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Molecular Genetic Evidence for Genetic Overlap between General Cognitive Ability and Risk for Schizophrenia: A Report from the Cognitive Genomics Consortium (COGENT)

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CONFLICT OF INTEREST

The authors report no conflict of interest related to the present work.

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Abstract

It has long been recognized that generalized deficits in cognitive ability represent a core component of schizophrenia, evident prior to full illness onset and independent of medication. The possibility of genetic overlap between risk for schizophrenia and cognitive phenotypes has been suggested by the presence of cognitive deficits in first-degree relatives of patients with schizophrenia; however, until recently, molecular genetic approaches to test this overlap have been lacking. Within the last few years, large-scale genome-wide association studies (GWAS) of schizophrenia have demonstrated that a substantial proportion of the heritability of the disorder is explained by a polygenic component consisting of many common SNPs of extremely small effect. Similar results have been reported in GWAS of general cognitive ability. The primary aim of the present study is to provide the first molecular genetic test of the classic endophenotype hypothesis, which states that alleles associated with reduced cognitive ability should also serve to increase risk for schizophrenia. We tested the endophenotype hypothesis by applying polygenic SNP scores derived from a large-scale cognitive GWAS meta-analysis (~5000 individuals from 9 non-clinical cohorts comprising the COGENT consortium) to four schizophrenia case-control cohorts. As predicted, cases had significantly lower cognitive polygenic scores compared to controls. In parallel, polygenic risk scores for schizophrenia were associated with lower general cognitive ability. Additionally, using our large cognitive meta-analytic dataset, we identified nominally significant cognitive associations for several SNPs that have previously been robustly associated with schizophrenia susceptibility. Results provide molecular confirmation of the genetic overlap between schizophrenia and general cognitive ability, and may provide additional insight into pathophysiology of the disorder.

Keywords

GWAS; schizophrenia; general cognitive ability; polygenic; endophenotype

INTRODUCTION

Schizophrenia (SCZ) is a brain disorder characterized by, on average, a reduction in general cognitive abilities of >1 SD below the population mean. Given the long-standing observation of subtle cognitive abnormalities in undiagnosed and unmedicated relatives of patients with SCZ, it has been suggested that cognitive deficits may serve as an endophenotype, permitting identification of SCZ risk genes using a quantitative phenotype more closely reflecting gene function.[1] Extensive family and twin data support the role of shared additive genetic factors underpinning both SCZ and cognitive deficits.[2] A recent

population-scale study of siblings and twins further suggested that the overlap between these phenotypes is largely genetic, but questioned the overall magnitude of the phenotypic correlation.[3] However, these family-based studies have two primary limitations: 1) they lack direct molecular assays of genetic variance, and 2) they have relied upon measurement of cognitive abilities in patients with SCZ, which are subject to potential confounds relating to illness process and state.

A direct test of the endophenotype hypothesis would examine molecular genetic variants associated with cognitive performance in the general (not clinically-referred) population, in order to see if these variants are also associated with SCZ. However, this approach has not been adequately tested due to the lack of strongly replicated cognition-associated single nucleotide polymorphisms (SNPs). By contrast, a number of candidate gene studies have applied a "reverse endophenotype" approach, in which SCZ risk variants are tested for association with cognition in the general population.[4,5]

Large-scale genome-wide association studies (GWAS) of schizophrenia have demonstrated that a substantial proportion of the heritability of the disorder is explained by a polygenic component consisting of thousands of common SNPs of extremely small effect.[6] Similarly, recent GWAS of general cognitive ability have indicated that a polygenic architecture accounts for a majority of the heritability, consistent with other normally-distributed traits in the general population, such as height.[7–9] The relationship of the underlying genetic architecture between two phenotypes can be examined using polygenic score tests, in which large numbers of alleles demonstrating subtle (not statistically significant) levels of association with a given phenotype are combined to produce a genetic risk profile.[10] The association of these alleles in a different cohort (measured on a different phenotype), can then be utilized to estimate the degree of molecular overlap between phenotypes.

Very recently, two reverse endophenotype studies have examined the ability of schizophrenia polygenic risk scores to predict cognitive abilities in independent cohorts.[11,12] Both studies draw from the work of the Psychiatric GWAS Consortium on Schizophrenia (PGC-SCZ), a large-scale mega-analytic GWAS of 17 Caucasian cohorts encompassing >9000 SCZ cases and >12,000 controls.[13] In one study[12], polygenic risk scores for SCZ were significantly associated with IQ in a cohort of patients with SCZ and controls, but these associations were not observed in the smaller (n=322) healthy cohort alone. However, in a much larger study[11], polygenic risk scores for SCZ were found to be significantly associated with general cognitive ability (as assessed by the first principal component of cognitive tests assessing multiple domains) in two moderately-sized (total N~1500) cohorts of psychiatrically normal older adults.

In this study, we sought to test the endophenotype hypothesis by comparing SCZ cases to controls on polygenic SNP scores derived from a large-scale meta-analysis of cognitive GWAS. We focused on general cognitive ability as the primary endophenotype for several reasons, which we have discussed in detail previously.[14] While a variety of specific cognitive traits have been proposed as SCZ endophenotypes, research to date has failed to conclusively demonstrate any specific cognitive signature of schizophrenia.[15] Overall, deficits in general cognitive ability follow the pattern required of an endophenotype[1]: they are observed in SCZ patients prior to illness onset, are largely independent of clinical state and medication status, and are familial in nature.[16,17]

It has been recognized for more than 100 years that most cognitive abilities in humans are not orthogonal traits, but tend to covary; the underlying factor accounting for this pattern of intercorrelation is termed general cognitive ability (or Spearman's *g*).[18] General cognitive ability is a robust phenotype, accounting for nearly half of the variance on the broad range of

specific neurocognitive traits identifiable in humans.[19] Moreover, general cognitive ability in the population is itself highly heritable,[9,20,21] and heritability studies have demonstrated substantial genetic overlap across most specific cognitive domains tested.[18,19,21] Crucially, general cognitive ability can be reliably estimated by extracting the first principal component of any appropriately diverse set of neurocognitive test scores, regardless of the specific components of the battery; it has been empirically demonstrated that estimates of *g* derived from varying batteries tend to be very highly correlated, with correlation coefficients often approaching 1.[22,23]

The present study represents the first empirical report of an international collaborative effort entitled, "The Cognitive Genomics Consortium (COGENT)."[14] COGENT aims to bring together human genetic datasets with both: 1) high-density genome-wide genotype data and 2) phenotype data on cognitive function in individuals drawn from the general population. At the time of the first data freeze, COGENT consists of nine sites across 7 countries, with approximately 5000 individuals with available genotype and phenotype data. Although genotyping platforms and phenotype measures vary by site, genetic imputation and factor analysis of cognitive scores were used to harmonize data across sites. Because generalized cognitive ability (*g*) can be robustly estimated from a variety of test batteries, we were able to perform meta-analysis of GWAS associations to *g* across the nine COGENT cohorts. From this meta-analysis, we derived polygenic allele scores associated with general cognitive ability. These allele scores were then applied to four SCZ case-control cohorts consisting of more than 11,000 independently ascertained subjects (>5000 cases and >5000 controls), as described in detail below. We additionally performed "reverse endophenotype" analyses, examining the effects of schizophrenia risk alleles (derived from PGC-SCZ) on cognitive scores in the 9 COGENT cohorts.

MATERIALS AND METHODS

Subjects – Cognitive GWAS cohorts

Volunteers for cognitive studies were drawn from nine cohorts, for which study investigators agreed to share data as part of the Cognitive Genomics Consortium (COGENT). Details on subject recruitment procedures for each cohort are described in the Supplementary Materials; summaries of each cohort are presented in Table 1. Although screening procedures differed somewhat across cohorts, subjects were drawn from the general population, either as epidemiologically representative cohorts or as recruited control cohorts for studies of schizophrenia and/or other mental illnesses. All subjects were of Caucasian descent (as confirmed by principal components analysis of genetic data). All subjects provided written, informed consent to protocols approved by their institutional ethics boards in accordance with the Helsinki declaration.

Subjects – Schizophrenia case-control cohorts

The primary test of the endophenotype hypothesis was performed in the Molecular Genetics of Schizophrenia (MGS) European-American case-control cohort. This dataset was selected for several reasons: it is large (n>5000), publicly available, has been extensively studied,[24–26] and contains an ethnic distribution that is comparable to our nine COGENT cohorts (primarily Northern European in ancestry but with a non-negligible Southern European component as well). To replicate and extend our findings, we secondarily tested three additional SCZ case-control cohorts of varying ethnicities: 1) A Japanese cohort with >1000 subjects;[27] 2) An Ashkenazi Jewish cohort with >2500 subjects;[28] and the African-American subcohort (n>2000) of the MGS sample.[25] Demographic details of these cohorts are presented in Table 2. It should be noted that increasing evidence suggests substantial common architecture of complex traits (including schizophrenia) across populations,[29,30]

but it would still be anticipated that replication samples would demonstrate attenuated effect sizes due to residual differences in allele frequencies and effect sizes.[31]

Genotyping, quality control, and imputation

As described in detail in the Supplementary Materials, all COGENT subjects were genotyped on one of three microarray platforms: Affymetrix 6.0 (~900K SNPs), Illumina 610K, or Illumina OmniExpress (~770K SNPs). A standardized quality control pipeline was applied to each COGENT GWAS dataset: SNP call rate > 95%; sample call rate > 90%; SNP Hardy-Weinberg equilibrium (HWE) $p>10^{-6}$; and X chromosome sex match with reported gender. For any pair of subjects with cryptic relatedness (pi-hat>.125 in PLINK[32] 1.07), the sample with the lower call rate was eliminated. For each dataset, a principal components analysis was performed (in SVS 7.7.4, GoldenHelix Inc., Bozeman, MT), and samples demonstrating non- Caucasian ancestry were eliminated.

After QC, all SNPs within a given cohort were strand-aligned to HapMap3 and phased using SHAPEIT[33] prior to imputation with IMPUTE2.[34] As recently recommended to increase imputation accuracy,[35] a large, cosmopolitan HapMap3 reference panel (n=1,011 individuals from Africa, Asia, Europe, and the Americas) was utilized (except for NCNG, which was the only dataset for which imputation was not performed centrally). Because our phenotype is a quantitative trait, we sought to avoid potentially spurious findings introduced by random association of rare alleles with a few extreme scores.[36] Therefore, imputed SNPs receiving a probability call >.90 were retained and converted to PLINK-format genotype calls. The imputed data were then recleaned using the same call rate and HWE criteria described above; additionally, SNPs with minor allele frequency <2.5% were dropped. For each cohort, ~3000 randomly selected genotyped SNPs were held out for concordance analysis with imputation results. As shown in Table 1, concordance exceeded 99% for seven COGENT cohorts, and ~1M SNPs were available for analysis in each cohort.

Neurocognitive assessment

Details of neurocognitive batteries for each cohort are provided in the Supplementary Materials. While the specific instruments varied across cohorts, each cohort was required to have test scores available across at least 3 domains of cognitive ability for computation of Spearman's *g*,[18,37] an estimate of general cognitive ability derived from principal components analysis (PCA).[22,23] (For one cohort, a validated estimate of general cognitive ability derived from two subscales of the Wechsler Adult Intelligence Scale was utilized.) For each of the cohorts, available measures were entered into PCA and the first unrotated component was extracted. Any variable with more than 5% of missing data was dropped from the analysis. Normality is not a strict requirement of principal components analysis implemented for the purpose of data reduction and so no variable was subject to transformation.[38] Moreover, inspection of box plots indicated that variables were generally normally distributed and no noticeable outliers were observed. In each cohort, as expected based on hundreds of prior studies,[39] the first principal component significantly loaded all measures and accounted for ~40% of the variance on average.

The dependent measure for the cognitive GWAS in each cohort was this first PC score, corrected for the following (using linear regression prior to GWAS): age, sex, age*sex, age^2, and age^2*sex, based on consistent evidence demonstrating the presence of both linear and quadratic effects of age on general cognitive ability across the lifespan[40].

Statistical analysis

Genome-wide association analysis of the quantitative cognitive phenotype was performed in each COGENT cohort using linear regression (additive model) in SVS7.7.4. As shown in

Table 1, lambda (genomic control) values for each cohort were at or near 1, indicating no significant effect of subtle population structure on association results. Fixed effects meta-analysis of β weights from the linear regression analyses was performed in PLINK 1.07[32] using data from all available cohorts possessing high-QC genotyped or imputed data for each given SNP. Only SNPs with data available in 3 or more cohorts were retained. By convention, a positive β weight for a given allele indicated an additive (allele-dose) relationship in the direction of higher cognitive phenotype scores.

Based on results of the meta-analysis, polygenic scores were computed in PLINK using β weights of alleles at varying statistical thresholds (nominal p<.10, .20, .30, .40, and .50) following the procedure originally described by Purcell et al.[10] For each statistical threshold, the *clump* procedure in PLINK was utilized to prune the set of SNPs for linkage disequilibrium (using r^2 threshold of .50 within a 250kb window), so as to avoid redundancy of SNPs representing a given association signal.

For each of the five statistical thresholds, the weighted allele scores of each "clumped" SNP were summed for each subject in each SCZ case-control cohort, thus creating a "cognitive polygene score." Thus, each subject in each SCZ case-control dataset had a set of 5 cognitive polygene scores: one for each of the statistical thresholds applied to the original COGENT meta-analytic results. For each SCZ case-control dataset, five logistic regression analyses were then used to compare cases and controls on cognitive polygene scores at each threshold. Nagelkerkes' pseudoR^2 was utilized to reflect estimated percent variance in the SCZ phenotype accounted for by cognitive polygene scores at each threshold.[10]

RESULTS

GWAS results for general cognitive ability

Meta-analytic results of the nine cognitive GWAS cohorts are presented as a Manhattan plot in Figure 1; no SNPs reached genomewide significance, and the overall lambda was 1.031 (see QQ plot in Supplementary Figure 1). This lambda value is higher than that for any individual cohort (Table 1), indicative of polygenic signal[41], but is lower than reported in similar recent studies of cognitive ability[7,9]. A list of top SNPs (p<.001) emerging from the meta-analysis are presented in Supplementary Table 1.

Primary test of endophenotype hypothesis – cognitive polygenic score analysis

We utilized a large, publicly available, Caucasian SCZ GWAS case-control cohort to test our primary endophenotype hypothesis. Using "clumped" SNPs at 5 different thresholds (nominal p<.10, .20, .30, .40, and .50), polygenic cognitive scores were computed for each of 2886 cases and 2056 controls in the MGS/GAIN European-American cohort. As predicted, cases had significantly lower cognitive polygenic scores across each of the five thresholds (p-values ranging from $6.56*10^{-6}$ to $3.73*10^{-7}$; see Figure 2). In other words, SCZ cases had fewer alleles associated with good cognitive performance and more alleles associated with poorer cognitive performance in the COGENT meta-analysis. The overall magnitude of the polygenic effect was small (R^2<.01), but comparable to the total variance explained by a similar approach applied from one cognitive cohort to another[7] and from a reverse endophenotype study.[11]

As replication, the same cognitive SNPs were tested in three smaller SCZ case-control cohorts of differing ethnicities. Because of the apparent dip in variance explained that appears at p<0.2 in the MGS EA cohort (Figure 1), we applied a p<0.3 threshold in our replication datasets. As depicted in Table 3, nominally significant results were observed in two cohorts (Japanese and Ashkenazi Jewish). Meta-analysis of these results across the four

SCZ case-control cohorts yielded a strongly significant effect of cognitive polygenic scores on prediction of schizophrenia risk ($p=3.6*10^{-7}$). Very similar results were observed using a clump threshold of $p<0.5$ (Supplementary Table 2; meta-analytic $p=3.8*10^{-7}$), and somewhat stronger results were observed when the IBG cohort (the only non-adult COGENT cohort) was removed prior to calculation of polygenic allele weights (Supplementary Table 3; meta-analytic $p=4.0*10^{-9}$).

Reverse endophenotype approach – examination of prior schizophrenia GWAS hits

As an additional examination of the relationship between cognitive GWAS results and the schizophrenia phenotype, we applied the commonly-employed "reverse endophenotype" approach described above. First, we selected all SNPs that have demonstrated genomewide significance ($p<5*10^{-8}$) in large-scale (total n>5000) published SCZ GWAS obtained from the NHGRI GWAS catalog (http://www.genome.gov/gwastudies/, downloaded Jan. 10, 2013). As shown in Table 4, four of the 13 independent SNPs (excluding the major histocompatibility complex) associated with schizophrenia have nominally significant ($p<.05$) associations with general cognitive ability in volunteers from the general population. While effect sizes for these SNPs on cognitive phenotypes are extremely modest, the number of SNPs achieving nominal significance exceeded that expected by chance (binomial test, p=.006, two-tailed). Although extensive linkage disequilibrium in the MHC has prohibited clear discernment of the source of SCZ GWAS signal, supplementary Table 4 demonstrates results for 5 SNPs in the region derived from published SCZ GWAS.

Reverse endophenotype approach – schizophrenia susceptibility polygenic score analysis

Finally, we performed a polygenic score analysis, comparable to the one presented in Table 2, but in the "reverse" direction. Specifically, we downloaded "clumped" SNPs derived from the publicly-available PGC[13] dataset (https://pgc.unc.edu/Sharing.php#SharingOpp). Because polygenic score approaches to schizophrenia have tended to demonstrate increasing variance explained at higher p-value thresholds[10], we utilized a threshold of $p<.50$ on the resulting clumped SNPs. These polygenic scores were then computed for each subject in each of the 9 COGENT cohorts separately; scores were then compared to cognitive ability (*g*) using linear regression in each cohort. As shown in Table 5, schizophrenia-derived polygenic scores were correlated with cognitive ability in the predicted direction (greater schizophrenia load associated with lower cognitive scores) in 7 of the 9 cohorts, with three cohorts demonstrating nominally significant (or nearly so) results. As with the primary analysis, total variance accounted for was small (R^2 range from 0–2%) but strongly significant ($p=1.4*10^{-4}$) in the combined analysis.

DISCUSSION

To our knowledge, this is the first study to present molecular genetic evidence supporting general cognitive ability as a true endophenotype for schizophrenia susceptibility. In a large Caucasian SCZ case-control cohort, we demonstrated that a set of polygenic alleles associated with lower general cognitive ability strongly predicted increased likelihood for the disorder. Consistent, though less strong, associations were observed in additional cohorts, despite the fact that they were drawn from populations of differing ethnicities.

While the statistical evidence (p-values ranging from $\sim10^{-6}$ to $\sim10^{-9}$) for association was strong, the overall amount of variance explained, even in the Caucasian SCZ cohort (~0.5%) was modest, a result that must be interpreted in the context of other studies of polygenic overlap. For example, in a recent study of cognition,[7] polygenic SNP scores accounted for only ~1% of the variance in a separate cognitive cohort (these cohorts are now included in COGENT). Nevertheless, these authors were able to demonstrate that nearly half of the

variation in cognitive ability could ultimately be accounted for by common SNPs. Similarly, the initial study of polygenic effects in schizophrenia identified only ~2–3% overlap between any two schizophrenia cohorts, and ~1–2% overlap between schizophrenia and bipolar cohorts.[10] Again, extensive simulations demonstrated that the polygenic SNPs tagged common genetic variation accounting for approximately one-third of the total variance in SCZ risk; this estimate has been replicated, indicating that the empirically observed cross-sample allelic overlap is a substantial under-estimate of the total polygenic effect.[6] Moreover, observed polygenic overlap tends to rapidly increase as a function of sample size; for example, the empirically observed variance explained by polygenic effects in schizophrenia has increased tenfold with larger sample sizes.[42] While the COGENT cohort represents the largest genetic sample of cognition to date, sample size remains small relative to polygenic studies of other quantitative traits such as height.[43,44]

Thus, the results of the present study are consistent with a model in which a substantial fraction of the molecular basis of general cognitive ability is shared with genetic risk for schizophrenia. These results are consistent with a large body of evidence from family-based studies which use twin and sibling correlations to model genetic effects.[2] While a recent population-based study using similar modeling strategies[3] found only limited phenotypic overlap between intelligence and psychosis, the source of this overlap was estimated to be largely (~90%) comprised of additive genetic variation. The present study is unique in directly testing molecular genetic variation, and utilizing non-clinical volunteers for the estimation of the cognitive genetic component. Our demonstration of parallel effects when examining genomewide overlap in the reverse direction (SCZ risk alleles predicting cognitive scores, Table 5) add further confidence to our conclusions, and are also consistent with a recent genomewide reverse endophenotype study, which demonstrated significant overlap between polygenic SCZ risk alleles and cognitive decline in two aging cohorts.[11]

Additionally, following the conventional “reverse endophenotype” approach, multiple GWAS-identified SCZ risk SNPs (4/13, or 31%) demonstrated nominal evidence of association to general cognitive ability in a large meta-analytic cohort of non-clinical volunteers. Three of these are intronic SNPs, in *MAD1LI, LSM1*, and *CNNM2*, and the present study represents the first report of human neurocognitive correlates of variants at these loci. Little is known about the functions of these genes in the central nervous system, and the structural and functional properties of their associated proteins vary widely. The fourth nominally significant locus is less than 5kb 5’ to *NRGN* (and is in an LD block encompassing the gene). *NRGN* encodes neurogranin, a well-characterized postsynaptic protein which binds to calmodulin and thereby modulates postsynaptic calcium signaling.[45] Although this locus did not show significant association with cognitive variables in a smaller prior study,[46] neuroimaging studies have previously associated this locus with structural and functional variation in the frontal cortex, cingulate, and hippocampus.[47–50] Although these results were significant in the aggregate (p=.006 by binomial test), it should be emphasized that the effect sizes for individual SNPs were extremely small, and p-values would not survive Bonferroni correction.

Based on the present results, it is likely that larger sample sizes will afford greater ability to predict schizophrenia using cognitive polygenic scores. This overlap can then be utilized to enhance schizophrenia gene detection using recently developed “pleiotropic enrichment” techniques.[51] At the same time, the study of the genetic basis of normal variation in cognition is likely to further our understanding of the mechanisms by which schizophrenia risk genes affect the central nervous system.

Several caveats should be placed on the interpretation of this study. First, the present study did not directly evaluate the genetic source of cognitive deficits in patients with

schizophrenia. It could be argued that GWAS of cognitive ability in schizophrenia cohorts would be required to test whether this putative endophenotype actually mediates the relationship between cognitive polygene score and schizophrenia risk. However, cognitive performance in patients with schizophrenia can be influenced by potential confounds such as effects of medication or acute symptomatology, which would tend to attenuate any genetic signal. Consequently, our approach of utilizing non-clinical samples was designed to maximize the potential power of GWAS.

Finally, it should be noted that no genomewide significant loci for cognition were identified in the present study, despite being the largest GWAS of cognitive ability in predominately adult cohorts. This result was anticipated based on recent large-scale GWAS results for childhood intelligence[9], as well as early GWAS (with comparable sample size to the present study) of potentially comparable quantitative traits, height[52] and weight[53]. It is also possible that power to detect genetic signals was reduced due to unavoidable heterogeneity in cognitive assessment methods across cohorts; such an interpretation is consistent with the relatively low lambda observed in our study. Future studies, ideally with prospectively collected cohorts utilizing harmonized approaches to phenotype assessment, will be required to tease out genomewide significant loci for cognitive ability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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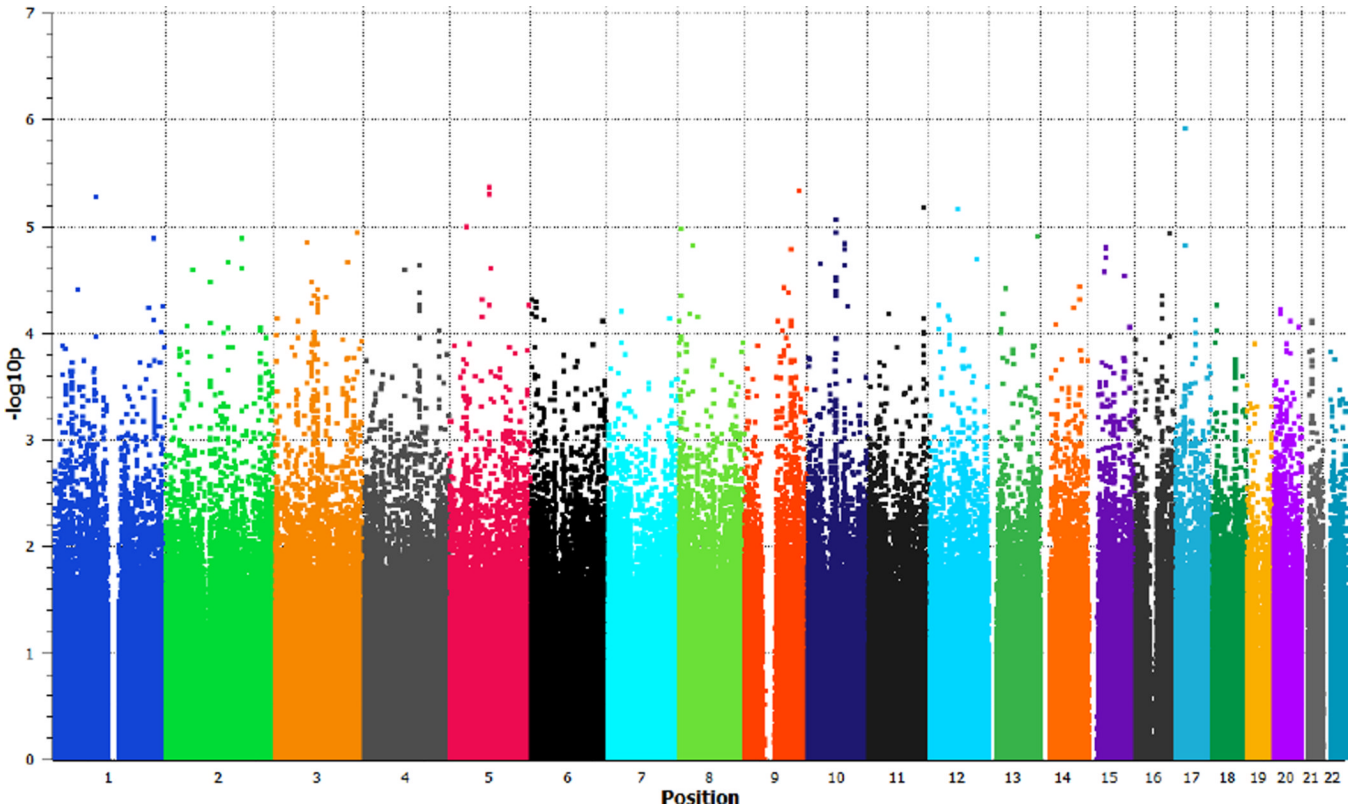

Figure 1.
Manhattan plot depicting results of COGENT meta-analysis.

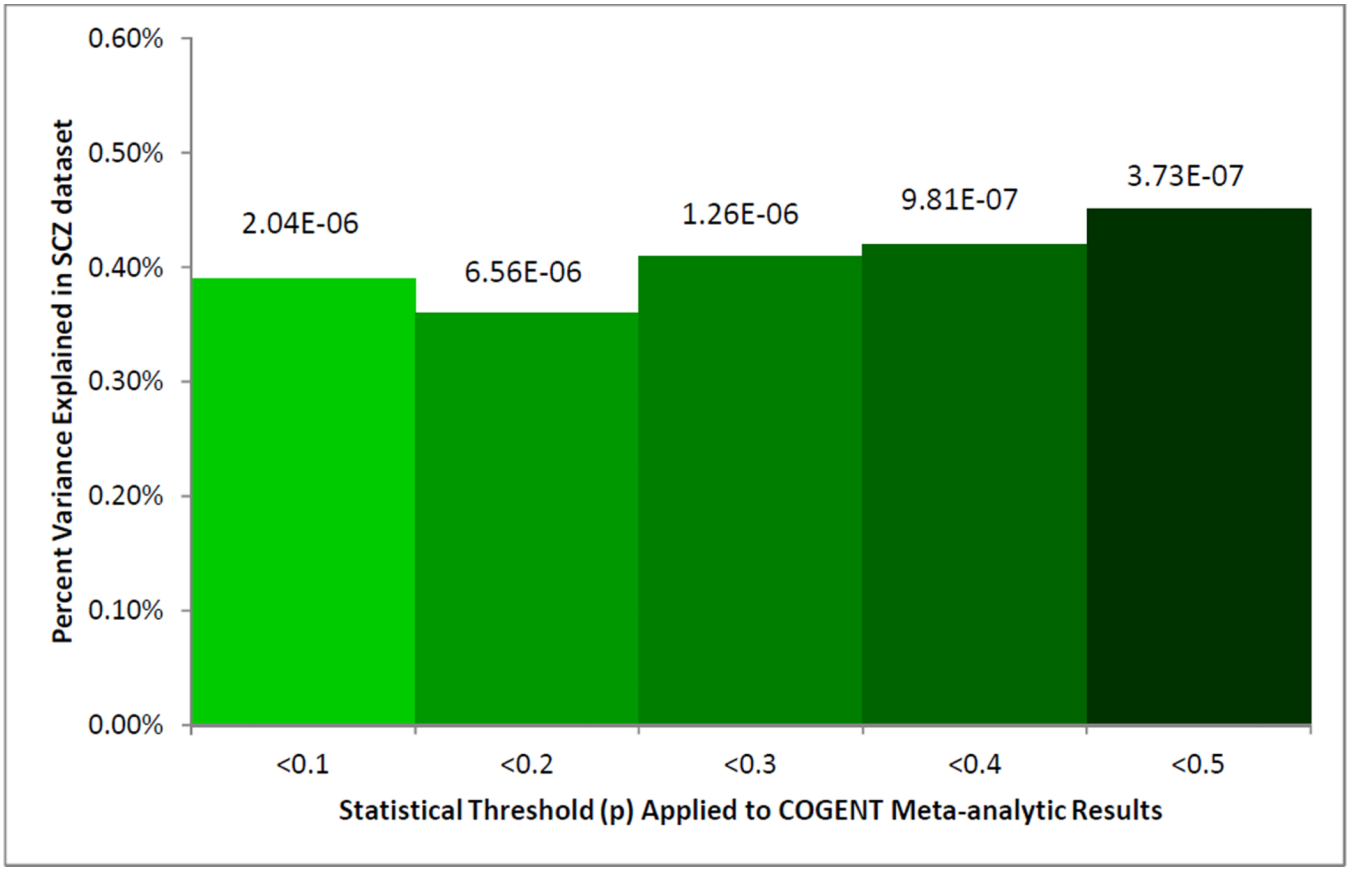

Figure 2.
Polygenic overlap between cognitive allele scores (derived from COGENT metaanalysis thresholded at varying p-values) and schizophrenia (SCZ) case-control status in the MGS European-American cohort.

Table 1

Description of COGENT cohorts.

Dataset[a]	Genotyping Platform	Concordance[b]	Genotypes after QC	N	%Male	Mean Age (SD)	Lambda[c]
Germany	Illumina OE [d]	99.50%	1,078,289	594	51%	54.0 (15.0)	1.01
LOGOS	Illumina OE	99.40%	835,287	802	100%	22.3 (3.8)	1.03
IBG	Affymetrix 6.0	99.59%	938,800	299	77%	15.9 (1.5)	1.00
LBC1936	Illumina 610	99.60%	1,058,722	1005	51%	69.5 (0.8)	1.01
TOP	Affymetrix 6.0	94.23%	917,315	351	48%	34.2 (9.8)	1.01
NCNG	Illumina 610	99.40%	944,135	629	32%	47.6 (18.3)	1.00
Manchester	Illumina 610	99.60%	1,059,916	697	30%	67.7 (2.8)	1.01
HBCS	Illumina 610	99.60%	1,043,380	318	100%	67.7 (2.3)	1.00
ZHH	Illumina OE	99.40%	1,043,785	201	47%	39.1 (1.8)	1.06

[a] Detailed descriptions of each cohort provided in Supplementary Text.

[b] Concordance between imputed and genotyped SNPs.

[c] Lambda to refers $\lambda_{GC,}$, a measure of the degree of statistical inflation in genomewide association studies.

[d] OE refers to the Illumina OmniExpress genotyping bead chip

Table 2

Description of schizophrenia case-control cohorts.

SCZ Dataset	N Cases	N Controls	GWAS platform
MGS European-American Shi et al. 2009	2681	2653	Affymetrix 6.0
Japan Ikeda et al. 2011	575	564	Affymetrix 5.0
Ashkenazi Jewish (Israel) Guha et al. 2013	904	1640	Illumina Omni1-Quad
MGS African-American Shi et al. 2009	1286	973	Affymetrix 6.0
Total	5446	5830	

Table 3

Polygenic overlap between cognitive alleles (derived from COGENT meta-analysis using p<0.3 threshold) and schizophrenia in four case-control cohorts.

SCZ Dataset	# overlapping SNPs	R^2 for SCZ	p value	direction
MGS European-American	17,237	0.41%	$1.3*10^{-6}$	negative
Japan	6,468	0.38%	0.039	negative
Ashkenazi Jewish	15,151	0.16%	0.041	negative
MGS African-American	17,382	0.00%	0.958	positive
Meta-analysis			$3.6*10^{-7}$	negative

Table 4

Examination of cognitive associations (in COGENT meta-analysis) for SNPs identified in published GWAS for schizophrenia (excluding MHC).

Source	SNP	Region	Gene	Risk Allele Freq[a]	OR_Sz[a]	COGENT studies	P_COGENT meta-analysis
Ripke (PGC) Nat Gen 2011	rs1625579	1p21.3	MIR137	0.8	1.12	8	0.4789
Shi (China) Nat Gen 2011	rs10489202	1q24.2	MPC2	0.141	1.23	9	0.9024
Ripke (PGC) Nat Gen 2011	rs6703335	1q43	SDCCAG8	0.56	1.09	6	0.9127
O'Donovan Nat Gen 2011	rs1344706	2q32.1	ZNF804A	0.59	1.12	9	0.4048
Ripke (PGC) Nat Gen 2011	rs17662626	2q32.3	PCGEM1	0.91	1.2	5	0.4509
Bergen (Swe) Mol Psy 2012	rs7709645	5q12.1	ZSWIM6	0.475	1.11	9	0.7207
Bergen (Swe) Mol Psy 2012[b]	rs12666575	7p22.3	MAD1L1	0.673	1.12	8	0.0320
Ripke (PGC) Nat Gen 2011	rs10503253	8p23.2	CSMD1	0.19	1.16	7	0.5874
Shi (China) Nat Gen 2011[c]	rs16887244	8p11.23	LSM1	0.683	1.19	9	0.0171
Ripke (PGC) Nat Gen 2011[b]	rs7914558	10q24.32	CNNM2	0.59	1.22	9	0.0368
Ripke (PGC) Nat Gen 2011	rs11191580	10q24.33	NT5C2	0.91	1.2	9	0.6575
Decode Nature 2009[c]	rs12807809	11q24.2	NRGN	0.83	1.15	8	0.0399
Ripke (PGC) Nat Gen 2011	rs12966547	18q21.2	TCF4	0.58	1.4	8	0.7327

[a] based on source publication

[b] schizophrenia risk allele associated with lower cognitive ability

[c] schizophrenia risk allele associated with higher cognitive ability

Table 5

Polygenic overlap between schizophrenia risk alleles (derived from PGC meta-analysis using p<0.5 threshold) and general cognitive ability in nine COGENT cohorts.

COGENT Dataset	# overlapping SNPs	R^2 for *g*	p value	Direction
Germany	89,360	0.08%	0.475	Positive
LOGOS	69,069	0.00%	0.985	Positive
IBG	89,353	0.04%	0.72	Negative
LBC1936	96,820	1.17%	0.0006	Negative
TOP	88,946	0.10%	0.5481	Negative
NCNG	87,934	0.04%	0.5925	Negative
Manchester	96,907	1.61%	0.0007	Negative
HBSC	93,890	0.11%	0.5467	Negative
ZHH	85,681	1.90%	0.0532	Negative
Meta-analysis			$1.4*10^{-4}$	negative