	G	C	0.02689	0.9145		G	C	0.8845	1.009		G	C	0.04575	0.7936
rs17525192	SNP_A-1917966	A	G	0.02791	1.118		T	C	0.5828	0.9546		T	C	0.4124	1.194
rs1864205	SNP_A-2133562	C	T	0.02797	1.083		G	A	0.05174	0.8913		G	A	0.7319	0.9628
rs3923209	SNP_A-4275672	T	A	0.02818	0.9087		T	A	0.6029	0.9678		T	A	0.03246	0.8179
rs4958560	SNP_A-1800957	C	T	0.03006	0.9097		G	A	0.4645	0.955		G	A	0.0424	0.8278
rs17546405	SNP_A-84598	G	A	0.03114	0.8659		G	A	0.2527	0.9208		G	A	0.2098	0.8701

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rs17566118	SNP_A-1937726	T	C	0.03156	0.9169		T	C	0.9707	1.002		T	C	0.09707	0.8268
rs4958556	SNP_A-8298471	A	G	0.03183	1.23		A	G	0.7937	0.9711		A	G	0.1124	0.8323
rs10515672	SNP_A-1984057	G	A	0.03209	0.9106		G	A	0.886	0.9903		G	A	0.2005	0.8647
rs4398624	SNP_A-2264725	C	T	0.03249	0.9176		C	T	0.4094	0.9491		C	T	0.04046	0.8599
rs300329	SNP_A-2083461	C	T	0.03253	1.101		C	T	0.9552	1.004		T	C	0.3083	0.9273
rs308271	SNP_A-2172410	T	A	0.03272	1.101		A	T	0.9303	1.006		T	A	0.1332	0.8967
rs217771	SNP_A-1868571	C	T	0.03273	1.101		C	T	0.9569	1.004		T	C	0.3083	0.9273
rs17113732	SNP_A-2043688	T	C	0.03419	1.195		A	G	0.5249	1.098		A	G	0.7036	1.047
rs1542485	SNP_A-8417187	A	G	0.03469	0.8757		T	C	0.3112	1.074		T	C	0.4365	0.9303
rs159760	SNP_A-1798262	G	T	0.03477	1.1		C	A	0.9471	0.9952		A	C	0.5496	0.9617
rs1422337	SNP_A-1893785	A	G	0.03683	1.094		A	G	0.3787	1.063		A	G	0.7909	0.9796
rs159969	SNP_A-2160842	T	C	0.03764	1.098		A	G	0.8992	1.009		G	A	0.138	0.8978
rs17568427	SNP_A-8368456	A	G	0.03955	0.8754		T	C	0.3828	0.9401		T	C	0.08357	0.7454
rs286956	SNP_A-1951209	C	A	0.04099	0.9284		C	A	0.3225	1.059		C	A	0.807	1.019
rs11951398	SNP_A-8330922	T	C	0.04129	1.25		T	C	0.5021	1.086		T	C	0.482	1.072
rs300330	SNP_A-1984073	A	G	0.04157	1.096		A	G	0.9423	0.9947		A	G	0.9905	1.001
rs17113236	SNP_A-1846295	A	T	0.04368	1.091		T	A	0.4456	1.055		T	A	0.6867	0.9668

	rs286969	SNP_A-8712067	A	G	0.04444	1.109		T	C	0.02924	0.8815		T	C	0.6371	1.033
	rs17451810	SNP_A-4245046	G	C	0.04705	0.9159		G	C	0.5431	0.9623		G	C	0.07593	0.7658
	rs7702336	SNP_A-2091282	A	C	0.04709	1.08		A	C	0.8426	1.013		A	C	0.4821	1.054
	rs4145744	SNP_A-1856113	G	C	0.04909	1.234		NA	NA	NA	NA		NA	NA	NA	NA
	rs286967	SNP_A-2108404	T	G	0.04988	0.9313		A	C	0.3181	1.06		A	C	0.9261	0.9932
GRIA4 (glutamate receptor, ionotrophic, AMPA 4)	rs649098	SNP_A-8339706	G	C	0.02792	0.8708		C	G	0.03531	1.127		C	G	0.02561	1.182
	rs1375423	SNP_A-8422687	T	A	0.03542	0.7788		T	A	0.04107	1.301		T	A	0.8884	1.017
	rs17104589	SNP_A-8339698	A	G	0.03609	1.288		T	C	0.1631	0.8254		NA	NA	NA	NA
GRIN2B (glutamate receptor, ionotropic, N-methyl D-aspartate 2B)	rs4363703	SNP_A-8376097	C	T	0.001569	0.8422		C	T	0.06983	1.113		C	T	0.6449	0.9679
	rs10845859	SNP_A-8709853	G	A	0.006213	0.8519		G	A	0.1573	1.098		G	A	0.4928	0.9419
	rs10772719	SNP_A-1940301	A	G	0.0072	0.8843		A	G	0.2784	1.077		A	G	0.904	0.9878
	rs12809496	SNP_A-1860379	G	A	0.008959	0.9089		G	A	0.63	0.9723		G	A	0.6795	1.047
	rs11055594	SNP_A-2057652	G	A	0.01394	0.9171		G	A	0.7284	0.9806		G	A	0.5463	1.042
	rs3924022	SNP_A-8645495	G	A	0.01481	0.8326		G	A	0.6964	0.9727		G	A	0.2343	0.8414
	rs11055792	SNP_A-4252160	T	C	0.01719	0.9193		A	G	0.7977	1.015		A	G	0.4974	1.065
	rs7314880	SNP_A-2135314	T	A	0.01979	1.188		A	T	0.8097	1.029		A	T	0.7632	0.9804
	rs12371702	SNP_A-2214762	C	G	0.02105	1.116		G	C	0.1355	1.124		G	C	0.8426	0.9803
	rs10845856	SNP_A-21652	C	T	0.02142	0.922		C	T	0.8446	0.9889		C	T	0.5474	0.953

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rs7970407	SNP_A-2057007	T	C	0.02211	0.8434		T	C	0.4744	0.9547		T	C	0.2822	0.9297
rs11055830	SNP_A-8375382	A	G	0.0229	0.8369		A	G	0.4181	1.069		A	G	0.3167	1.164
rs11055597	SNP_A-1889450	T	C	0.02369	1.083		A	G	0.5329	0.9654		A	G	0.1874	0.9144
rs219872	SNP_A-2096985	G	A	0.02466	0.8939		G	A	0.907	1.009		G	A	0.8656	1.012
rs11055664	SNP_A-1833355	G	A	0.02501	0.9237		G	A	0.874	0.991		G	A	0.5168	0.9494
rs2284428	SNP_A-2175964	G	A	0.02611	0.8875		G	A	0.01849	0.8112		G	A	0.7955	0.9776
rs10492134	SNP_A-4272433	G	C	0.03138	0.923		G	C	0.3173	0.9422		G	C	0.617	1.067
rs11055930	SNP_A-8676241	C	T	0.03724	0.8884		G	A	0.5654	1.037		G	A	0.6144	1.037
rs2268135	SNP_A-4296729	C	G	0.03763	0.8895		C	G	0.01749	0.8018		C	G	0.7824	0.9759
rs11055595	SNP_A-4274330	T	C	0.03812	0.9235		A	G	0.7232	0.9802		A	G	0.4647	1.052
rs2300268	SNP_A-1924051	A	G	0.03931	1.243		T	C	0.9241	1.018		T	C	0.2097	1.155
rs16909619	SNP_A-2053592	A	C	0.03986	0.8398		T	G	0.4416	1.104		T	G	0.6384	1.081
rs2268133	SNP_A-4287349	G	A	0.03991	1.081		G	A	0.03101	1.14		G	A	0.009764	1.215
rs7306014	SNP_A-8656195	A	G	0.04004	0.9017		A	G	0.2675	0.9392		G	A	0.7119	0.9741
rs2300252	SNP_A-8697084	T	C	0.04201	0.8937		A	G	0.563	1.036		A	G	0.193	1.103
rs2193150	SNP_A-2172398	C	A	0.04389	0.9133		G	T	0.2582	0.92		G	T	0.2428	1.081
rs7970144	SNP_A-2034427	A	T	0.04498	0.9135		T	A	0.3701	0.9358		T	A	0.2939	1.073

	rs10772769	SNP_A-8511818	A	G	0.04869	1.107		T	C	0.6875	0.9766		T	C	0.2365	0.8976
	rs219904	SNP_A-4303294	T	C	0.04922	1.078		T	C	0.5016	1.039		T	C	0.1279	1.106
	rs10845826	SNP_A-2034499	A	C	0.04941	1.074		T	G	0.7343	0.9804		T	G	0.2197	0.9194
GRM5 (glutamate receptor, metabotropic 5)	rs992259	SNP_A-2275445	A	G	0.00259	1.191		A	G	0.6651	0.9591		G	A	0.7554	1.023
	rs7396702	SNP_A-4252496	C	G	0.00236	1.295		G	C	0.4099	0.9222		C	G	0.2545	1.085
	rs11020781	SNP_A-1953906	C	A	0.00238	1.211		C	A	0.6162	0.9521		A	C	0.1885	1.098
	rs12362135	SNP_A-8455819	G	C	0.00354	1.326		C	G	0.371	0.9053		C	G	0.8322	0.9851
	rs12279598	SNP_A-8376176	A	G	0.00429	1.731		A	G	0.3522	0.8182		A	G	0.6363	0.9526
	rs10831155	SNP_A-8511977	C	T	0.00465	1.299		C	T	0.6108	0.9477		C	T	0.3842	0.9376
	rs11020748	SNP_A-4207207	T	C	0.00601	1.191		A	G	0.4184	0.9249		G	A	0.4082	1.061
	rs12802146	SNP_A-2120393	A	G	0.00693	1.17		T	C	0.4651	0.9318		C	T	0.4002	1.062
	rs982010	SNP_A-2122098	C	T	0.00884	1.166		G	A	0.4665	0.9322		A	G	0.3426	1.07
	rs4488199	SNP_A-2170370	C	T	0.01	1.24		G	A	0.5411	0.943		A	G	0.9429	1.005
	rs308765	SNP_A-4282258	T	C	0.01333	1.377		T	C	0.06779	0.6904		T	C	0.1426	1.159
	rs656544	SNP_A-8403143	A	G	0.01973	1.57		T	C	0.4594	1.159		T	C	0.7231	0.9616
	rs541279	SNP_A-8339269	G	T	0.02189	1.349		G	T	0.8657	1.025		G	T	0.04929	0.8491
	rs17770948	SNP_A-8603715	T	C	0.02375	1.268		A	G	0.2719	0.8726		A	G	0.3906	0.8735
	rs41352345	SNP_A-18655	T	A	0.02452	0.8872		T	A	0.6123	0.9605		T	A	0.2955	1.26

		05														
	rs16914531	SNP_A-8458560	T	C	0.02754	1.479		T	C	0.5973	1.125		NA	NA	NA	NA
	rs1846475	SNP_A-8465906	A	T	0.03047	1.556		A	T	0.8852	0.9659		A	T	0.001263	0.3769
	rs167569	SNP_A-8463370	T	C	0.03187	1.477		A	G	0.82	1.044		A	G	0.9353	0.9905
	rs2513417	SNP_A-2299874	C	G	0.03208	1.315		G	C	0.02417	0.6273		G	C	0.5045	1.065
	rs10830770	SNP_A-8554115	C	T	0.03233	1.155		C	T	0.1105	0.884		C	T	0.3671	1.074
	rs170110	SNP_A-1846902	T	A	0.03398	1.299		A	T	0.01842	0.6354		A	T	0.2289	1.119
	rs12273907	SNP_A-4260980	A	G	0.03549	0.8975		A	G	0.8465	0.9853		A	G	0.3894	0.9305
	rs10830909	SNP_A-4200902	C	T	0.03748	1.076		G	A	0.8016	0.986		G	A	0.8268	1.022
	rs308766	SNP_A-4254197	T	C	0.03982	1.311		A	G	0.02691	0.6286		A	G	0.3443	1.093
	rs11020528	SNP_A-8311366	C	T	0.04402	1.568		G	A	0.8958	1.031		NA	NA	NA	NA
GSN (gelsolin)	rs12376078	SNP_A-8458322	A	G	0.04739	1.26		T	C	0.03655	1.361		T	C	0.2964	1.133
HINT1 (histidine triad nucleotide binding protein 1)	rs11242025	SNP_A-4259792	A	G	8.67E-05	2.326		NA	NA	NA	NA		NA	NA	NA	NA
	rs12653613	SNP_A-1865003	C	T	0.0005705	2.098		C	T	0.1253	1.435		C	T	0.1573	0.8863
	rs6868888	SNP_A-8707240	C	A	0.004355	1.196		G	T	0.4069	1.048		T	G	0.5225	0.9451
	rs7716702	SNP_A-2285906	A	T	0.005513	1.444		A	T	0.09647	1.281		A	T	0.5098	0.9539
	rs7737208	SNP_A-4236353	T	C	0.01273	1.248		A	G	0.1536	1.158		G	A	0.5814	0.9632
	rs6860180	SNP_A-2125625	G	A	0.01453	1.168		C	T	0.08297	1.194		C	T	0.07654	0.8874

	rs6880604	SNP_A-8351226	G	A	0.01481	1.809		G	A	0.05151	1.676		G	A	0.1697	0.8894
	rs17640142	SNP_A-8510942	C	G	0.01556	1.416		G	C	0.5952	0.9186		G	C	0.1223	0.8612
	rs7734177	SNP_A-8327241	T	C	0.02928	1.299		T	C	0.008637	1.436		C	T	0.6232	1.033
	rs1363696	SNP_A-8665172	G	A	0.04845	1.119		C	T	0.2637	1.073		T	C	0.2559	0.9122
HSPA1B (heat shock 70kDa protein 1B)	rs2763979	SNP_A-1867908	T	C	0.0009003	0.8831		T	C	0.06573	0.8954		C	T	0.0987	1.121
HTR2A (5-hydroxytryptamine (serotonin) receptor 2A)	rs7985155	SNP_A-1859137	G	A	0.02014	1.154		C	T	0.08358	0.8389		C	T	0.2674	1.107
	rs1805055	SNP_A-8586895	T	G	0.02387	1.462		A	C	0.5468	1.121		NA	NA	NA	NA
	rs9595613	SNP_A-8443824	G	C	0.03275	1.485		C	G	0.2172	1.277		C	G	0.2813	0.9154
	rs1326469	SNP_A-8536748	C	T	0.04418	0.8109		G	A	0.9177	0.9883		A	G	0.6157	0.9662
	rs9534696	SNP_A-8394779	T	C	0.04735	0.813		T	C	0.9971	1		C	T	0.6766	0.9729
KALRN (kalirin, RhoGEF kinase)	rs3772756	SNP_A-2294814	G	T	0.006285	1.22		C	A	0.6004	1.059		C	A	0.7724	0.9685
	rs3772751	SNP_A-8512582	T	C	0.009416	1.27		T	C	0.4302	1.089		T	C	0.2524	0.9193
	rs3772753	SNP_A-1815916	T	C	0.01374	1.18		T	C	0.6004	1.059		T	C	0.6774	0.9552
	rs16835783	SNP_A-8296014	A	G	0.02737	1.184		T	C	0.03994	0.8328		T	C	0.4101	1.077
	rs3772790	SNP_A-8462780	T	G	0.02938	0.8204		A	C	0.7057	0.9631		A	C	0.2114	1.089
	rs6766433	SNP_A-8700370	T	C	0.03776	0.7272		A	G	0.3458	1.157		A	G	0.2018	1.136
	rs13087377	SNP_A-8294864	G	T	0.03893	1.112		G	T	0.6843	0.9767		G	T	0.9775	0.9981
	rs16835412	SNP_A-84816	T	A	0.03981	1.231		A	T	0.8354	0.9757		A	T	0.09278	0.6801

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	rs333307	SNP_A-8623259	A	T	0.0438	0.8777		T	A	0.7827	0.9803		T	A	0.6632	0.9681
	rs7621976	SNP_A-8451938	T	C	0.04785	1.165		T	C	0.04495	0.8366		T	C	0.7688	1.024
KIF2A (kinesin heavy chain member 2A)	rs6864793	SNP_A-4156821	C	T	0.005374	1.348		C	T	0.9752	0.9965		C	T	0.4832	1.077
	rs185227	SNP_A-8524823	C	G	0.01534	1.148		G	C	0.4179	0.9498		G	C	0.8106	1.016
	rs414568	SNP_A-2203552	T	C	0.02761	1.116		T	C	0.4581	0.9472		T	C	0.3719	1.064
	rs1876683	SNP_A-2173382	G	A	0.04853	0.8629		G	A	0.7886	0.9778		G	A	0.4592	0.9139
MBP (myelin basic protein)	rs12959006	SNP_A-4236221	T	C	0.01002	1.122		T	C	0.7617	1.021		T	C	0.7293	0.9426
	rs4890910	SNP_A-8479764	T	C	0.02377	0.8744		A	G	0.595	0.9652		A	G	0.9961	1.001
	rs9966136	SNP_A-2043418	A	T	0.02582	1.126		T	A	0.1442	1.123		T	A	0.9557	0.996
	rs12956305	SNP_A-8497881	T	C	0.03278	0.8714		A	G	0.08567	1.13		A	G	0.891	0.9853
	rs3900176	SNP_A-8622419	T	C	0.03766	0.8957		A	G	0.6998	1.023		G	A	0.6813	0.9724
MOBP (myelin-associated oligodendrocyte basic protein)	rs1708044	SNP_A-4216830	G	C	0.003529	1.301		G	C	0.8484	1.027		NA	NA	NA	NA
	rs1768198	SNP_A-2226901	G	A	0.00526	1.193		G	A	0.9057	1.008		G	A	0.4108	1.056
	rs1708099	SNP_A-8496795	A	G	0.005777	1.397		T	C	0.9926	0.9987		T	C	0.7615	0.9732
	rs1768141	SNP_A-2141739	G	A	0.0062	1.279		G	A	0.9603	1.007		G	A	0.9911	1.001
	rs1609646	SNP_A-4278544	C	T	0.00835	1.122		G	A	0.9751	0.9978		A	G	0.4794	0.9543
	rs1707956	SNP_A-1911769	T	C	0.008352	1.118		A	G	0.8633	0.9884		G	A	0.2213	0.9156

	rs500507	SNP_A-1972436	T	C	0.009826	1.119		T	C	0.9631	0.9968		C	T	0.5145	0.9578
	rs1609647	SNP_A-2147245	T	C	0.01069	1.118		T	C	0.9373	0.9945		C	T	0.4449	0.9507
	rs1768158	SNP_A-1815872	G	A	0.01439	1.113		C	T	0.9812	1.002		T	C	0.7246	0.977
	rs1629282	SNP_A-4261371	G	A	0.01543	1.112		C	T	0.9806	0.9983		T	C	0.5021	0.9564
	rs1707958	SNP_A-1934756	T	C	0.01785	1.11		T	C	0.9583	0.9963		T	C	0.1871	1.09
	rs1707960	SNP_A-1832007	G	A	0.02101	1.107		C	T	0.9871	1.001		C	T	0.2098	1.085
	rs538867	SNP_A-2098043	T	C	0.02128	1.322		NA	NA	NA	NA		NA	NA	NA	NA
	rs2233204	SNP_A-8618501	T	C	0.02384	0.8883		T	C	0.2172	1.076		T	C	0.2393	0.8788
	rs7631217	SNP_A-4289048	T	A	0.02401	1.104		A	T	0.9982	0.9998		A	T	0.2098	1.085
	rs6599028	SNP_A-1972434	C	G	0.03685	1.101		G	C	0.8438	0.9867		C	G	0.1709	0.9059
	rs1527558	SNP_A-2193442	T	G	0.04144	0.9152		T	G	0.3689	0.9442		T	G	0.9606	1.003
	rs9868941	SNP_A-4263458	C	T	0.04308	0.9226		C	T	0.4113	0.949		C	T	0.9901	0.9992
	rs9835143	SNP_A-8425066	T	C	0.0478	1.141		T	C	0.9663	1.003		T	C	0.1456	1.131
NCAM1 (neural cell adhesion molecule 1)	rs11214441	SNP_A-2139990	A	T	0.003917	1.159		T	A	0.1322	1.091		T	A	0.3003	1.072
	rs1940733	SNP_A-8343537	A	G	0.005925	1.15		T	C	0.1477	1.087		T	C	0.1693	1.096
	rs10789894	SNP_A-2219775	G	A	0.007769	1.124		C	T	0.9332	0.9941		C	T	0.3894	1.06
	rs7126748	SNP_A-8403197	C	T	0.007806	1.147		C	T	0.08545	1.104		C	T	0.5581	1.039
	rs11214457	SNP_A-21310	G	A	0.008474	1.143		G	A	0.301	0.9198		G	A	0.4561	1.102

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rs1945116	SNP_A-1955576	C	G	0.009507	1.124		C	G	0.8566	0.9873		G	C	0.7343	0.9777
rs10750016	SNP_A-4286366	A	T	0.009705	1.141		A	T	0.2118	1.074		A	T	0.0375	1.146
rs1945101	SNP_A-4237618	G	A	0.009896	1.12		C	T	0.792	0.9815		C	T	0.9784	0.9982
rs10891434	SNP_A-2180192	G	C	0.009937	1.104		G	C	0.04571	0.8926		G	C	0.5908	1.051
rs10891379	SNP_A-1936552	T	C	0.01097	1.13		T	C	0.9596	1.004		T	C	0.686	1.028
rs7948394	SNP_A-2290782	T	A	0.01144	1.118		T	A	0.9983	0.9998		T	A	0.6227	1.036
rs17598303	SNP_A-8649761	T	C	0.01267	1.157		A	G	0.4316	0.9484		A	G	0.1704	0.7953
rs10891385	SNP_A-4235482	G	A	0.01347	1.115		C	T	0.9233	1.007		C	T	0.5602	1.039
rs11214240	SNP_A-2227769	G	A	0.01421	1.115		C	T	0.5921	0.9624		C	T	0.6643	1.029
rs4937870	SNP_A-4293042	G	A	0.01584	1.103		G	A	0.1741	1.085		G	A	0.5323	1.05
rs10891375	SNP_A-8347753	G	A	0.01695	0.882		G	A	0.5726	0.9675		G	A	0.6435	1.033
rs17582738	SNP_A-8631251	T	A	0.02167	1.215		A	T	0.007865	1.247		A	T	0.1582	1.337
rs1006826	SNP_A-4259317	C	T	0.02341	1.095		G	A	0.1912	0.9175		G	A	0.02291	0.698
rs11214468	SNP_A-2189086	T	C	0.02922	1.091		T	C	0.5043	0.9581		T	C	0.2037	1.112
rs2212450	SNP_A-4282285	C	T	0.03038	1.079		C	T	0.1273	1.09		C	T	0.06807	1.127
rs6589354	SNP_A-2030349	A	T	0.03084	1.08		A	T	0.1436	1.088		A	T	0.1057	1.114
rs7926312	SNP_A-4270595	G	A	0.03132	1.08		C	T	0.1285	1.091		C	T	0.1134	1.111

	rs1892983	SNP_A-1814603	C	T	0.03201	1.08		C	T	0.1953	1.077		C	T	0.1109	1.112
	rs1940724	SNP_A-2268149	G	A	0.03325	1.079		C	T	0.1296	1.091		C	T	0.1239	1.108
	rs7105462	SNP_A-1934006	G	A	0.03415	1.085		G	A	0.07706	1.106		A	G	0.04261	0.8728
	rs10891487	SNP_A-4242990	A	G	0.0347	1.085		A	G	0.1353	1.089		A	G	0.129	1.106
	rs3802847	SNP_A-2090194	C	T	0.03504	1.078		C	T	0.1613	1.084		C	T	0.09798	1.117
	rs17114687	SNP_A-2120176	G	A	0.03513	1.194		G	A	0.01228	1.229		G	A	0.1324	1.151
	rs2212449	SNP_A-2224508	T	G	0.03556	1.078		A	C	0.1296	1.091		A	C	0.1379	1.104
	rs11214469	SNP_A-1812077	A	T	0.04103	1.083		A	T	0.1223	1.093		A	T	0.1134	1.111
	rs2054266	SNP_A-2264574	G	C	0.04658	0.9325		G	C	0.3028	0.9437		C	G	0.6808	1.038
	rs11214331	SNP_A-1895352	A	G	0.04941	0.9212		T	C	0.6475	1.031		C	T	0.8425	0.9861
	rs7116022	SNP_A-4285980	T	C	0.04965	0.9304		T	C	0.3162	0.9429		T	C	0.9455	0.9945
	rs10502163	SNP_A-2019302	T	C	0.04967	1.081		A	G	0.6345	0.97		A	G	0.4475	1.063
	rs4447204	SNP_A-2093307	C	G	0.04992	0.9324		G	C	0.03489	1.128		G	C	0.2615	0.9014
NDUFV2 (NADH dehydrogenase (ubiquinone) flavoprotein 2, 24kDa)	rs8084822	SNP_A-1952887	T	A	0.003243	0.8663		T	A	0.676	0.9686		T	A	0.1669	1.124
	rs1785560	SNP_A-8482169	C	T	0.006002	0.8232		G	A	0.884	0.9888		G	A	0.6124	1.063
	rs1784773	SNP_A-4300374	C	T	0.008768	0.8791		C	T	0.8543	1.014		C	T	0.9226	1.008
	rs2032161	SNP_A-1876443	C	T	0.009535	0.8955		C	T	0.129	0.9089		C	T	0.2687	0.8907
	rs1703820	SNP_A-42304	A	G	0.01303	0.885		A	G	0.8727	0.9877		A	G	0.107	0.7447

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	rs11081448	SNP_A-8305985	C	A	0.01501	0.8826		C	A	0.05962	0.8973		A	C	0.9962	0.9997
	rs1573321	SNP_A-8430718	G	T	0.01572	0.8734		C	A	0.1199	0.9069		C	A	0.6579	1.037
	rs987850	SNP_A-8430719	G	A	0.02976	0.8894		C	T	0.1845	0.9229		C	T	0.9628	1.004
	rs16954628	SNP_A-8584055	G	A	0.03681	1.151		C	T	0.02394	1.19		C	T	0.3048	1.082
	rs11081446	SNP_A-8587834	G	A	0.04385	0.9039		G	A	0.04409	0.8929		A	G	0.8226	0.9849
	rs8092661	SNP_A-8654363	C	T	0.0466	0.9016		G	A	0.4177	0.9542		G	A	0.8053	0.984
NR4A2 (nuclear receptor subfamily 4, group A, member 2)	rs12465886	SNP_A-8496375	T	G	0.0006887	0.7463		A	C	0.3023	0.9256		A	C	0.9872	0.9988
	rs843229	SNP_A-4262325	T	C	0.00429	0.9034		T	C	0.9095	0.9935		T	C	0.8056	1.016
	rs843220	SNP_A-1913686	A	G	0.004904	0.9046		A	G	0.9623	0.9973		A	G	0.7517	1.021
	rs278881	SNP_A-1902238	A	G	0.005153	0.9029		T	C	0.3281	1.059		T	C	0.9658	0.9971
	rs11888593	SNP_A-2152768	C	T	0.005277	1.177		C	T	0.9065	0.9922		NA	NA	NA	NA
	rs2691786	SNP_A-1908125	G	C	0.005391	1.104		G	C	0.5218	1.037		G	C	0.9745	1.002
	rs17226595	SNP_A-1900557	T	C	0.005957	1.111		A	G	0.8142	1.014		A	G	0.09702	0.8058
	rs2691775	SNP_A-1965492	A	G	0.006209	1.101		T	C	0.7726	0.9838		T	C	0.8761	0.9899
	rs12991533	SNP_A-1908820	A	G	0.007067	1.101		A	G	0.502	1.039		A	G	0.9207	1.007
	rs2677479	SNP_A-2142560	G	C	0.00707	1.099		C	G	0.766	0.9834		C	G	0.9224	1.006
	rs2691787	SNP_A-4202806	A	G	0.01248	0.9147		T	C	0.8501	0.9892		T	C	0.8852	1.01

	rs843219	SNP_A-2081107	A	T	0.01304	0.9083		A	T	0.6852	1.026		A	T	0.8787	1.011
	rs13016588	SNP_A-8559979	G	A	0.01549	0.8825		G	A	0.684	0.9768		G	A	0.7593	0.9792
	rs1316293	SNP_A-8576185	G	A	0.01583	0.8834		C	T	0.7088	0.9788		C	T	0.9317	0.9942
	rs1402070	SNP_A-1824820	C	G	0.01646	1.106		G	C	0.01531	0.8458		G	C	0.9477	1.009
	rs2350796	SNP_A-2294126	A	T	0.017	1.139		A	T	0.8914	1.012		A	T	0.2271	1.085
	rs10175502	SNP_A-8536945	G	C	0.01724	0.7311		C	G	0.719	0.9522		NA	NA	NA	NA
	rs16839220	SNP_A-1871945	C	G	0.02361	1.105		C	G	0.3933	1.063		C	G	0.5016	0.9007
	rs7571452	SNP_A-2071553	C	T	0.02522	0.9209		C	T	0.5375	1.038		C	T	0.8414	1.014
	rs1528454	SNP_A-2086364	C	T	0.03383	0.9197		C	T	0.6509	0.9719		C	T	0.65	0.9698
	rs7564747	SNP_A-1852734	C	G	0.03771	0.9248		G	C	0.292	0.9379		G	C	0.4007	0.9406
	rs2133972	SNP_A-2129869	A	G	0.0387	1.121		A	G	0.7282	1.032		A	G	0.8192	1.017
	rs13426050	SNP_A-1909156	A	G	0.04273	0.8803		A	G	0.7535	0.9692		A	G	0.7946	1.02
NRCAM (neuronal cell adhesion molecule)	rs10250083	SNP_A-8316761	C	T	0.00623	1.211		NA	NA	NA	NA		NA	NA	NA	NA
	rs7790875	SNP_A-2225717	C	G	0.00681	1.12		C	G	0.3568	0.9446		C	G	0.9105	1.009
	rs13227836	SNP_A-4224193	C	T	0.00882	1.116		C	T	0.2751	0.9349		C	T	0.7302	1.026
	rs10226935	SNP_A-1847308	T	C	0.01298	1.131		A	G	0.3372	0.9387		A	G	0.6992	1.028
	rs1990711	SNP_A-8668330	C	T	0.0146	1.162		G	A	0.2085	0.9291		G	A	0.2772	1.076
	rs2300052	SNP_A-22662	A	G	0.01495	1.107		T	C	0.2749	0.935		T	C	0.8671	0.9874

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	rs13238841	SNP_A-1894176	A	G	0.01717	1.104		T	C	0.3666	0.9461		T	C	0.9852	1.001
	rs4142284	SNP_A-2161817	T	C	0.01743	0.9124		T	C	0.03029	1.145		T	C	0.6592	0.9551
	rs1990713	SNP_A-8417469	T	C	0.01922	0.8802		T	C	0.4582	1.046		T	C	0.0882	0.8856
	rs13225168	SNP_A-2216366	T	G	0.01969	0.914		T	G	0.07709	1.116		T	G	0.6979	0.9687
	rs2111202	SNP_A-1927223	T	C	0.02232	0.9157		T	C	0.08109	1.114		T	C	0.9223	0.9897
	rs10953569	SNP_A-1800120	A	G	0.02406	1.093		A	G	0.4061	0.9524		A	G	0.69	1.029
	rs13230316	SNP_A-4251808	G	C	0.02554	0.9144		C	G	0.9613	1.003		C	G	0.4867	1.054
	rs7795834	SNP_A-8584593	A	T	0.02906	1.16		A	T	0.01782	0.8607		A	T	0.9197	0.9931
	rs2284284	SNP_A-8370696	G	A	0.03558	1.122		C	T	0.05315	0.8891		T	C	0.4684	1.049
	rs2023503	SNP_A-8454924	G	C	0.03828	1.115		G	C	0.1383	0.9174		C	G	0.8433	0.987
	rs7792321	SNP_A-1953659	G	C	0.03888	1.079		G	C	0.4232	0.9537		NA	NA	NA	NA
	rs11974528	SNP_A-2304415	T	C	0.03924	0.749		A	G	0.994	1.001		A	G	0.3835	0.9294
	rs12673676	SNP_A-2287636	T	G	0.04253	0.9168		T	G	0.4382	1.055		T	G	0.9481	1.008
	rs16872495	SNP_A-1990855	C	A	0.04263	0.916		G	T	0.6724	1.03		G	T	0.9333	1.009
	rs12705470	SNP_A-1839823	T	C	0.04683	1.089		T	C	0.3708	0.946		T	C	0.8115	1.018
	rs17155335	SNP_A-2058654	T	A	0.04801	1.089		T	A	0.009156	0.8498		A	T	0.5968	1.035
NRG1 (neuregulin 1)	rs1158001	SNP_A-8348754	A	C	0.001731	0.8305		T	G	0.9317	0.9943		NA	NA	NA	NA

rs12541516	SNP_A-8282006	T	C	0.002285	0.8345		T	C	0.6038	1.035		T	C	0.1012	1.114
rs954009	SNP_A-8282007	C	T	0.003191	0.8391		C	T	0.9254	1.006		C	T	0.04591	1.172
rs16879809	SNP_A-2187755	T	C	0.007758	1.14		T	C	0.05128	1.17		T	C	0.9974	1.001
rs11780004	SNP_A-8281583	G	A	0.01245	0.8819		C	T	0.7865	0.9849		C	T	0.005521	0.7685
rs4535704	SNP_A-8361899	G	A	0.01432	0.8794		G	A	0.9511	0.9964		G	A	0.4197	0.9391
rs11991036	SNP_A-2110514	T	C	0.0155	0.9136		T	C	0.09759	1.103		T	C	0.3499	1.068
rs2553250	SNP_A-8586262	G	A	0.01625	0.8863		G	A	0.4646	0.9597		A	G	0.3331	0.9338
rs7012873	SNP_A-8374215	T	C	0.01629	0.5963		T	C	0.5199	1.159		T	C	0.3871	1.099
rs4268090	SNP_A-2171675	T	C	0.0193	1.089		T	C	0.1928	1.078		T	C	0.1154	0.8876
rs4035323	SNP_A-8281578	G	A	0.0209	0.8623		G	A	0.8777	0.9913		A	G	0.5621	0.9628
rs13439388	SNP_A-8644106	A	G	0.02139	0.8906		A	G	0.4771	0.9608		A	G	0.9873	1.001
rs12681411	SNP_A-2255315	G	C	0.02147	1.088		G	C	0.07185	1.111		G	C	0.005903	0.7455
rs10954863	SNP_A-1826569	A	G	0.02171	0.8909		T	C	0.624	0.9727		T	C	0.1549	0.8722
rs10954864	SNP_A-8580728	G	C	0.02482	1.119		C	G	0.9123	0.9938		C	G	0.7732	0.9805
rs7818821	SNP_A-1992951	G	A	0.02687	1.088		G	A	0.7514	1.02		G	A	0.6146	1.034
rs11775675	SNP_A-4287161	T	C	0.02899	0.8832		T	C	0.3961	0.9484		T	C	0.3581	0.9278
rs11506112	SNP_A-1837924	C	G	0.03244	1.147		NA	NA	NA	NA		NA	NA	NA	NA
rs10954887	SNP_A-42888	G	A	0.03734	1.123		NA	NA	NA	NA		NA	NA	NA	NA

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	rs17642273	SNP_A-4247908	C	A	0.04091	0.8612		G	T	0.2944	0.9195		G	T	0.011	0.6327
	rs3847131	SNP_A-8281579	A	G	0.04257	0.8977		T	C	0.749	0.9812		T	C	0.4233	0.9476
	rs13272876	SNP_A-1799924	T	A	0.04398	0.92		A	T	0.3236	0.9354		A	T	0.1936	0.8115
	rs1898210	SNP_A-1873492	T	A	0.04452	0.9292		A	T	0.5688	1.034		A	T	0.6137	1.037
	rs7845747	SNP_A-2255719	C	T	0.04531	0.8007		G	A	0.6203	0.9201		G	A	0.1666	1.194
	rs1623372	SNP_A-8514672	G	A	0.04656	0.898		C	T	0.411	0.9516		C	T	0.3237	1.07
PDE4B (phosphodiesterase 4B, cAMP-specific)	rs6588193	SNP_A-4224697	G	C	0.003042	1.11		G	C	0.3473	1.054		C	G	0.4673	0.9405
	rs1321172	SNP_A-2177920	C	G	0.003177	1.109		G	C	0.4168	1.047		C	G	0.5122	0.9463
	rs502958	SNP_A-1866228	A	T	0.003879	1.107		A	T	0.2563	1.067		A	T	0.6121	1.036
	rs6688020	SNP_A-4296993	G	T	0.004013	1.106		C	A	0.4658	1.042		A	C	0.5053	0.9454
	rs6700403	SNP_A-2135531	T	C	0.004327	1.106		T	C	0.1924	1.077		C	T	0.1392	0.902
	rs536858	SNP_A-4242711	G	C	0.009832	1.106		G	C	0.2157	1.074		G	C	0.4999	1.049
	rs538336	SNP_A-4247653	C	T	0.01719	1.089		G	A	0.2219	1.073		G	A	0.5213	1.047
	rs17128076	SNP_A-2116543	A	G	0.01787	0.7863		A	G	0.7392	1.055		A	G	0.8574	1.026
	rs17417507	SNP_A-2084832	T	C	0.01945	0.838		A	G	0.8987	1.015		A	G	0.000103	0.2986
	rs524770	SNP_A-4229990	A	G	0.02169	1.086		A	G	0.2179	1.073		A	G	0.4779	1.052
	rs641262	SNP_A-2153696	T	C	0.02175	1.084		A	G	0.2676	1.065		G	A	0.2009	0.8969

	rs2840677	SNP_A-2188463	A	T	0.02238	0.9227		T	A	0.05376	0.8971		T	A	0.07104	0.8887
	rs4492586	SNP_A-4204922	T	C	0.02494	0.8343		A	G	0.2263	1.168		A	G	0.06282	1.358
	rs554120	SNP_A-8481741	A	G	0.0262	1.12		A	G	0.2638	1.066		A	G	0.899	0.9915
	rs558550	SNP_A-8462316	A	T	0.02763	0.8924		T	A	0.4183	0.9546		T	A	0.2979	0.9244
	rs575056	SNP_A-2127808	C	T	0.03044	1.081		C	T	0.3073	1.06		C	T	0.4843	1.048
	rs546784	SNP_A-2022741	T	C	0.03305	1.078		A	G	0.3249	1.057		G	A	0.2775	0.9145
	rs7537687	SNP_A-8715728	T	C	0.03325	0.8169		A	G	0.045	1.233		A	G	0.6283	0.9355
	rs2455012	SNP_A-2000104	A	G	0.03812	0.8457		T	C	0.2236	1.17		T	C	0.06282	1.358
	rs6683977	SNP_A-4272130	G	C	0.03875	1.077		C	G	0.3352	1.057		G	C	0.4265	0.9178
	rs12137080	SNP_A-8683613	C	T	0.0395	1.11		G	A	0.2792	1.063		A	G	0.3399	0.9297
	rs12137115	SNP_A-4283348	C	G	0.04291	1.081		C	G	0.3556	1.054		G	C	0.3703	0.9292
	rs1937443	SNP_A-8402710	C	G	0.04724	0.9044		C	G	0.4432	0.9576		C	G	0.9215	0.9933
PRKCA (protein kinase C, alpha)	rs6504428	SNP_A-8490444	G	A	0.007991	0.8094		C	T	0.1004	0.8667		C	T	0.9586	1.004
	rs4630585	SNP_A-1955964	G	A	0.01096	0.816		G	A	0.1004	0.8667		G	A	0.982	0.9984
	rs6504432	SNP_A-4287828	A	G	0.01337	0.7932		NA	NA	NA	NA		T	C	0.3984	1.061
	rs16959714	SNP_A-2233134	T	C	0.01557	1.275		T	C	0.3482	1.157		T	C	0.7047	0.9059
	rs4424941	SNP_A-8462947	T	G	0.01851	0.8325		A	C	0.3288	1.074		A	C	0.6903	1.031
	rs4502257	SNP_A-82884	T	C	0.03651	0.7727		A	G	0.05193	0.7578		A	G	0.09795	0.7758

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	rs4791022	SNP_A-2273374	T	C	0.04099	1.11		NA	NA	NA	NA		NA	NA	NA	NA
	rs7215091	SNP_A-1942222	T	C	0.04204	0.8937		T	C	0.1681	1.118		C	T	0.09695	0.8971
	rs17689224	SNP_A-8439372	T	C	0.04205	1.128		A	G	0.6702	1.029		A	G	0.5825	0.9172
RAB18 (RAB18, member RAS oncogene family)	rs12261690	SNP_A-1942786	G	A	0.03817	1.287		NA	NA	NA	NA		G	A	0.9386	1.008
RELN (reelin)	rs2711865	SNP_A-2068476	T	G	0.01368	0.8856		T	G	0.8264	0.9844		NA	NA	NA	NA
	rs2711838	SNP_A-2311413	T	C	0.01399	0.9081		A	G	0.4811	1.045		A	G	0.1583	1.097
	rs2528864	SNP_A-2180542	C	G	0.02092	0.908		G	C	0.3664	1.062		C	G	0.01268	0.8493
	rs10953394	SNP_A-1796688	A	T	0.02154	1.1		A	T	0.6271	0.9684		A	T	0.7369	0.9738
	rs2245617	SNP_A-4243581	T	C	0.04907	1.087		T	C	0.9913	1.001		T	C	0.9107	0.9837
RGS4 (regulator of G-protein signaling 4)	rs4657235	SNP_A-8679457	T	C	0.004835	1.254		A	G	0.6014	1.049		A	G	0.1017	1.119
	rs10157628	SNP_A-4232432	A	G	0.01609	0.8123		A	G	0.3375	1.079		A	G	0.4521	1.064
	rs12735998	SNP_A-2248074	T	C	0.02304	1.097		T	C	0.8436	1.013		C	T	0.202	0.9199
	rs12124253	SNP_A-8480260	A	C	0.02514	1.137		A	C	0.7652	1.019		C	A	0.008285	0.8014
	rs4657233	SNP_A-1950294	C	T	0.027	1.144		C	T	0.8706	0.9841		C	T	0.5105	1.044
	rs4657237	SNP_A-1882915	T	C	0.02886	1.147		A	G	0.8618	0.9826		G	A	0.02626	0.8647
	rs10917632	SNP_A-8449773	C	T	0.03359	1.13		C	T	0.5279	1.042		NA	NA	NA	NA
	rs12043369	SNP_A-	A	G	0.03839	1.088		A	G	0.7419	0.9785		A	G	0.3883	1.066

		2183358													
	rs951438	SNP_A-8579091	T	G	0.03883	0.9012		T	G	0.4148	1.047		T	G	0.8919	0.9899
SLC1A2 (solute carrier family 1 (glial high affinity glutamate transporter), member 2)	rs3794086	SNP_A-8349382	A	C	0.02565	1.123		T	G	0.4893	1.041		T	G	0.5055	0.9435
	rs12273644	SNP_A-8535231	C	A	0.02851	1.12		C	A	0.3341	1.058		C	A	0.6856	0.9693
	rs17379710	SNP_A-8549821	T	C	0.04	1.109		A	G	0.3795	1.051		A	G	0.6182	0.9656
	rs736374	SNP_A-8381417	A	G	0.04739	1.108		A	G	0.4063	1.05		A	G	0.8783	0.9822
SNAP25 (synaptosomal-associated protein, 25kDa)	rs6032783	SNP_A-4294089	C	T	0.01815	0.8513		G	A	0.7874	0.9707		G	A	0.3542	0.9328
	rs994919	SNP_A-8348966	G	A	0.02045	1.132		C	T	0.6953	1.024		C	T	0.9708	1.003
	rs362585	SNP_A-4238404	T	G	0.03084	0.8455		T	G	0.4797	0.9144		T	G	0.6273	0.9602
	rs362582	SNP_A-2123088	A	T	0.03678	0.85		T	A	0.6495	0.9442		T	A	0.9187	0.9918
	rs362574	SNP_A-8322474	A	C	0.04111	1.109		T	G	0.4381	0.9569		T	G	0.3798	1.062
	rs362563	SNP_A-2021062	C	T	0.04346	0.8347		NA	NA	NA	NA		C	T	0.9058	0.9898
SYN2 (synapsin II)	rs2960421	SNP_A-8566858	G	A	0.003144	0.8238		G	A	0.8224	1.017		G	A	0.6613	0.9357
	rs3755724	SNP_A-8346003	T	C	0.01529	0.8794		A	G	0.4188	1.049		A	G	0.5086	0.9436
	rs167467	SNP_A-1819097	C	T	0.02335	0.9234		G	A	0.481	0.9611		A	G	0.8328	1.014
	rs3773364	SNP_A-8438364	G	A	0.02792	0.8567		G	A	0.858	0.986		G	A	0.9998	1
	rs2600271	SNP_A-8520412	T	C	0.04593	1.153		A	G	0.1893	1.108		NA	NA	NA	NA
TCF4 (transcription factor 4)	rs17594665	SNP_A-4203722	A	G	0.0002902	1.517		A	G	0.01039	1.468		A	G	0.5109	0.9291

rs17594526	SNP_A-2043531	T	C	0.000467	1.446		A	G	0.01369	1.448		A	G	0.1981	0.8872
rs41452747	SNP_A-2299999	A	G	0.00043	1.315		T	C	0.5099	1.077		T	C	0.2724	1.212
rs11152369	SNP_A-2162934	C	A	0.000467	1.445		C	A	0.01943	1.42		C	A	0.2425	0.896
rs9646596	SNP_A-2048694	A	G	0.000516	1.43		T	C	0.02363	1.398		T	C	0.2833	0.9037
rs8099483	SNP_A-2025191	A	T	0.0012	1.247		T	A	0.3669	1.102		T	A	0.6148	1.047
rs10401120	SNP_A-2224936	T	C	0.001341	1.314		A	G	0.2482	1.159		A	G	0.9987	0.9999
rs17596267	SNP_A-4259735	A	T	0.002183	1.389		A	T	0.03964	1.339		A	T	0.904	1.021
rs12326693	SNP_A-2070226	T	C	0.002694	0.8885		A	G	0.5733	0.9648		A	G	0.8096	1.023
rs41421645	SNP_A-2230421	A	T	0.002851	0.7449		A	T	0.09892	0.7845		A	T	0.7371	1.032
rs1377242	SNP_A-2105319	T	C	0.005119	0.797		T	C	0.1339	0.809		T	C	0.4646	0.8817
rs12457949	SNP_A-1843919	G	A	0.007208	0.8743		C	T	0.6008	0.9612		C	T	0.1694	0.8093
rs17509991	SNP_A-4201017	A	G	0.008441	1.517		A	G	0.01899	1.425		A	G	0.2127	0.8887
rs4800933	SNP_A-4203749	T	C	0.01148	0.8926		A	G	0.6522	0.9675		A	G	0.4724	1.073
rs9966779	SNP_A-8452997	T	C	0.01353	0.7713		T	C	0.4289	1.1		T	C	0.4148	0.9021
rs17594358	SNP_A-8485945	G	A	0.01483	1.315		C	T	0.6296	1.06		C	T	0.8525	0.9451
rs10164195	SNP_A-2041483	C	A	0.01493	0.7174		C	A	0.3116	0.8538		NA	NA	NA	NA
rs8095770	SNP_A-8471138	C	T	0.01716	1.279		G	A	0.5077	1.076		G	A	0.4762	1.122
rs4801016	SNP_A-86004	T	A	0.01888	0.7397		T	A	0.2203	0.8349		T	A	0.2013	1.454

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	rs17533219	SNP_A-8597318	C	A	0.02091	0.8866		G	T	0.5448	0.9653		G	T	0.3693	0.9283
	rs17090119	SNP_A-8318001	C	T	0.02339	0.6573		C	T	0.5891	1.114		C	T	0.7612	1.052
	rs7241077	SNP_A-8295702	A	T	0.0239	1.133		A	T	0.3288	1.063		A	T	0.04004	1.229
	rs4632206	SNP_A-8475385	G	T	0.024	1.144		C	A	0.1198	1.112		C	A	0.6377	0.923
	rs2588477	SNP_A-8494352	G	A	0.02413	0.8917		C	T	0.9424	0.9959		T	C	0.2605	1.08
	rs9949821	SNP_A-1813452	A	G	0.02668	1.099		A	G	0.03078	1.158		A	G	0.2368	0.8914
	rs4131791	SNP_A-2005672	T	C	0.02821	0.9246		A	G	0.9159	0.9939		A	G	0.621	0.9664
	rs1893431	SNP_A-8372748	A	G	0.0294	1.119		A	G	0.7622	1.018		A	G	0.09793	1.125
	rs9965625	SNP_A-2178958	A	G	0.02952	0.9255		T	C	0.912	0.9937		T	C	0.5113	1.044
	rs11874716	SNP_A-1793542	G	T	0.02956	0.9251		C	A	0.9832	1.001		C	A	0.7756	0.9804
	rs1261070	SNP_A-1792662	A	G	0.03094	0.8742		T	C	0.9271	0.9909		T	C	0.8056	1.067
	rs398854	SNP_A-8371561	C	T	0.03114	0.8932		C	T	0.6249	0.9717		C	T	0.07779	0.8473
	rs9319830	SNP_A-8388607	G	C	0.03185	1.113		G	C	0.6738	0.9766		G	C	0.9604	1.003
	rs17089826	SNP_A-4246785	T	C	0.03431	0.8139		A	G	0.2709	0.8809		A	G	0.6209	1.05
	rs17511755	SNP_A-2179208	C	G	0.04115	1.195		C	G	0.07765	1.26		C	G	0.3086	1.239
TNIK (TRAF2 and NCK interacting kinase)	rs260769	SNP_A-8522141	C	T	0.001377	0.8417		G	A	0.8397	1.012		A	G	0.5017	0.9553
	rs2131017	SNP_A-2105629	C	T	0.001602	1.204		NA	NA	NA	NA		NA	NA	NA	NA

rs1353020	SNP_A-1906431	A	T	0.002069	1.208		T	A	0.03244	1.23		T	A	0.8972	0.9905
rs4894814	SNP_A-8625872	A	T	0.002333	0.7445		T	A	0.3335	0.9059		T	A	0.3334	1.25
rs360414	SNP_A-4295709	T	C	0.002929	0.9002		A	G	0.2666	0.939		G	A	0.5234	1.043
rs6444983	SNP_A-4300538	A	C	0.00681	1.197		T	G	0.06318	1.21		T	G	0.707	1.036
rs11927009	SNP_A-2188964	T	G	0.00884	1.105		T	G	0.7402	0.9815		T	G	0.62	1.035
rs902952	SNP_A-4247905	A	G	0.01009	1.205		A	G	0.05978	1.214		A	G	0.7736	0.9787
rs4894536	SNP_A-2009299	C	T	0.01102	0.913		G	A	0.4361	0.9562		G	A	0.9583	1.005
rs9846083	SNP_A-1869674	T	C	0.01204	0.9142		T	C	0.4619	0.9586		T	C	0.8566	1.017
rs2422224	SNP_A-1787302	G	C	0.01745	1.173		C	G	0.0549	1.221		C	G	0.9877	1.001
rs1565567	SNP_A-2028733	A	T	0.01764	1.111		T	A	0.5691	1.038		T	A	0.6678	1.035
rs7641627	SNP_A-8597362	G	A	0.02256	0.7822		C	T	0.2576	0.8687		C	T	0.9864	1.002
rs9867647	SNP_A-8675678	A	T	0.02823	0.8947		A	T	0.356	1.054		A	T	0.383	0.944
rs1353021	SNP_A-4225515	A	G	0.02969	1.087		T	C	0.2321	1.07		C	T	0.05394	0.8196
rs9844925	SNP_A-1819684	T	C	0.03062	0.9083		T	C	0.7607	0.9788		C	T	0.8893	0.9909
rs187229	SNP_A-1868251	T	C	0.03741	0.9271		A	G	0.01565	0.8681		G	A	0.8203	0.9839
rs6788198	SNP_A-4231193	A	G	0.03745	0.9003		T	C	0.08128	1.152		T	C	0.1285	0.7973
rs902953	SNP_A-1975299	C	T	0.03837	0.9299		G	A	0.9753	0.9983		G	A	0.8616	0.9886
rs181715	SNP_A-21575	A	T	0.03886	0.9276		T	A	0.01057	0.861		A	T	0.8692	1.011

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	rs360457	SNP_A-2138782	G	T	0.03972	0.8951		NA	NA	NA	NA		NA	NA	NA	NA
	rs11916004	SNP_A-1798646	G	A	0.04041	0.905		G	A	0.6957	0.9725		A	G	0.3759	0.9429
	rs9844740	SNP_A-1787640	A	C	0.04254	0.9102		T	G	0.6553	1.033		T	G	0.7011	0.9751

Table S4: An example of how Intra- Pathway Epistasis Testing (INPEP) Identifies Genes That May Work Together. Inside the canonical pathway Glutamate Receptor Signaling, we tested for pairwise epistatic interactions between the best p-value SNPs from the ISC GWAS (Table 1) in glutamate receptor genes in the pathway that are part of our list of top candidate genes, as a way of identifying and prioritizing interactions. The top epistatic interactions are depicted in bold and underlined. As a caveat, the p-value was not corrected for multiple comparisons. The corresponding genes merit future follow-up work to elucidate the biological and pathophysiological relevance of their interactions. In particular, GRIA4 has suggestive evidence for interaction with 2 other genes (GRM7 and GRIN2B) in this pathway.

	GRIA1	GRIA4	GRIN2A	GRIN2B	GRM1	GRM4	GRM5	GRM7
GRIA1		0.131	0.5841	0.4687	0.5963	0.6463	0.1614	0.062
GRIA4	0.131		0.2857	**0.0497**	0.1236	0.4803	0.7363	**0.0174**
GRIN2A	0.5841	0.2857		0.8176	0.9805	0.6123	0.3202	0.2206
GRIN2B	0.4687	**0.0497**	0.8176		0.1301	0.7771	0.6268	0.8746
GRM1	0.5963	0.1236	0.9805	0.1301		0.2372	0.3898	0.4186
GRM4	0.6463	0.4803	0.6123	0.7771	0.2372		0.0695	0.7195
GRM5	0.1614	0.7363	0.3202	0.6268	0.3898	0.06945		0.9429
GRM7	0.062	**0.0174**	0.2206	0.8746	0.4186	0.7195	0.9429	

Figure S2: Glutamate Receptor Signaling: From Genes to Biology