No Evidence That Schizophrenia Candidate Genes Are More Associated With Schizophrenia Than Non-Candidate Genes

Supplemental Information

Supplemental Methods and Supplemental Figures

Here we cover a few of the analysis steps in more detail, but refer the reader to CA de Leeuw et al. (2015) (1) for in-depth questions about statistical details, assumptions, and implementation of the MAGMA gene-set analysis program: Link to primary publication.

Our analysis script is available upon request, and almost all of the datasets used in our analyses are publically available. The most current export from the SZGene (2) database is available in .csv format upon request from Dr. Matthew McQueen (Matt.McQueen@colorado.edu).

SNP annotation and calculation of the gene-wise *p*-value

First, SNPs were matched to genes using NCBI Build 37 gene locations. As in Farrell et al. (3), we specified that SNPs in a 25 kb window around each gene be assigned to that gene, in order to capture the effects of any variants that might lie outside strict gene boundaries but still act on the nearest gene (e.g. variants in nearby enhancer or promoter regions). We repeated the same analyses with strict gene boundaries as defined in NCBI Build 37.

Next, the joint association of SNPs with the phenotype was computed for each gene, using the PGC GWAS summary statistics as input and the 1000 Genomes (4) European samples as the reference sample to calculate the LD between SNPs. The gene-level p-values were calculated by summing the -log(*p*) for all SNP *p*-values in the boundary of gene *i* (the distribution of this sum is unknown but is approximated by a scaled chi-square distribution, with degrees of freedom (*df*) and scaling a function of the squared SNP-SNP correlation matrix, which simultaneously accounts for LD between SNPs). This sum(-log(*p*)) was the gene-level test statistic used in our primary analyses, but we also repeated these procedures using the minimum SNP *p*-value in a gene as the gene-level statistic and report those results in Table S2.

Variations on the gene set test: self-contained, competitive, and relative tests

The "self-contained" analysis, which is equivalent to a single-sample t-test of association, restricts the model to only include the genes in the gene set and tests whether those genes are associated with schizophrenia by testing whether the mean *z*-score of the set (the intercept in the model) is different from zero: this is implemented as testing the null hypothesis H_0: $\beta_0 = 0$ against the alternative hypothesis H_a: $\beta_0 > 0$ in the regression model $z_i = \beta_0\vec{1} + \beta_{2_i}C_i + \varepsilon_i$, where the gene-level *z* -score, representing the association of each gene *i* with schizophrenia ($z_i = \Phi(1-p_i)$ with p_i being the *p*-value for gene *i*), is the outcome variable, and the residual covariance, modeled using estimated gene-gene correlations to account for LD between genes, is represented here as the vector ε_i. Gene size, SNP density, and minor allele count (as well as the log of these gene characteristics), and any other covariates of interest (gene annotations, etc.) are

included as a matrix of covariates (represented here as the C term in the regression framework). The *p*-value for the self-contained test with the set of 25 candidate genes was highly significant (*p* = 1e-14). However, this result is not of great relevance because, with a highly polygenic trait and enough statistical power, virtually any random set of genes could be significantly associated with a trait. We report this result here because it demonstrates that even gene sets which are not close to statistically significant when controlling for baseline association across the genome (as we demonstrate below and in the main text) can appear highly significant when that baseline level of association is not accounted for.

The competitive analysis is implemented as a one-tailed test of the b term in the model: $z = \alpha + G_1\beta + C\vec{\gamma} + \varepsilon$. z represents the gene-level z -score (the association of each gene with schizophrenia), G_1 is a dummy-coded predictor indicating gene set membership, and C is a matrix of possible confounders including gene length, SNP density, minor allele count, and their log transforms. Because gene level statistics are correlated with those from neighboring genes, the residuals ε cannot be assumed to be independent. The covariances of the residuals are therefore modeled as the estimated gene-gene correlations ($\hat{\Sigma}$) scaled by a residual variance term (σ_e^2), ie. $\varepsilon \sim MVN(0, \sigma_e^2\hat{\Sigma})$.

The “relative” test is implemented in the following (simplified) regression framework: $z = \alpha + G_1\beta_1 + G_2\beta_2 + C\vec{\gamma} + \varepsilon$, where G_1 is a dummy-coded variable representing gene set membership (i.e. $G_1 = 1$ if the gene is in gene set 1, $G_1 = 0$ otherwise), and G_2 is a dummy-coded variable representing membership in a comparison gene set. By default,

the relative analysis tests the null hypothesis H_0: $\beta_1 = \beta_2$ against the alternative hypothesis H_a: $\beta_1 > \beta_2$, or in other words: is the association of genes in set 1 with the phenotype significantly stronger than the association of the genes in set 2? However, we specified a two-tailed test in MAGMA, such that the null hypothesis H_0: $\beta_1 = \beta_2$ is tested against the alternative hypothesis H_a: $\beta_1 \neq \beta_2$, since, presumably, we are also interested in the possibility that the set of genes associated with height, for example, might be more strongly related to schizophrenia than the set of actual schizophrenia candidate genes. More information on these gene set analysis variations is given in the original MAGMA publication (1).

Tests for sensitivity and specificity

In addition to the main analyses outlined in the manuscript, we ran three additional analyses to ensure that our method was both sensitive and specific. We first conducted a very basic, proof-of-concept check for sensitivity: we tested whether a gene set made up of the most significantly-associated gene from each autosome from the PGC GWAS was more associated with schizophrenia when tested as a gene set in MAGMA. As expected, this gene set was much more significantly associated with schizophrenia than all other genes ($\beta = 2.44$, SE = 0.22, $p = 2.96\times10^{-28}$ in a competitive test), confirming that our analysis correctly rejected the null hypothesis when appropriate. MAGMA also appeared to be sensitive under the alternative when testing whether the set of 1028 genes associated with synaptic processes was more associated with schizophrenia than other genes ($\beta = 0.152$, SE = 0.04, $p = 1.94e^{-05}$ for the competitive test). Finally, to test specificity under the null, we used genes implicated in height GWAS and confirmed

that these genes were not significantly associated with schizophrenia more than expected by chance (β = 0.05, SE = 0.08, p = 0.27 for the competitive test).

Examining the effect of the size of gene set on power in competitive tests

To test whether the competitive test on the 86 candidate genes was more significant than the competitive test on the 25 candidate genes was simply due to increased power due to different gene set sizes, we randomly sampled from 1 to 100 genes from the full set of 1028 genes involved in synaptic processes, which as a group are more associated with schizophrenia than other genes (β = 0.152, SE = 0.04, $p = 1.94e^{-05}$ for the competitive test; set taken from Ruano et al. (5) and Lips et al. (6)) and then performed a basic competitive gene set test in MAGMA, with the randomly sampled genes grouped as the gene set of interest and all other non-synaptic genes in the genome as the comparison set (we excluded all genes related to synaptic processes from the genome-wide comparison set at the beginning of our simulations, in order to control for the possibility of confounding by varying numbers of comparison genes being included in the test.) We repeated this sampling process 5,000 times and recorded the gene set p-value returned from MAGMA for each of the iterations. We then calculated the average p-value across all samples for each size gene set (i.e., there were approximately 50 samples for each size gene set n from 1 to 100). These 100 average p-values, for each size gene set from 1 to 100, are plotted in Figure S2. The results demonstrated that as the size of a set of genes known to be associated with a trait increased, power of the MAGMA competitive test also increased: the correlation

between the gene set size and average *p*-value was negative (r = -0.90) and highly significant ($p < 2.2e-16$).

Does differential gene set size affect power in relative tests?

We were also interested in whether differential gene set sizes could potentially affect power and bias results when comparing sets of genes in a relative test. For example, in the relative test of the top candidate genes versus the set of genes related to height, does the discrepancy in gene set size (25 schizophrenia candidate genes vs. 258 height-related genes) negatively affect the power to detect a significant association in the smaller gene set? We did not expect differential gene set sizes to affect power of the relative test because gene set size is explicitly controlled for in the regression. Nevertheless, to test this possibility, we permuted sets of 25 genes from the full set of 258 height genes, performed a relative test in MAGMA comparing the association of the top 25 candidate genes with that of the set of 25 height genes, and repeated this process 1,000 times. The average *p*-value from these relative tests was 0.48, suggesting that the set of 25 historical candidate genes is not significantly more related to schizophrenia than random sets of 25 genes associated with height, and confirming what we found in the relative test comparing the 25 candidate genes with the 258 height-related genes (*p*-value = 0.39). This demonstrated that discrepancy in gene set size does not have a large effect on power in the relative tests, and did not influence our results.

What is the probability of having at least nine genes significantly associated with schizophrenia within sets of 25 randomly chosen genes?

We also wanted to test whether the *number* of significant genes among our set of top 25 candidate genes was larger than expected by chance. In other words, in any given sample of 25 genes, how likely are there to be at least nine genes significantly associated with schizophrenia? To examine this question, we randomly sampled sets of 25 genes from across the genome, simply recorded the *M* number of genes with gene-level test statistics associated with schizophrenia at $\alpha < 0.05$, and repeated this procedure 1,000 times to create a distribution of the number of statistically significant genes in each random sample of 25 genes. As seen in Figure S6, finding nine genes significantly associated with schizophrenia within a random sample of 25 genes is not unexpected: 25.2% of the distribution lies above the nine-gene threshold.

Comparing the significance of the most associated historical candidate genes relative to other sets of significantly-associated genes throughout the genome

While our study provides no robust evidence to support the notion that the aggregate set of 25 historical candidate genes harbors more causal variants for schizophrenia than other genes on average, one possible takeaway is that there *are* candidate genes worthy of follow-up (e.g. *NOTCH4, DRD2*) and thus the candidate gene enterprise has not failed on the whole. As described in the main text, to investigate this issue we performed a relative test in MAGMA of the 9 significant candidate genes versus all other genes significantly ($p < .05$) related to schizophrenia in the genome, and found evidence that the strength of the associations of these 9 genes was greater than that among

other significant genes (β = 0.789, SE = 0.28, *p* = .005). Results remained significant when we dropped MHC genes from both sets (β = 0.738, SE = 0.32, *p* = .02) and when we compared the 7 significant non-MHC candidate genes to all other significantly related non-MHC synaptic genes (β = 0.896, SE = 0.42, *p* = .03).

Analyses excluding genes originally studied because of evidence from prior linkage studies

One possible comment on our analysis is that genes selected for further study because of their presence under a linkage peak could be expected to have more statistical evidence in their favor compared to candidate genes chosen due to their presence in interesting pharmacological pathways or role in biological hypotheses; perhaps these genes then are more likely to be driving the signal in the expanded 86-gene set.

However, while it is true that genes chosen from linkage studies do carry more statistical evidence than, say, a gene chosen because of involvement in an interesting biological pathway, linkage peaks tend to cover megabases (e.g. spanning up to 45 centimorgans (7)) of the genome, making it difficult to determine exactly which gene(s) under the linkage peak are truly responsible for any causal variation. Approximately 23% (20 of 86) of the genes in the expanded set (n_{genes} = 86) were originally studied at least partly due to evidence from previous linkage studies, compared to about 28% (8 of 25) of the primary set of 25 historical candidate genes (from Table 1 of Farrell et al. 2015). To explicitly test whether these genes chosen because of evidence from linkage studies were the ones driving the signal in the expanded 86-gene gene set, we re-ran

the gene set analyses (using the primary test statistic, the sum(-log(*p*))) with the 86 genes minus the 20 genes from linkage analyses and the 25 top genes minus the 8 genes from linkage analyses - results are included in Supplemental Table S4. The conclusions did not change - the set of 66 candidate genes were significantly more associated with schizophrenia, both compared to the rest of the genome and relative to the set of genes involved in Type 2 diabetes, while the set of 17 historical candidate genes not motivated by linkage showed no evidence for association with schizophrenia.

Comparing gene-level p-values from MAGMA and VEGAS2

In order to confirm that our results were relatively robust to the gene set method of choice, we also calculated gene-level test statistics and p-values using the VEGAS2 version 2 software (8). Tables S5 and S6 compare the results from MAGMA and VEGAS2 for the top 25 historical candidate genes. The $-\log_{10}$(*p*-values) did not differ greatly between the methods, though there was some variation, particularly for *NOTCH4* and *DRD2*. In most discrepancies, the *p*-value from MAGMA was smaller than that from VEGAS2.

Supplementary Table S1. Descriptives of the top 86 most-studied candidate genes. Included are all candidate genes studied more than five times and not motivated by GWAS results. The average numbers of cases and controls were calculated from the SZGene database, excluding GWAS and family-based studies. Gene rankings are based on the genes' *z* statistics from MAGMA, which quantify each gene's association with schizophrenia.

Gene	NCBI_Entrez_ID	Average Number of Cases	Average Number of Controls	Association Statistic (*z*) from MAGMA	Rank (Including MHC)
NOTCH4	4855	208	285	8.78	18
SRR	63826	266	273	6.36	232
DRD2	1813	196	266	5.92	278
NOS1	4842	343	402	5.58	338
CYP2D6	1565	154	192	5.54	346
KCNN3	3782	154	154	5.03	477
ERBB4	2066	376	565	4.95	496
GRM3	2913	590	678	4.60	624
TNF	7124	159	214	4.28	762
PDE4B	5142	329	399	4.23	789
ZDHHC8	29801	303	401	4.11	871
PPP3CC	5533	683	763	3.47	1420
PPP1R1B	84152	294	423	3.25	1658
EGF	1950	193	296	3.15	1802
ATXN1	6310	110	172	3.12	1841
BDNF	627	243	292	3.01	1985
GRIN2B	2904	195	214	2.96	2065
TPH1	7166	260	360	2.79	2325
NR4A2	4929	205	201	2.74	2404
ACE	1636	198	246	2.67	2518
FZD3	7976	279	370	2.53	2798
RTN4	57142	235	285	2.44	2961
CLDN5	7122	371	420	2.40	3050
DGCR2	9993	661	737	2.36	3121
DRD5	1816	175	259	2.31	3255
GC	2638	275	771	2.13	3737
NTF3	4908	128	130	2.11	3780
DAO	1610	440	542	1.87	4504
CHRFAM7A	89832	119	116	1.77	4863
SYN3	8224	292	330	1.66	5241
SLC6A4	6532	173	207	1.64	5314

Gene	NCBI_Entrez_ID	Average Number of Cases	Average Number of Controls	Association Statistic (*z*) from MAGMA	Rank (Including MHC)
ARVCF	421	262	376	1.59	5473
RELN	5649	319	474	1.57	5592
TSNAX	7257	385	386	1.39	6286
GRIN1	2902	204	226	1.38	6380
SOD2	6648	203	267	1.23	6997
MLC1	23209	157	258	1.23	7039
MTHFR	4524	221	290	1.20	7139
TP53	7157	359	307	1.16	7311
SNAP25	6616	322	369	1.15	7357
HP	3240	233	315	1.09	7654
NPY	4852	204	263	1.04	7923
TAAR6	319100	440	578	1.01	8075
GAD1	2571	218	268	0.97	8276
GRIK3	2899	191	253	0.93	8481
HTR6	3362	146	155	0.86	8847
COMT	1312	238	383	0.85	8858
DDC	1644	163	218	0.82	9009
HTR1B	3351	162	264	0.75	9386
CNR1	1268	194	229	0.72	9555
NOS1AP	9722	293	427	0.61	10057
ERBB3	2065	279	527	0.57	10281
YWHAH	7533	198	264	0.49	10744
DRD1	1812	178	251	0.42	11121
RGS4	5999	401	497	0.42	11122
ATN1	1822	54	42	0.29	11869
TF	7018	278	530	0.25	12081
DBH	1621	131	180	0.19	12384
MAOA	4128	84	114	0.14	12658
DRD3	1814	168	198	0.11	12865
AKT1	207	458	539	0.07	13063
DRD4	1815	202	227	0.06	13119
NRG1	3084	383	489	0.03	13253
CNTF	1270	159	209	-0.05	13674
PLA2G4A	5321	150	215	-0.12	14053
MAOB	4129	105	115	-0.13	14105
PRODH	5625	235	320	-0.16	14272
DTNBP1	84062	385	436	-0.30	14958

Gene	NCBI_Entrez_ID	Average Number of Cases	Average Number of Controls	Association Statistic (*z*) from MAGMA	Rank (Including MHC)
SLC18A1	6570	187	281	-0.30	14972
HTR2A	3356	215	224	-0.32	15073
CCKAR	886	175	321	-0.32	15093
PIP5K2A	5305	250	381	-0.44	15664
CHRNA7	1139	302	316	-0.59	16327
IL1RN	3557	214	282	-0.60	16384
DISC1	27185	348	416	-0.66	16597
HTR2C	3358	103	160	-0.76	16983
IPO5	3843	385	557	-0.81	17152
TH	7054	201	259	-0.82	17199
DAOA	267012	393	526	-0.83	17225
SLC6A3	6531	180	234	-0.91	17508
IL10	3586	243	248	-0.94	17590
CNP	1267	466	584	-0.94	17596
GABRB2	2561	192	230	-1.05	17876
IL1B	3553	159	242	-1.16	18118
GSK3B	2932	339	438	-1.28	18355
APOE	348	143	211	-1.30	18380

Supplementary Table S2. MAGMA gene set analyses, using the minimum p-value as the gene-level test statistic. All tests controlled for gene size, SNP density, and minor allele count (MAC) (as well as the log(gene size), log(SNP density), and log(MAC).) P-values in bold and starred are significant at $\alpha < 0.05$.

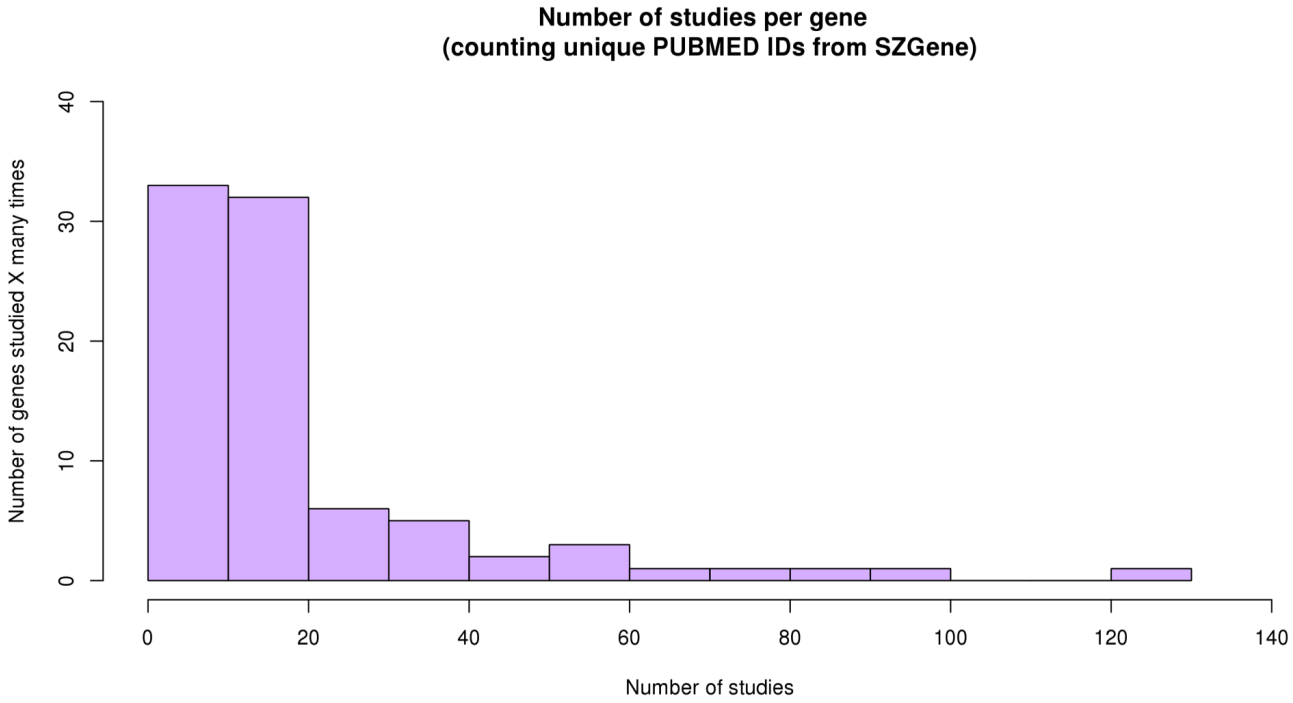
			(+/- 25 kb window)		(strict gene boundaries)	
Model	**Target Gene Set**	**Comparison Gene Set**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**
1	Historical 25 candidate genes	All other genes	0.15 (0.18)	0.21	0.21 (0.21)	0.15
2	Historical 25 candidate genes	Height associated genes	0.18 (0.20)	0.36	0.29 (0.22)	0.19
3	Historical 25 candidate genes	Type 2 Diabetes associated genes	-0.06 (0.23)	0.80	-0.12 (0.25)	0.64
4	Historical 25 candidate genes	Genes involved in synaptic processes	0.08 (0.19)	0.68	0.12 (0.21)	0.55
5	86 most-studied candidate genes	All other genes	0.15 (0.10)	0.07	**0.20 (0.12)**	**0.048***
6	86 most-studied candidate genes	Height associated genes	0.19 (0.12)	0.12	**0.28 (0.14)**	**0.047***
7	86 most-studied candidate genes	Type 2 Diabetes associated genes	-0.03 (0.18)	0.86	-0.09 (0.19)	0.64
8	86 most-studied candidate genes	Genes involved in synaptic processes	0.08 (0.11)	0.43	0.11 (0.12)	0.39

			(+/- 25 kb window)		(strict gene boundaries)	
Model	**Target Gene Set**	**Comparison Gene Set**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**
9	Historical 25 candidate genes minus MHC genes	All other genes	0.04 (0.19)	0.42	0.31 (0.21)	0.07
10	Historical 25 candidate genes minus MHC genes	Height associated genes	0.05 (0.20)	0.81	0.33 (0.23)	0.15
11	Historical 25 candidate genes minus MHC genes	Type 2 Diabetes associated genes	-0.14 (0.24)	0.56	-0.02 (0.26)	0.94
12	Historical 25 candidate genes minus MHC genes	Genes involved in synaptic processes	-0.03 (0.27)	0.88	0.22 (0.22)	0.30
13	86 Most-studied candidate genes minus MHC genes	All other genes	0.14 (0.10)	0.09	**0.24 (0.12)**	**0.02***
14	86 Most-studied candidate genes minus MHC genes	Height associated genes	0.15 (0.12)	0.21	0.26 (0.14)	0.06
15	86 Most-studied candidate genes minus MHC genes	Type 2 Diabetes associated genes	-0.02 (0.17)	0.90	-0.04 (0.19)	0.83
16	86 Most-studied candidate genes minus MHC genes	Genes involved in synaptic processes	0.07 (0.11)	0.51	0.15 (0.12)	0.22

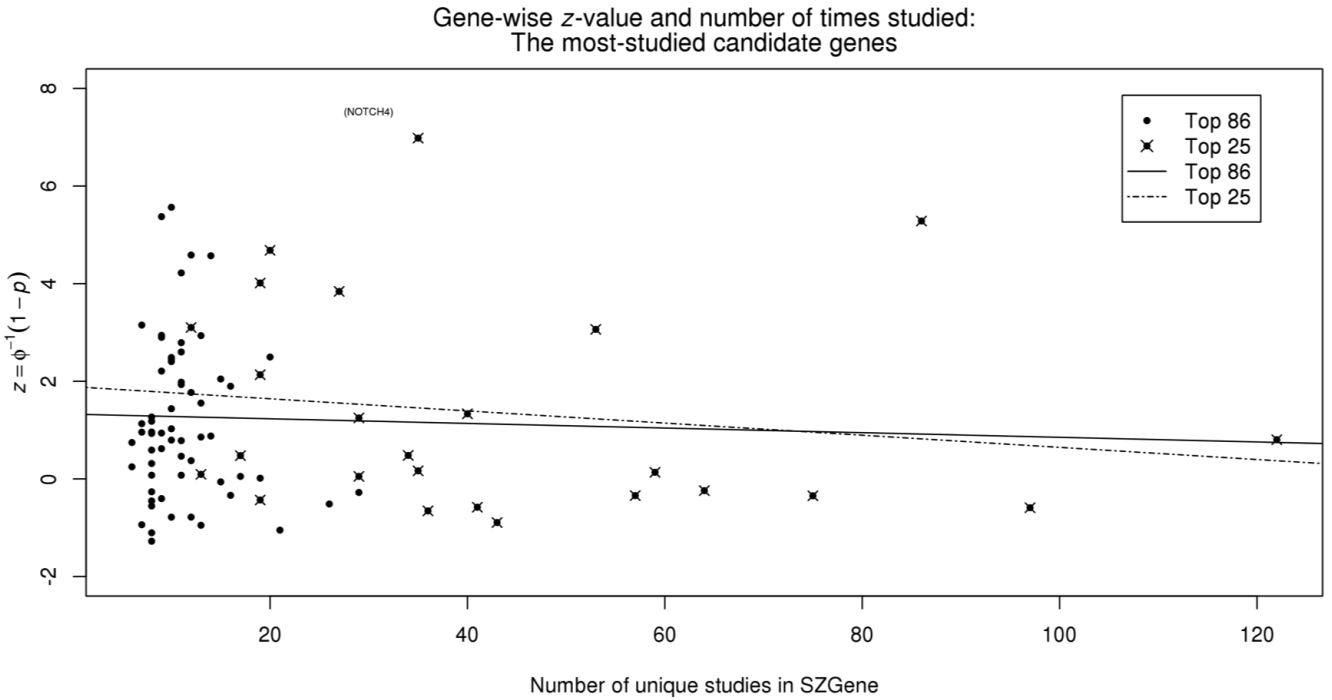
Supplementary Table S3. MAGMA gene set analyses, using a strict gene boundary. These tests used the sum of the negative log of the p-values as the gene-level test statistic. All tests controlled for gene size, SNP density, and minor allele count (MAC) (as well as the log(gene size), log(SNP density), and log(MAC).) P-values in bold and starred are significant at $\alpha < 0.05$.

Model	Target Gene Set	Comparison Gene Set	Beta (SE)	P-value
1	Historical 25 candidate genes	All other genes	0.27 (0.21)	0.10
2	Historical 25 candidate genes	Height associated genes	0.16 (0.23)	0.49
3	Historical 25 candidate genes	Type 2 Diabetes associated genes	0.28 (0.27)	0.29
4	Historical 25 candidate genes	Genes involved in synaptic processes	0.17 (0.22)	0.43
5	86 most-studied candidate genes	All other genes	**0.26 (0.12)**	**0.01***
6	86 most-studied candidate genes	Height associated genes	0.15 (0.14)	0.29
7	86 most-studied candidate genes	Type 2 Diabetes associated genes	0.37 (0.20)	0.07
8	86 most-studied candidate genes	Genes involved in synaptic processes	0.16 (0.12)	0.19
9	Historical 25 candidate genes minus MHC genes	All other genes	0.34 (0.23)	0.07
10	Historical 25 candidate genes minus MHC genes	Height associated genes	0.23 (0.24)	0.34

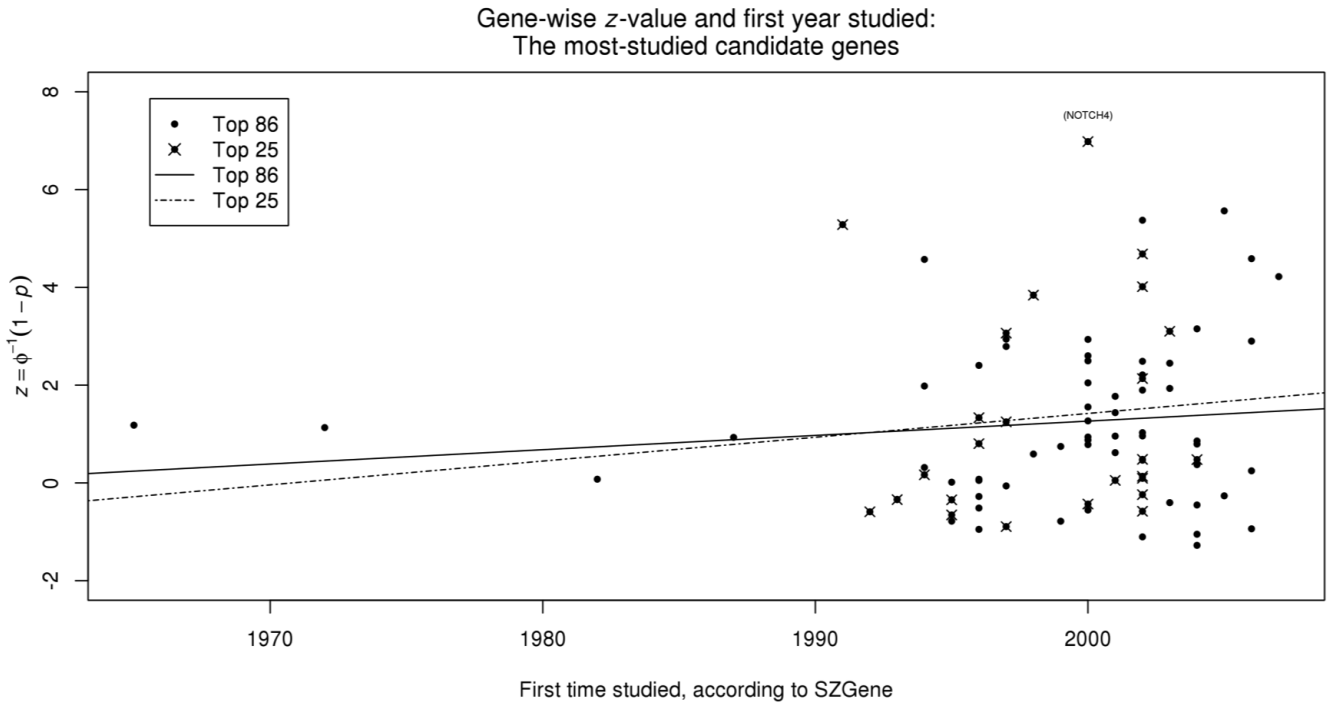
Model	Target Gene Set	Comparison Gene Set	Beta (SE)	P-value
11	Historical 25 candidate genes minus MHC genes	Type 2 Diabetes associated genes	0.34 (0.28)	0.22
12	Historical 25 candidate genes minus MHC genes	Genes involved in synaptic processes	0.23 (0.23)	0.31
13	86 Most-studied candidate genes minus MHC genes	All other genes	**0.28 (0.12)**	**0.009***
14	86 Most-studied candidate genes minus MHC genes	Height associated genes	0.18 (0.14)	0.22
15	86 Most-studied candidate genes minus MHC genes	Type 2 Diabetes associated genes	0.38 (0.20)	0.06
16	86 Most-studied candidate genes minus MHC genes	Genes involved in synaptic processes	0.17 (0.12)	0.16



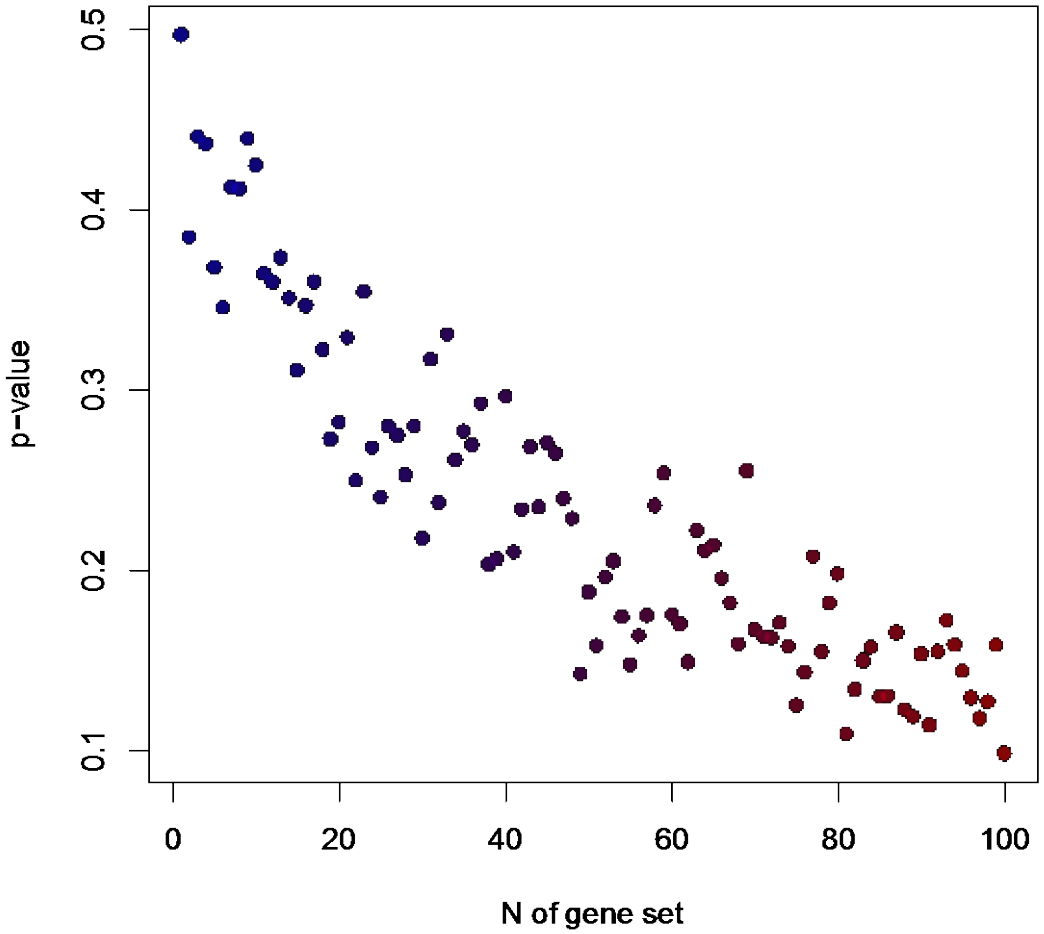
Supplemental Figure S1. Distribution of the number of studies per gene for the 86 candidate genes studied more than five times and not motivated by GWAS.



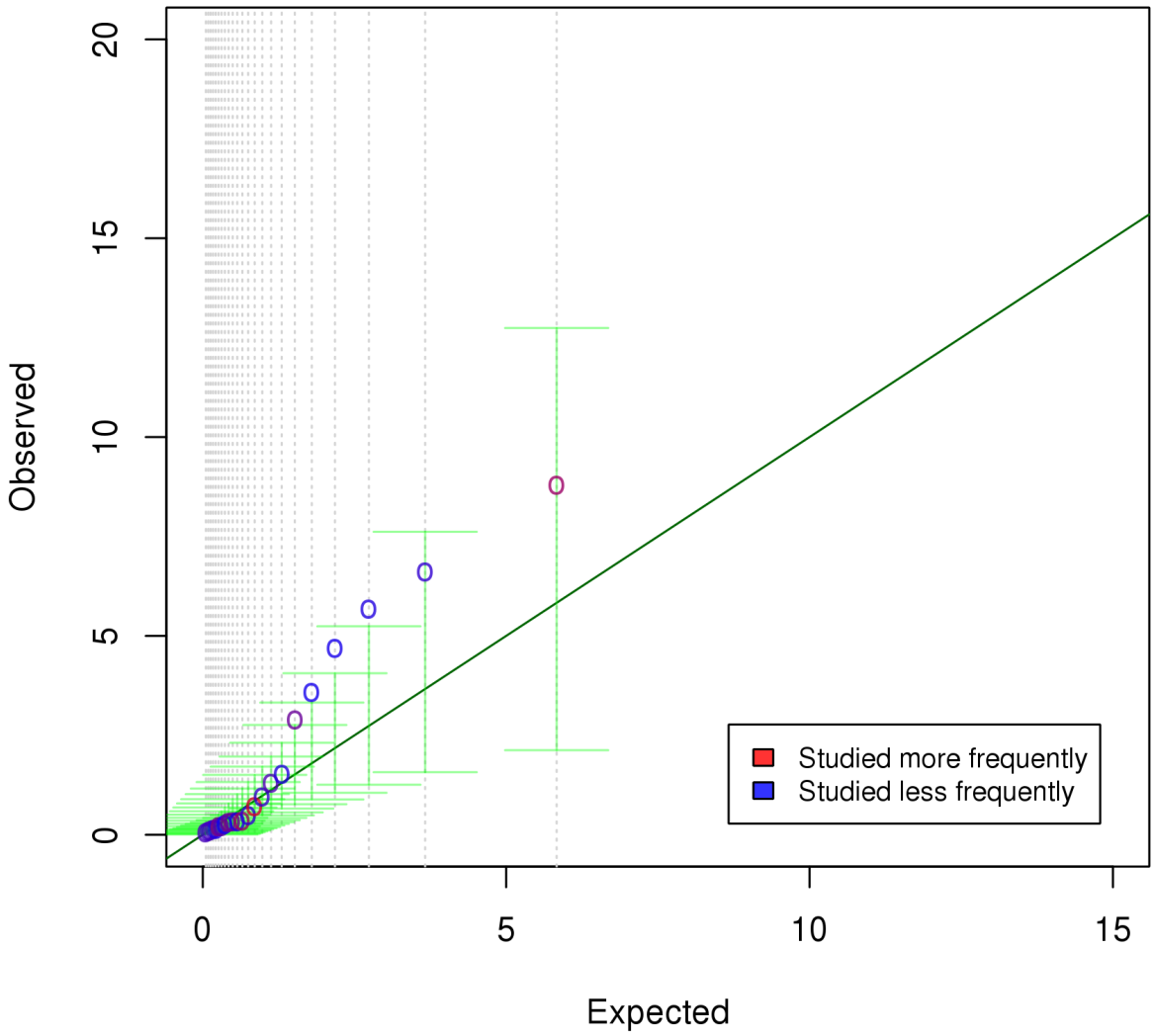
Supplemental Figure S2. Is a gene's association with schizophrenia correlated with how often it has been studied? Plot of the correlation of the gene-wise *Z*-value from MAGMA's gene-level analysis for the top 86 most-studied candidate genes and the number of times each gene was studied. This relationship was not statistically significant (r = -0.06, p = 0.61).



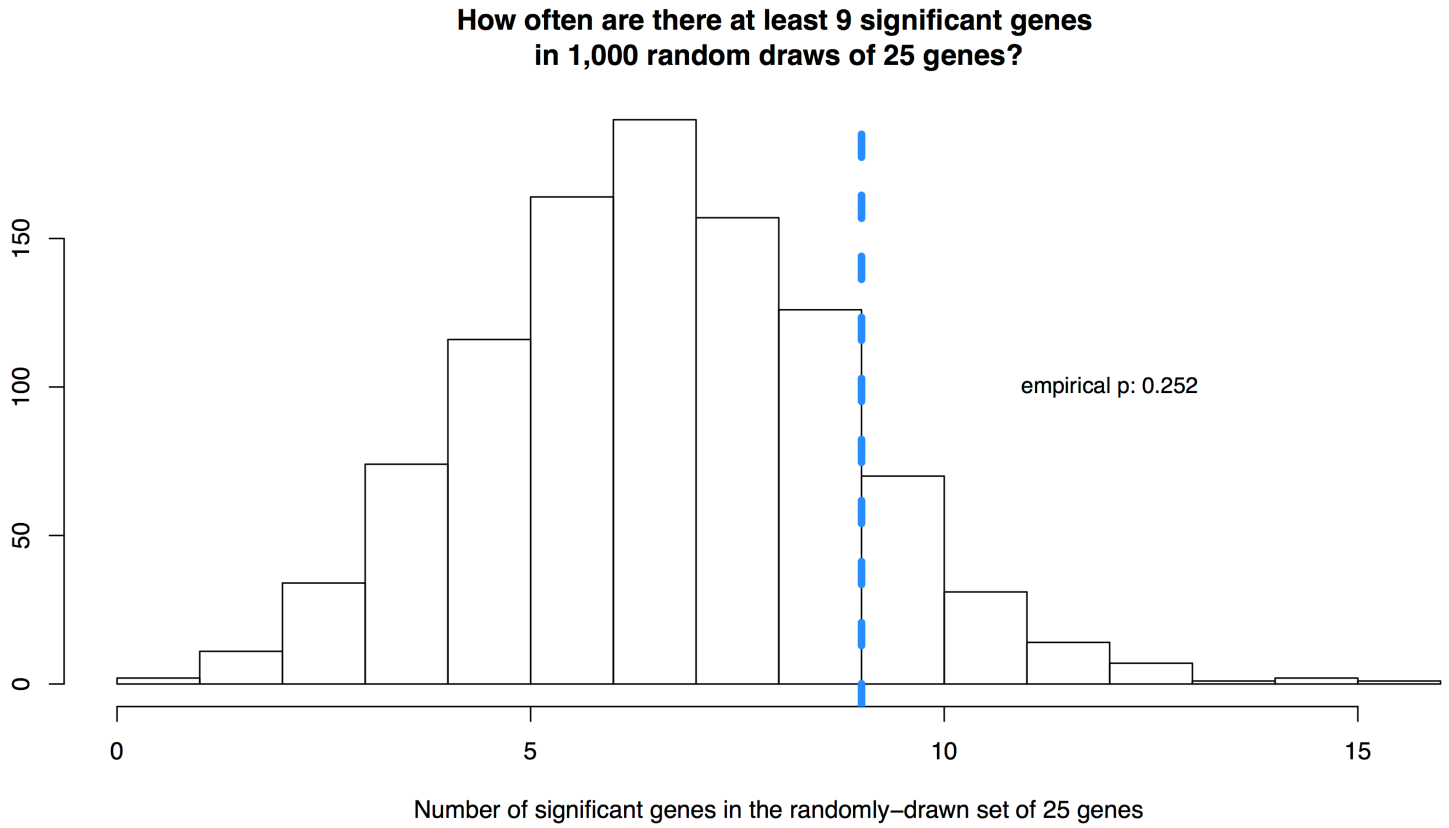
Supplemental Figure S3. Are candidate genes first investigated more recently more likely to be associated with schizophrenia? Plot of the correlation of the gene-wise *Z*-value from MAGMA's gene-level analysis for the top 86 most-studied candidate genes and the first year each gene was studied, according to the SZGene database records. This relationship was not statistically significant ($r = 0.11$, $p = 0.34$).



Supplemental Figure S4. Examining effect of gene set size on power of competitive gene set analysis. Gene sets were created by randomly sampling *n* from 1 to 100 genes from the full set of genes involved in synaptic processes (taken from Ruano et al. (5) and Lips et al. (6)) and then performing a basic competitive gene set test in MAGMA, with the randomly sampled synaptic genes grouped as the gene set of interest and all other non-synaptic genes in the genome used as the comparison set. This sampling process was repeated 5,000 times and the gene set *p*-value returned from MAGMA recorded for each of the iterations (i.e., there were approximately 50 *p*-values for each size gene set from 1 to 100). The plot below shows the average gene-set analysis *p*-value for each size of gene set, from $n = 1$ to $n = 100$. At least for the set of genes involved in pre- and post-synaptic processes, there is evidence that increasing the size of the gene set increases the power of MAGMA's test (correlation between average *p*-value and gene set size *n*: $r = -0.90$, $p = 2.2e-16$).



Supplemental Figure S5. Quantile-quantile plot of the -log10 *p*-values from the 25 most-studied candidate genes, excluding any genes located in the MHC region. Observed gene-level -log10 *p*-values from MAGMA are plotted on the y-axis, with expected -log10 *p*-values plotted on the x-axis. Points are heat map colored according to the number of times each gene has been studied, and the vertical green lines are bootstrapped 95% confidence intervals.



Supplemental Figure S6. The distribution of the number of significant (α < 0.05) genes found in random samples of 25 genes. Although there was little evidence that the set of candidate genes as a group is highly related to schizophrenia, there were 9 genes in the set of 25 candidates with significant ($p < .05$) associations with schizophrenia. To understand how surprising this result is for a highly polygenic trait such as schizophrenia, we permuted sets of 25 genes from the entire genome and observed 9 or more nominally significant genes in 25.2% of permutations (a one-tailed empirical *p*-value).

Supplementary Table S4. MAGMA gene set analyses, not including genes chosen from linkage studies. These tests used the sum of the negative log of the p-values as the gene-level test statistic. All tests controlled for gene size, SNP density, and minor allele count (MAC) (as well as the log(gene size), log(SNP density), and log(MAC).) P-values in bold and starred are significant at $\alpha < 0.05$.

			(+/- 25 kb window)		(strict gene boundaries)	
Model	**Target Gene Set**	**Comparison Gene Set**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**
1	Historical 17 candidate genes not motivated by linkage	All other genes	0.38 (0.31)	0.11	0.33 (0.25)	0.09
2	Historical 17 candidate genes not motivated by linkage	Height associated genes	0.33 (0.32)	0.30	0.22 (0.26)	0.39
3	Historical 17 candidate genes not motivated by linkage	Type 2 Diabetes associated genes	0.49 (0.35)	0.15	0.35 (0.30)	0.24
4	Historical 17 candidate genes not motivated by linkage	Genes involved in synaptic processes	0.25 (0.31)	0.42	0.23 (0.25)	0.35
5	66 most-studied candidate genes not motivated by linkage	All other genes	**0.31 (0.14)**	**0.01***	**0.32 (0.13)**	**0.009**
6	66 most-studied candidate genes not motivated by linkage	Height associated genes	0.26 (0.16)	0.11	0.20 (0.15)	0.18

			(+/- 25 kb window)		(strict gene boundaries)	
Model	**Target Gene Set**	**Comparison Gene Set**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**
7	66 most-studied candidate genes not motivated by linkage	Type 2 Diabetes associated genes	**0.52 (0.21)**	**0.02***	**0.42 (0.21)**	**0.04***
8	66 most-studied candidate genes not motivated by linkage	Genes involved in synaptic processes	0.17 (0.15)	0.24	0.22 (0.14)	0.11

Supplementary Table S5. Comparison of VEGAS2 version 2 gene-based test with MAGMA results – strict gene boundary. The MAGMA results are from the gene-level test with a strict gene boundary (not including the +/- 25kb regions upstream or downstream) and used the sum of the negative log of the p-values as the gene-level test statistic. The VEGAS results are from the VEGAS2 version 2 gene-level test, with all parameters set to the program defaults. The correlation between the VEGAS2 and MAGMA –log10(p) was +.962.

Gene	Chr	Gene Start Position	Gene Stop Position	nSNPs (VEGAS2)	$-\log_{10}(P_{VEGAS2})$	nSNPs (MAGMA)	$-\log_{10}(P_{MAGMA})$	$-\log_{10}(P_{VEGAS2}) + \log_{10}(P_{MAGMA})$
AKT1	14	105235686	105262080	68	0.481	68	0.500	-0.019
APOE	19	45409039	45412650	6	0.111	6	0.129	-0.018
BDNF	11	27676440	27743605	120	2.712	120	2.962	-0.249
CHRNA7	15	32322691	32462384	295	0.135	295	0.176	-0.041
COMT	22	19929263	19957498	129	0.664	129	0.676	-0.012
DAO	12	109273857	109294710	76	1.603	75	1.785	-0.183
DAOA	13	106118216	106143383	125	0.149	125	0.143	0.005
DISC1	1	231762561	232177018	1191	0.176	1191	0.089	0.086
DRD2	11	113280317	113346001	177	5.699	177	7.199	-1.500
DRD3	3	113847557	113897899	125	0.126	125	0.141	-0.015
DRD4	11	637305	640706	12	0.393	11	0.198	0.195
DTNBP1	6	15523032	15663289	335	0.407	335	0.351	0.057
GRM3	7	86273230	86494192	454	4.444	454	5.849	-1.406
HTR2A	13	47407513	47471169	243	0.239	242	0.197	0.041

Gene	Chr	Gene Start Position	Gene Stop Position	nSNPs (VEGAS2)	$-\log_{10}(P_{VEGAS2})$	nSNPs (MAGMA)	$-\log_{10}(P_{MAGMA})$	$-\log_{10}(P_{VEGAS2}) + \log_{10}(P_{MAGMA})$
KCNN3	1	154669938	154842754	536	3.633	536	4.213	-0.580
MTHFR	1	11845787	11866160	86	0.963	84	0.976	-0.013
NOTCH4	6	32162620	32191844	128	6.000	128	11.836	-5.836
NRG1	8	31496820	32622558	3783	0.275	3783	0.226	0.050
PPP3CC	8	22298596	22398638	187	2.663	187	3.017	-0.354
PRODH	22	18900287	18924066	128	0.336	128	0.335	0.001
RGS4	1	163038396	163046592	17	0.608	17	0.502	0.106
SLC6A3	5	1392905	1445543	196	0.472	196	0.362	0.109
SLC6A4	17	28523376	28562954	71	1.126	71	1.040	0.086
TNF	6	31543350	31546112	5	0.371	5	0.319	0.052
ZDHHC8	22	20119364	20135530	50	3.866	50	4.525	-0.659

Supplementary Table S6. Comparison of VEGAS2 version 2 gene-based test with MAGMA results – +/- 25kb region around gene boundaries. The MAGMA results are from the gene-level test with extended gene boundaries (including the +/- 25kb regions upstream or downstream of gene start and end points) and used the sum of the negative log of the p-values as the gene-level test statistic. The VEGAS results are from the VEGAS2 version 2 gene-level test, with all parameters set to the program defaults except for the addition of the –upper and –lower flags specifying the 25kb region upstream and downstream of the gene start and end points.

Gene	Chr	Gene Start Position	Gene Stop Position	nSNPs (VEGAS2)	$-\log_{10}(P_{VEGAS2})$	nSNPs (MAGMA)	$-\log_{10}(P_{MAGMA})$	$-\log_{10}(P_{VEGAS2}) + \log_{10}(P_{MAGMA})$
AKT1	14	105235686	105262080	202	0.330	202	0.325	0.005
APOE	19	45409039	45412650	136	0.029	136	0.044	-0.015
BDNF	11	27676440	27743605	224	2.569	224	2.886	-0.318
CHRNA7	15	32322691	32462384	387	0.134	387	0.141	-0.007
COMT	22	19929263	19957498	360	0.648	360	0.707	-0.059
DAO	12	109273857	109294710	243	1.459	243	1.515	-0.056
DAOA	13	106118216	106143383	292	0.114	292	0.099	0.015
DISC1	1	231762561	232177018	1368	0.151	1368	0.128	0.023
DRD2	11	113280317	113346001	316	6.000	316	8.796	-2.796
DRD3	3	113847557	113897899	292	0.370	292	0.340	0.030
DRD4	11	637305	640706	238	0.410	238	0.321	0.089
DTNBP1	6	15523032	15663289	485	0.271	485	0.210	0.061
GRM3	7	86273230	86494192	560	4.167	560	5.666	-1.499

Gene	Chr	Gene Start Position	Gene Stop Position	nSNPs (VEGAS2)	$-\log_{10}(P_{VEGAS2})$	nSNPs (MAGMA)	$-\log_{10}(P_{MAGMA})$	$-\log_{10}(P_{VEGAS2}) + \log_{10}(P_{MAGMA})$
HTR2A	13	47407513	47471169	385	0.263	385	0.205	0.059
KCNN3	1	154669938	154842754	638	4.959	638	6.600	-1.641
MTHFR	1	11845787	11866160	356	0.951	356	0.942	0.009
NOTCH4	6	32162620	32191844	360	6.000	360	18.096	-12.096
NRG1	8	31496820	32622558	3917	0.377	3917	0.313	0.065
PPP3CC	8	22298596	22398638	300	3.133	300	3.582	-0.448
PRODH	22	18900287	18924066	272	0.242	272	0.250	-0.008
RGS4	1	163038396	163046592	213	0.549	213	0.474	0.075
SLC6A3	5	1392905	1445543	390	0.097	390	0.087	0.010
SLC6A4	17	28523376	28562954	142	1.309	142	1.295	0.014
TNF	6	31543350	31546112	248	4.131	248	5.035	-0.904
ZDHHC8	22	20119364	20135530	252	3.674	252	4.695	-1.021

Supplementary Table S7. The top 100 genes (excluding those in the MHC region) most strongly associated with schizophrenia, ranked by *z* statistic. Genes are ranked by their gene-level *z* score calculated by MAGMA, excluding genes in the MHC region. These gene-level results were conducted with extended gene boundaries (i.e. including the +/- 25kb regions upstream or downstream of gene start and end points) and used the sum of the -log(*p*) of the SNP *p*-values as the gene-level test statistic.

Gene	NCBI_Entrez_ID	Chromosome	Association Statistic (*z*) from MAGMA	Rank
CACNA1C	775	12	8.9187	1
BTN2A1	11120	6	8.7705	2
DPYD	1806	1	8.7298	3
BTN3A2	11118	6	8.5887	4
AS3MT	57412	10	8.567	5
CACNA1I	8911	22	8.4697	6
TCF4	6925	18	8.4521	7
C10orf32	119032	10	8.3206	8
CNNM2	54805	10	8.1076	9
FOXP1	27086	3	8.0353	10
PPP1R16B	26051	20	7.7184	11
BTN2A2	10385	6	7.6911	12
NT5C2	22978	10	7.6026	13
CACNB2	783	10	7.5212	14
BTN1A1	696	6	7.4992	15
IGSF9B	22997	11	7.4907	16
CYP17A1	1586	10	7.4905	17
SLC17A3	10786	6	7.4698	18
HIST1H1E	3008	6	7.3549	19
ZFYVE21	79038	14	7.3009	20
HIST1H3A	8350	6	7.2692	21
HFE	3077	6	7.2524	22
HIST1H1A	3024	6	7.2311	23
ZSWIM6	57688	5	7.2078	24
HIST1H4A	8359	6	7.205	25
PITPNM2	57605	12	7.0991	26
ABT1	29777	6	7.0972	27
C12orf65	91574	12	7.0799	28
ESAM	90952	11	7.0789	29
SLC17A1	6568	6	7.0676	30
AMBRA1	55626	11	7.0548	31

Gene	NCBI_Entrez_ID	Chromosome	Association Statistic (*z*) from MAGMA	Rank
TRANK1	9881	3	7.0475	32
XRCC3	7517	14	7.0314	33
VSIG2	23584	11	7.0119	34
NGEF	25791	2	7.0088	35
BTN3A3	10384	6	6.9821	36
HIST1H2AB	8335	6	6.9707	37
HIST1H4B	8366	6	6.9641	38
BAG5	9529	14	6.9618	39
CHRNB4	1143	15	6.9471	40
NRGN	4900	11	6.9425	41
SDCCAG8	10806	1	6.9355	42
PPP1R13B	23368	14	6.9346	43
HIST1H3B	8358	6	6.9222	44
HIST1H3C	8352	6	6.9154	45
HIST1H2BB	3018	6	6.9078	46
SPATS2L	26010	2	6.9056	47
C2orf69	205327	2	6.9018	48
FXR1	8087	3	6.8526	49
CHRM4	1132	11	6.8073	50
FURIN	5045	15	6.8038	51
TSNARE1	203062	8	6.7943	52
UBE2Q2L	100505679	15	6.7885	53
MDK	4192	11	6.7871	54
FES	2242	15	6.7833	55
HIST1H1T	3010	6	6.7673	56
TYW5	129450	2	6.7505	57
SETD8	387893	12	6.7436	58
HIST1H4C	8364	6	6.7197	59
CDK2AP1	8099	12	6.7047	60
ARL6IP4	51329	12	6.6977	61
DNAJC19	131118	3	6.6696	62
ZNF322	79692	6	6.6653	63
APOPT1	84334	14	6.6584	64
MPHOSPH9	10198	12	6.6283	65
C2orf47	79568	2	6.6188	66
HIST1H1C	3006	6	6.6161	67
BCL11B	64919	14	6.603	68
MAD1L1	8379	7	6.589	69

Gene	NCBI_Entrez_ID	Chromosome	Association Statistic (*z*) from MAGMA	Rank
DGKZ	8525	11	6.5885	70
SNX19	399979	11	6.582	71
ITIH3	3699	3	6.5814	72
HSPE1-MOB4	100529241	2	6.5795	73
OGFOD2	79676	12	6.5766	74
MOB4	25843	2	6.5747	75
ITIH4	3700	3	6.5541	76
HIST1H2BC	8347	6	6.5477	77
VRK2	7444	2	6.5357	78
SMG6	23293	17	6.5163	79
SNAP91	9892	6	6.5071	80
HIST1H2AC	8334	6	6.5046	81
SF3B1	23451	2	6.4796	82
ZSCAN2	54993	15	6.4732	83
MSRA	4482	8	6.467	84
RILPL2	196383	12	6.4655	85
TMEM219	124446	16	6.4149	86
ATG13	9776	11	6.3942	87
KCTD13	253980	16	6.3916	88
SRR	63826	17	6.3551	89
CHRNA3	1136	15	6.3548	90
GIGYF2	26058	2	6.3485	91
SFMBT1	51460	3	6.3397	92
TMEM110	375346	3	6.3386	93
ACTR5	79913	20	6.336	94
TAOK2	9344	16	6.2604	95
ABCB9	23457	12	6.2576	96
CNTN4	152330	3	6.2487	97
TRIM38	10475	6	6.2299	98
SLC45A1	50651	1	6.2049	99
GALNT10	55568	5	6.2043	100

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