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Genetic Predictors of Risk and Resilience in Psychiatric Disorders: A Cross-Disorder Genome-wide Association Study of Functional Impairment in Major Depressive Disorder, Bipolar Disorder, and Schizophrenia

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Abstract

Functional impairment is one of the most enduring, intractable consequences of psychiatric disorders and is both familial and heritable. Previous studies have suggested that variation in functional impairment can be independent of symptom severity. Here we report the first genome-wide association study (GWAS) of functional impairment in the context of major mental illness. Participants of European-American descent (N=2,246) were included from three large treatment studies of bipolar disorder (STEP-BD) (N=765), major depressive disorder (STAR*D) (N=1091), and schizophrenia (CATIE) (N=390). At study entry, participants completed the SF-12, a widely-used measure of health-related quality of life. We performed a GWAS and pathway analysis of the mental and physical components of health-related quality of life across diagnosis (~1.6 million single nucleotide polymorphisms), adjusting for psychiatric symptom severity. Psychiatric

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symptom severity was a significant predictor of functional impairment, but it accounted for less than one-third of the variance across disorders. After controlling for diagnostic category and symptom severity, the strongest evidence of genetic association was between variants in *ADAMTS16* and physical functioning (p=5.87 × 10^{-8}). Pathway analysis did not indicate significant enrichment after correction for gene clustering and multiple testing. This study illustrates a phenotypic framework for examining genetic contributions to functional impairment across psychiatric disorders.

Keywords

SF-12; health-related quality of life; disability; genetics; *ADAMTS16*

Introduction

Functional impairment is one of the most enduring, intractable consequences of psychiatric disorders (Awad and Voruganti, 2012; IsHak et al., 2012; Shippee et al., 2011). By the term "functional impairment," we refer to the persistent interference in daily life activities and role performance by psychiatric or related symptoms. Even when psychiatric symptoms abate through intervention, quality of life does not always improve (Harvey et al., 2011; IsHak et al., 2012). Effective treatments for functional impairment have been scarce, making etiological studies valuable for informing novel treatment approaches.

Although functional impairment is a required dimension of DSM-IV psychiatric diagnoses, there are also individual differences in the extent of impairment, even for a given level of symptom severity (Eack and Newhill, 2007; Priebe et al., 2011; Verboom et al., 2011). This evidence coincides with clinical observations that some patients are nearly incapacitated by relatively mild symptoms of psychiatric disorders while other patients are able to sustain activities of daily living despite moderate to severe psychiatric symptoms. This partial disassociation between psychiatric symptoms and disability has led to proposals for DSM-5 to separate and more clearly delineate the two dimensions (APA, 2010). Our hypothesis is that individual variation in functional impairment, given a specific level of symptom severity, reflects an axis of risk/resilience that is partly distinct from risk for the psychiatric disorder itself.

Genetic contributions to functional impairment have not been extensively explored, but there is increasing interest in this topic (Raat et al., 2010; Sprangers et al., 2009). There is evidence from twin and family studies in clinical and population samples to support a genetic contribution (J. McGrath et al., 2009; Romeis et al., 2005; Steenstrup et al., 2013). Two large population-based twin studies (N~3000, N~46,000) using the same functional impairment measures as the current study, reported heritability of the composite scores of h^2~.35 (range .34–.37) (Romeis et al., 2005) and h^2~.25 (range .11–.35) with variability due to age and gender (Steenstrup et al., 2013). Two family studies have investigated the familial aggregation of functional impairment in relatives with schizophrenia. Both found strong evidence for the familiality of functional impairment (h^2~.60) that was notably higher than

for other behavioral traits more closely related to symptoms of schizophrenia (Kendler et al., 1995; J. McGrath et al., 2009).

This study is the first genome-wide association study (GWAS) of functional impairment in psychiatric disorders. We hypothesize an axis of risk/resilience for functional impairment that transcends diagnostic boundaries, allowing us to exploit the increased sample size of a cross disorder design to maximize power for gene-finding under this set of assumptions. Our approach resonates with increasing interest in identifying fundamental dimensions of individual difference that transcend diagnostic boundaries as exemplified by the NIMH research domain criteria (RDoC) initiative (Insel et al., 2010). This study used the three largest psychiatric treatment effectiveness studies for major depressive disorder, bipolar disorder, and schizophrenia (STAR*D, STEP-BD, and CATIE, respectively). Each of the studies collected extensive phenotypic data, including the SF-12 or SF-36, which are widely used, extensively validated, self-report measures of health-related quality of life (Contopoulos-Ioannidis et al., 2009; McHorney et al., 1994; McHorney et al., 1993; Ware et al., 1996; Ware and Sherbourne, 1992). The questionnaires measure general, rather than disease-specific, health status.

Consistent with our conceptualization of an axis of risk/resilience that is partly independent from psychiatric symptom severity, we developed a functional impairment phenotype that controlled for psychiatric symptom severity. This phenotype captured the extent to which an individual was more or less impaired than expected given his/her specific psychiatric symptom profile. Here we report the results of the first GWAS and pathway (i.e. gene set) analysis of functional impairment across psychiatric disorders.

Methods and Materials

Primary Analysis

Sample Description—For each cohort, study protocols and informed consent procedures were approved by institutional review boards at each participating clinical site. Details regarding the primary clinical samples and genotyping have reported elsewhere as part of a GWAS of cross-disorder disease risk (Huang et al., 2010). The following is a brief description.

Major Depressive Disorder (Sequenced Treatment Alternatives to Relieve Depression [STAR*D])—STAR*D was a multisite, prospective, randomized multiphase clinical trial of outpatients with nonpsychotic major depressive disorder that enrolled 4,041 participants over a 3-year period (Fava et al., 2003; Rush et al., 2004). Eligibility required meeting DSM-IV criteria for a single or recurrent nonpsychotic major depressive episode coupled with a score of ≥ 14 on the 17 item Hamilton Depression Rating Scale (Hamilton, 1960; Hamilton, 1967). The relevant exclusion criteria were: history of bipolar disorder, schizophrenia, schizoaffective disorder, or psychosis not otherwise specified. As previously described, 1953 individuals from the larger study were enrolled in a genetic sub-study (Garriock et al., 2010; Shyn et al., 2011).

Bipolar Disorder (Systematic Treatment Enhancement Program for Bipolar Disorder [STEP-BD])—STEP-BD was a national, longitudinal public health initiative which including randomized and standard care components designed to evaluate the effectiveness of bipolar treatments (Kogan et al., 2004; Sachs et al., 2003). Over a 7-year period, 4,361 participants were enrolled across 20 sites and followed for up to 2 years. Eligibility required a consensus DSM-IV bipolar spectrum diagnosis (bipolar I, bipolar II, bipolar not otherwise specified, or cyclothymia) on both the Affective Disorders Evaluation and Mini-International Neuropsychiatric Interview-PLUS semistructured interviews (Sachs et al., 2003). As previously described, 2,089 individuals from the larger study were enrolled in a genetic sub-study (Sklar et al., 2008).

Schizophrenia (Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE])—CATIE was a multiphase randomized controlled trial of antipsychotic medications comprising 1,460 individuals with schizophrenia followed for up to 18 months (Lieberman et al., 2005; Stroup et al., 2003). Final study diagnoses of DSM-IV schizophrenia were established by CATIE clinicians using the Structured Clinical Interview for DSM-IV (Spitzer R et al., 1996) and review of clinical records. Relevant exclusion criteria were: diagnosis of schizoaffective disorder, pervasive developmental disorder, mental retardation, other cognitive disorder, or single psychotic episode; history of treatment resistance; and serious adverse reaction to the study treatments (Stroup et al., 2003). As previously described, 738 individuals from the larger study were enrolled in a genetic sub-study (Sullivan et al., 2008).

Genotyping—As previously described, genotyping of STEP-BD and CATIE samples was performed using the Affymetrix GeneChip Human Mapping 500K Array Set (Affymetrix, Inc., Santa Clara, Calif.) (Huang et al., 2010). Approximately half of the STAR*D samples were genotyped with the same 500K array and the second half with the Affymetrix Human Single Nucleotide Polymorphism (SNP) Array 5.0. Genotyping of the STEP-BD samples was performed at the Broad Institute (Sklar et al., 2008). Genotyping of the CATIE samples was performed at Perlegen Sciences (Mountain View, Calif.) (Sullivan et al., 2008). Genotyping of the STAR*D samples run on the Affymetrix 500K array was performed at Affymetrix, and genotyping of the STAR*D samples run on the Affymetrix 5.0 array was performed at the University of California, San Francisco (Garriock et al., 2010; Shyn et al., 2011).

Quality control and harmonization of genotype data—Quality control (QC) of the genotypic datasets was first performed within each study and then across the combined genotypic dataset. Quality control procedures were performed using PLINK 1.07 (http://pngu.mgh.harvard.edu/purcell/plink/) (Purcell et al., 2009) using standard thresholds (Huang et al., 2010; Sklar et al., 2008). Briefly, individuals were excluded if they had overall call rates <95%, excess or insufficient heterozygosity, inconsistent gender between genotype and phenotype data, or apparent relatedness. We only included non-Hispanic Caucasian individuals with European ancestry based on self-reported race and ethnicity information. We then confirmed the self-reported ancestry using the PLINK nearest neighbor method (Purcell et al., 2007) to detect potential ancestry outliers based on the first 10

multidimensional scaling factors. We also visually inspected the clustering of samples with HapMap populations to identify any additional outliers. The QC sample size eligible for further analysis was 3102 (1507 from STEP-BD, 1199 from STAR*D, and 396 from CATIE). This sample size was further reduced based on availability of clinical phenotypes (see phenotype description below).

SNPs were excluded if they had a call rate <95%, had a minor allele frequency <1%, failed Hardy-Weinberg equilibrium at a p value of $<1\times10^{-6}$, showed haplotype-based nonrandom missingness, or showed differential rates of missingness in patients and controls (Sklar, 2008; Huang, 2010). Note that the control dataset was not employed in the current quantitative case-only analyses, but these SNPs were excluded to maintain consistency with previous QC procedures (Huang et al., 2010).

A total of 224,826 genotyped SNPs passed QC criteria across each of the samples. We used BEAGLE, Version 3.1.0, (http://www.stat.auckland.ac.nz/~bbrowning/beagle/beagle.html) to impute missing genotypes, with HapMap2 (Centre d'Etude du Polymorphisme Humain from Utah population, release 23, forward strand) as the reference panel (hg18). Individuals were imputed in 10 separate sets that were composed of randomly selected individuals from each study. We selected only the highest quality imputed SNPs based on a plink imputation quality score (INFO) between 0.8 and 1.2 and minor allele frequency >2%. The INFO metric is based on the ratio of empirical and expected variance in dosage where better imputation quality is expected for values closer to 1. Values greater than 1 indicate strong departure from Hardy-Weinberg Equilibrium. After QC, a total of 1,633,452 SNPs were available for final analysis using the imputed dosages.

Phenotypic Definition

The current study focuses on the baseline measurement of functional impairment that was given at entry into each treatment study. STEP-BD administered the SF-36 (Ware et al., 1994), while STAR*D and CATIE administered the SF-12 (version 1) which is a subset of the SF-36 items (Ware et al., 1995). The SF-12 score can be obtained using the SF-36 by scoring only the 12 overlapping items (Ware et al., 1995). The SF-12 is further divided into two sub-dimensions, each with 6 items, the Mental Component Summary (MCS) scale and the Physical Component Summary (PCS) scale. As part of the scoring algorithm, the MCS and PCS scales are transformed to have a mean of 50 and a standard deviation of 10 in the general U.S. population. The MCS and PCS were developed to be independent measures of health-related quality of life with a negligible correlation in population samples (Ware et al., 2002). The reliability and validity of the SF-12 has been found to be satisfactory for psychiatric clinical samples (Russo et al., 1998; Salyers et al., 2000; Tunis et al., 1999). In the current sample, Cronbach's alpha was in the satisfactory range for the MCS and PCS of each study (STEP-BD MCS α=.84, PCS α=.84; STAR*D MCS α = .68, PCS α =.85; CATIE MCS α = .79, PCS α = .82). The convergent validity of the SF-12/SF-36 in the current sample has been demonstrated in previous reports from STEP-BD and STAR*D showing that poorer health-related quality of life was associated with clinical and demographic characteristics, such as depression severity and disadvantaged sociodemographic background (Daly et al., 2010; Trivedi et al., 2006; Zhang et al., 2006).

Table 1 shows the means and standard deviations of the MCS and PCS in the final sample included in the analysis.

A primary concern for our phenotypic conceptualization was that, to the extent possible, ratings of mental and physical health-related quality of life should be independent from the current severity of psychiatric symptoms. As a result, we constructed novel phenotypes which were derived from the residuals of independent regressions of the MCS and PCS on psychiatric symptom severity, age, and gender (details below). To capture psychiatric symptom severity, we selected constructs that captured the defining features of the primary disorders: depressed mood, irritability, elevated mood, and psychosis. Across samples, we selected the most comparable items from the available measures (see Supplementary Table 1).

We selected one among several possible strategies for constructing residuals. For example, one might consider controlling for an entire psychiatric measure (i.e., the *Hamilton Depression Rating Scale* in STAR*D, the *Positive and Negative Syndrome Scale* in CATIE, the *Young Mania Rating Scale* and *Montgomery–Asberg Depression Rating Scale* in STEP-BD) rather than individual items as in the current study. This approach of regressing out different measures across studies has the potential benefit of controlling for psychiatric symptom severity more comprehensively, but two important limitations. First, this approach would increase the conceptual heterogeneity of the residuals since different symptoms would be regressed out across studies, making the interpretability of results more difficult. Secondly, many of the scales include items that are related to functional impairment. As such, we wanted to retain this variance of interest while still controlling for severity of core psychiatric symptoms and the correlated functional impairment attributable to these core symptoms.

A 14 day window was used to ensure broadly concurrent administration of the SF-12 and psychiatric symptom measures, while simultaneously minimizing missing data. The sample sizes reported in Table 1 reflect the total number of individuals in the final analysis who passed QC and had concurrent SF-12 and psychiatric symptom measures.

The MCS and PCS phenotypes for genetic analysis consisted of residuals from the previously described regressions, standardized within study. Supplementary Tables 2 and 3 present the regression results along with the adjusted model R^2. As expected, more of the variance was shared with psychiatric symptoms for the MCS than for the PCS. Standardized residuals were chosen in order to equate the units for a cross-disorder analysis and control for mean differences between disorders. This standardized residual represents a within-disorder statistic that captures the deviation of an individual from an expected functional impairment score given their level of psychiatric symptom severity. We conceptualize this quantitative phenotype as an index of functional risk/resilience in the context of a psychiatric disorder.

Analysis

Control for confounding by population stratification was performed by calculating the first 10 multidimensional scaling (MDS) components for all those individuals in the merged

genotypic dataset who had complete SF-12 phenotypes and concurrent psychiatric measures. To examine the effect of each of the 10 MDS components (C1–C10), we calculated the genomic inflation factor (λ) from a GWAS using each component (C1–C10) as the dependent variable as described by Huang et al. (2010). We plotted the λ's against each of the components (analogous to a scree plot) and found excessive values only for C1–C3. Thus, we used these first three MDS components as covariates in our GWAS.

Quantitative genetic association analyses were performed with PLINK, version 1.07 (Purcell et al., 2007) using linear regression of the MCS or PCS standardized residuals on single SNP allelic dosage, adjusting for the first three MDS components and a dummy variable denoting each contributing study. The alpha level for genome-wide significance was set at $p<2.5 \times 10^{-8}$ which represents the conventional genome-wide significance level ($p<5 \times 10^{-8}$) (Pe'er et al., 2008) corrected for two phenotypes tested.

Genotyping confirmation of top GWAS imputed signal

Because the top signal from the cross-disorder GWAS was primarily imputed, we selected 6 SNPs for confirmation genotyping in the linkage disequilibrium block identified by the imputed dataset. Primers were designed using MassARRAY Assay Design (Sequenom) and run through e-PCR using an in-house alignment tool highly sensitive for short primer sequences (A Kirby, unpublished).

SNP genotyping was performed on the Sequenom MassArray platform at the Massachusetts General Hospital Center for Human Genetic Research. Following DNA amplification by multiplex PCR, a pooled single base extension reaction was performed using the Sequenom iPLEX Gold assay. Allelic differentiation was detected with MassARRAY MALDI-TOF mass spectrometry. After baseline correction and peak identification, the spectra were analyzed using Sequenom MassARRAY Typer 4. The following quality control thresholds were used for exclusion: sample pass rate < 90%, SNP pass rate < 90%, minor allele frequency < 0.01, and Hardy-Weinberg equilibrium (HWE) p-value < 1×10^{-5} (actual HWE p-values were p>.3 for the 6 SNPs). Genotyping concordance rate for duplicate samples after removal of low quality data (n = 22 pairs) was 100%. All six of the selected SNPs passed QC criteria. Two individuals failed QC resulting in a final dataset of 2244 individuals.

Pathway analysis

Meta-Analysis Gene-set Enrichment of variaNT Associations (MAGENTA; http://www.broadinstitute.org/mpg/magenta) (Segre et al., 2010) was used to test whether specific biological pathways were enriched for associations to the phenotypes of MCS and PCS (separately). MAGENTA assigns scores to specific genes based on the most significant SNP in the gene and user-specified flanking regions (35kb upstream, 10kb downstream). The resulting gene score is corrected for important confounders such as gene size, SNP density, linkage disequilibrium (LD) properties, and recombination hotspots. We removed the HLA region from the analysis due to high LD and gene density in this region (MAGENTA default chr6:29,710,331–33,150,000 hg18). MAGENTA requires user-specified thresholds for nominal significance of gene-level p-values in order to calculate pathway significance. We

used the MAGENTA defaults of the 95th and 75th percentile cut-offs. We chose to analyze pathways in the Kyoto Encyclopedia of Genes and Genomes (KEGG) (N=186 pathways, mean # of genes per pathway = 86 (SD = 68), range 10–389) because they are curated with high standards for evidence. See Segre et al. (2010) for other details about the MAGENTA method.

Results

The regression analyses to derive the MCS and PCS functional impairment residuals, controlling for psychiatric symptom severity, age, and gender are reported in Supplementary Tables 2 and 3. From these analyses, it is clear that psychiatric symptom severity and demographic variables were significant predictors of functional impairment, but these variables accounted for less than one-third of the variance in both measures, across the three cohorts (MCS 20–31%, PCS 5–19%). The fact that more of the variance in MCS than PCS was accounted for by psychiatric symptoms is consistent with the item content of the MCS in which three of the six items are closely related to symptoms of depression (i.e., sadness, fatigue, calmness). Overall, these analyses indicated that there is variance remaining in functional impairment scores after controlling for psychiatric symptoms and demographic variables. The rest of our analyses utilized the residuals from these regressions standardized within disorder.

To establish the validity of these functional impairment residuals, we also tested for a relationship with a widely-used objective measure of functional impairment, current employment status. In each cohort, we conducted a logistic regression of employment status on MCS and PCS residual scores. Individuals who reported full-time or part-time employment were grouped together and compared to those who were unemployed. Both the MCS and PCS residuals showed significant relationships with employment status across all 3 disorder samples, with the exception of the MCS in CATIE. Because the sample size is smallest and employment rates were lowest in CATIE (15% compared to 49% in STEP-BD and 58% in STAR*D), power was limited in this sample, but the odds ratio (OR) of the effect for MCS in CATIE (OR=1.13) was comparable to the other samples (ORs = 1.13–1.18). Across samples, the PCS residual was more strongly related to occupational status (ORs = 1.4–1.8) than the MCS residual (see Supplementary Table 4).

The top 10 GWAS results using the MCS and PCS residuals as phenotypes in the combined psychiatric sample are reported in Tables 2 and 3 as linkage disequilibrium clumped regions. Supplementary Tables 5 and 6 report all regions with $p< 10^{-4}$. Supplementary Figures 1 and 2 show Q-Q and Manhattan plots (λ MCS = 1.007, λ PCS = .995). The strongest association evidence was between SNPs in the gene *ADAMTS16* with PCS. Figure 1 shows the regional plot of this gene. The top association signal (p=5.87 × 10^{-8}) approached genome-wide significance, although it did not meet our strict alpha criteria of 2.5 × 10^{-8}. Further investigation of this region indicated that the strongest signal was derived from imputed SNPS with only modest evidence from the nearby genotyped SNPs (see Figure 1). Follow-up genotyping of the top imputed SNPs confirmed the signal with a similar effect size and *p*-value, ruling out technical or imputation artifacts as a source of the signal (see Supplementary Table 7 and diamonds denoted in Figure 1). Figure 2 shows the forest plot of

the effect sizes for the top SNP, rs16875288, across the 3 psychiatric disorders. There was no statistically significant evidence of heterogeneity according to the Cochrane's Q statistic (p=.34) which was supported by the I^2 heterogeneity index (I^2= 7.35).

Pathway analysis did not reveal any significant enrichment after correction for gene clustering and multiple testing (2 phenotypes (MCS, PCS), 2 thresholds (75%, 95%), and 186 pathways; corrected alpha threshold = 6.7×10^{-5}) (Supplementary Tables 8 and 9). Before accounting for gene clustering, two pathways related to inflammation and autoimmune disorders showed evidence of enrichment of genetic associations to PCS (Supplementary Table 8). However, these two pathways shared 13 interferon alpha genes, 12 of which (IFNA genes: 2, 4, 5, 6, 7, 8, 10, 13, 14, 16, 17, 21) are clustered in a gene dense, LD block on chromosome 9 (Supplementary Figure 5). Because pathway analysis statistics can be inflated by gene dense areas with strong LD, we completed a secondary analysis in which we excluded all but the most significant gene in the interferon alpha region. Although this was a conservative approach, it was justified by the fact that conditional SNP analysis did not reveal any evidence of independent signals in the region. Following this correction, the p-values of the previously significant pathways decreased by several orders of magnitude and were no longer significant (Supplementary Table 8).

Discussion

Mood and psychotic disorders are known to be associated with substantial disability, but prior research and clinical experience suggest that variation in functional impairment does not necessarily track with symptom severity. We hypothesized that there is an axis of functional risk/resilience in the presence of psychiatric illness that is separable from symptom burden and diagnostic category. In light of prior evidence that functional status (indexed by the SF-36) is moderately heritable, we conducted a genome-wide search for variants associated with this phenotype.

To isolate genetic influences on mental and physical functioning, we controlled for psychiatric symptom severity, diagnostic group, and other relevant covariates. These analyses revealed that psychiatric symptom severity accounted for a minority of the variance in functional impairment, consistent with our hypothesis that there is an axis of risk/resilience that is distinct from severity of the disorder. In essence, our phenotypic approach was designed to identify genetic modifiers that affect the functional impact of psychiatric disorder irrespective of whether they influence risk for the disorder itself (Fanous and Kendler, 2005).

The strongest association evidence we observed was between variants in *ADAMTS16* (ADAM metallopeptidase with thrombospondin type 1 motif, 16) and physical health-related quality of life (PCS) (p=5.87×10^{-8}). We interpret these results cautiously given that the association signal did not exceed genome-wide significance. This gene has been previously implicated in hypertension via converging evidence from fine-mapping of quantitative trait loci in rats and association and linkage analyses in humans (Joe et al., 2009), although *ADAMTS16*, did not emerge as a candidate in the recent large-scale GWAS for hypertension involving 200,000 individuals (Ehret et al., 2011). *ADAMTS16* is expressed

in the adult brain, but has had limited biological characterization to date (Cal et al., 2002; Porter et al., 2005; Surridge et al., 2009). In our study, SNPs with the strongest association signals in *ADAMTS16* are intronic and do not have documented eQTL annotations in brain tissue (Gibbs et al., 2010; Myers et al., 2007) or in lymphoblastoid cell lines (Stranger et al., 2012; Yang et al., 2010) leaving the functional implications of these SNPs unknown. Further biological and genetic studies are needed to understand the potential role of *ADAMTS16* in functional impairment and resilience. Future analyses may also examine the genetic and phenotypic relationship between risk/resilience for functional impairment in the context of psychiatric disorders and other traits that may impact health-related quality of life, including personality traits (e.g., Kentros et al., 1997), motivation (e.g., Foussias et al., 2011), social-cognition (e.g., Hoertnagl et al., 2011; Maat et al., 2012), and neurocognitive functioning (e.g., Depp et al., 2012; Green, 1996; Tolman and Kurtz, 2012).

After careful correction for multiple testing and gene clustering, there was no evidence of association for any of the KEGG pathways. Although there was an initial signal in autoimmune and inflammatory processes for PCS, follow-up analyses suggested that results were artifactually driven by a single signal within the interferon alpha gene cluster on chromosome 9. These results emphasize the importance of controlling for LD patterns in pathway analyses and suggest that, like the HLA region, the interferon alpha region on chromosome 9 can be problematic.

Our results should be interpreted in the context of their limitations. First, based on the available sample size, we had >80% power to detect a locus explaining 2% or more of the variance in MCS or PCS scores. Our strongest result approached but did not exceed a genome-wide threshold of statistical significance. Thus, analyses in larger samples will be essential to clarify our findings. To our knowledge, there are no comparable psychiatric samples with functional impairment measures and GWAS data available. As a result, we could not attempt replication of these results or examine cross-sample correspondence via more advanced statistical genetic approaches (i.e., polygenic scoring, Purcell et al., 2009). Fortunately, there is an ongoing data collection effort aimed at examining genetic predictors of quality of life, the GENEQOL consortium (Sprangers et al., 2009), so future datasets with rich quality of life and genetic data will become available to examine correspondence with these results.

Second, self-report measures are only one strategy among many for measuring functional status (Awad, 2011; Bromley and Brekke, 2010; Harvey et al., 2011). Alternative measures include real-world outcomes (i.e., occupational status, residential status, educational attainment) and functional capacity (i.e., ability to perform real-world skills such as managing money, paying bills). Of note, our derived mental and physical functioning measure was significantly associated with employment status across the three disorders, after controlling for psychiatric symptom severity, supporting their relevance to real world outcomes. Recently, functional capacity, with an emphasis on performance-based testing, has been advanced as a candidate endophenotype for genetic studies of severe mental illness (Harvey et al., 2011). Genetic investigations of alternative measures of functional impairment will be complementary to the current analyses and important for characterizing genetic effects on functional vulnerability/resilience in the context of psychopathology.

Third, the psychiatric symptom measures were different across the three disorder samples which may have provided different degrees of control for psychiatric symptom severity across the disorders. To address this limitation, we chose clinician-rated scales with similar wording and scales wherever possible (see Supplementary Table 1). Moreover, mental functioning, as measured by the SF-12, was more difficult to distinguish from psychiatric symptom severity than physical functioning given the overlap of constructs, particularly with depressive features (i.e., fatigue, calmness, sadness). This fact may have differentially diminished our power for the MCS analyses relative to the PCS.

Despite these limitations, we believe these results contribute to the emerging literature on genetic risk factors for functional impairment in psychiatric disorders. Our phenotypic approach of capturing functional impairment independent of concurrent psychiatry symptom severity provides a model for future genetic studies. The overall approach of identifying modifier genes that impact functional impairment across psychiatric disorders could provide valuable insight into novel treatment approaches that might directly impact functional impairment in the context of psychopathology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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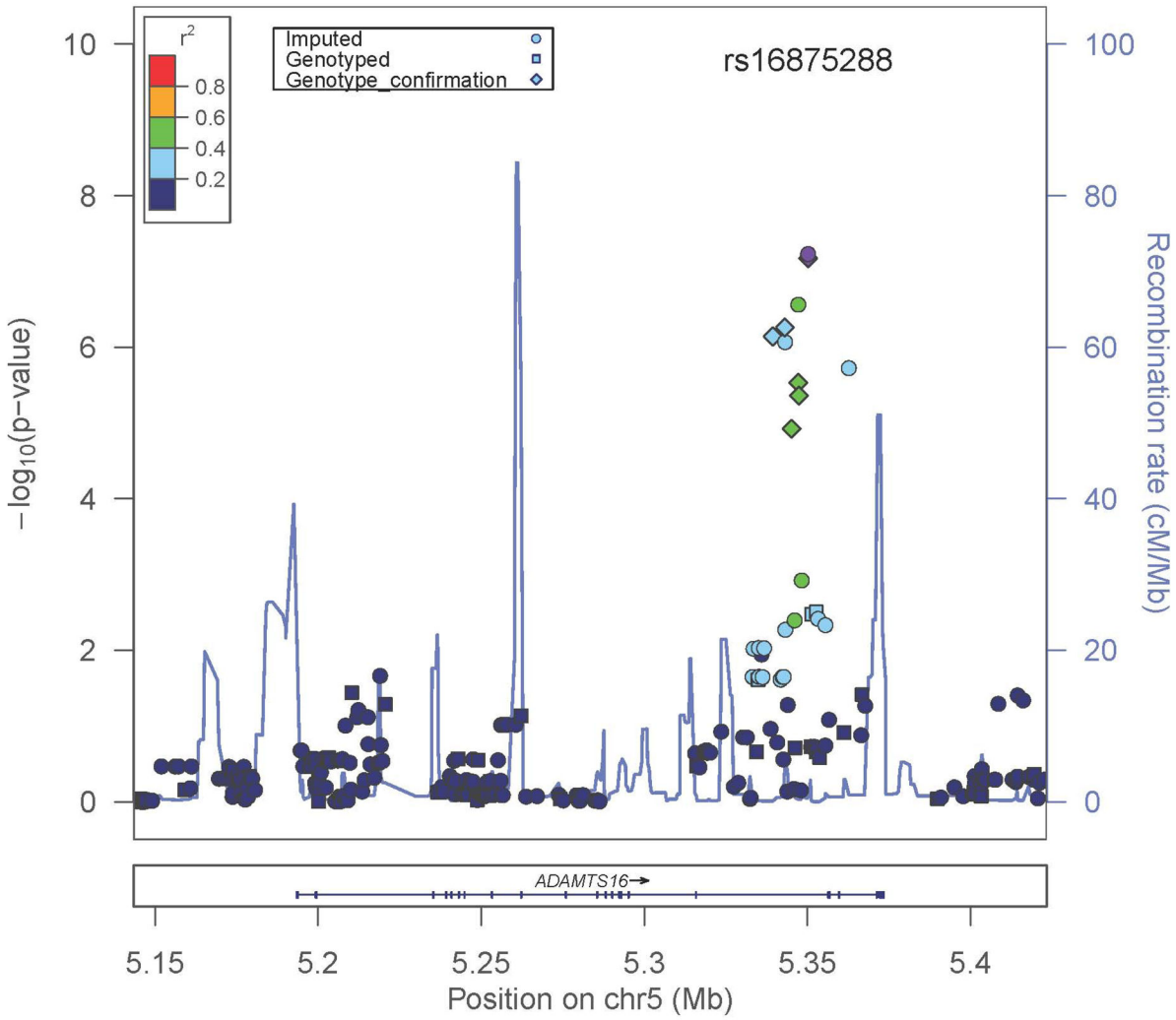

Figure 1.

Regional plot of the strongest associated SNPs in *ADAMTS16* with the PCS. Marker shapes indicate whether the SNP was genotyped, imputed, or confirmed with follow-up genotyping. Plotted using LocusZoom (Pruim et al., 2010)

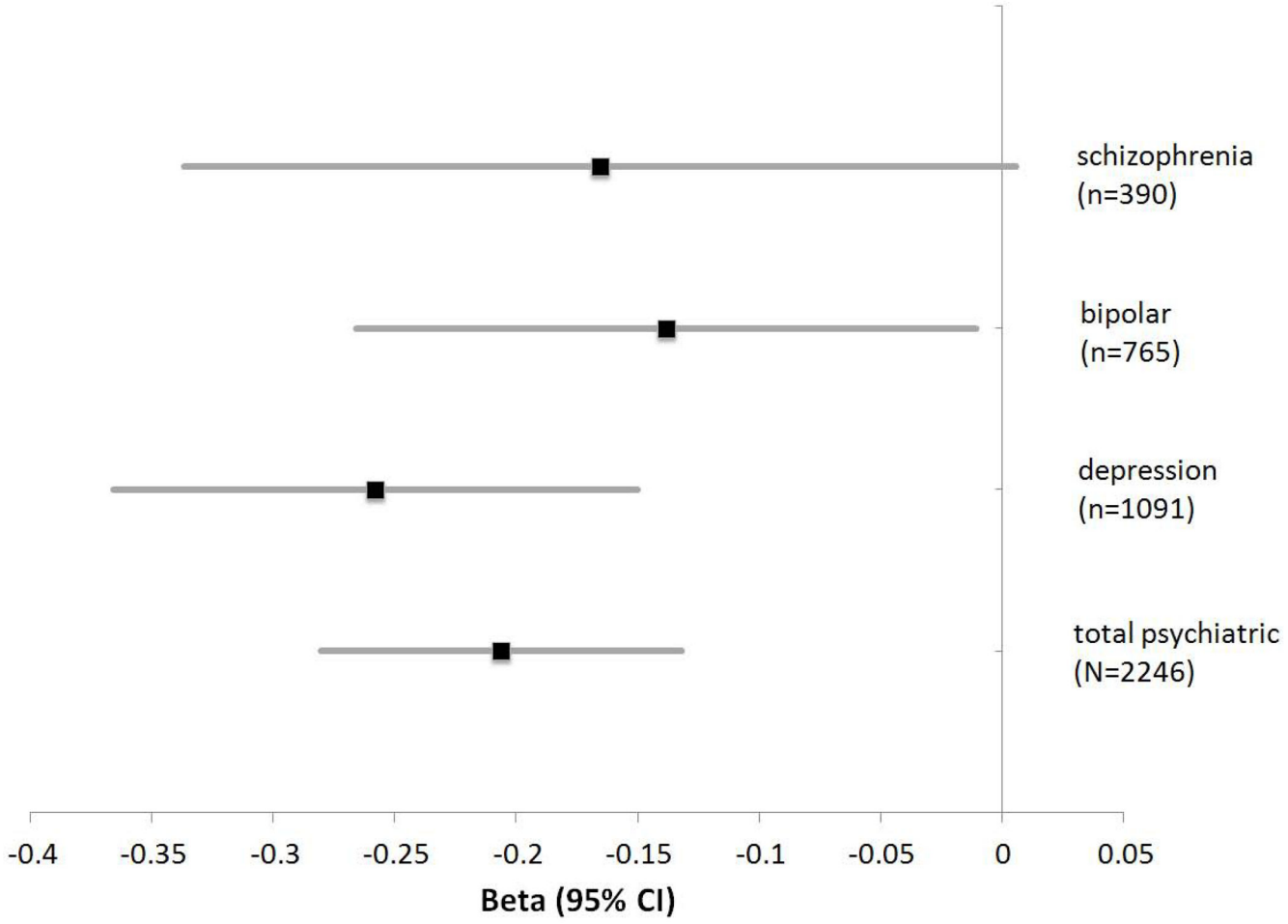

Figure 2.
Forest plot of effect sizes across the psychiatric samples for rs16875288.

Table 1

Phenotypic descriptive across samples. The population mean and standard deviation for the SF-12 is *M*=50, *SD*=10.

	STAR*D	STEP-BD	CATIE	Total
Sample size *N*	1091	765	390	2246
MCS *M (SD)*	26.1 (8.3)	32.6 (12.3)	40.0 (11.6)	30.7 (11.6)
PCS *M (SD)*	50.9 (11.8)	47.0 (10.9)	47.8 (10.3)	49.0 (11.4)

Table 2

Loci showing strongest evidence of association with MCS.

Chromosome	SNP	p	Additional SNPs (p<.0001), r2>.25	Nearest Genes (within 50kb)
3	rs4681346	2.61E-06	32	[]
1	rs7535475	3.23E-06	5	[HSPA6,FCGR3A,FCGR2A]
8	rs2736871	3.42E-06	4	[ST3GAL1]
12	rs10878563	1.10E-05	1	[]
10	rs10883890	1.59E-05	3	[SH3PXD2A,NEURL]
5	rs888643	1.63E-05	5	[]
9	rs988954	1.81E-05	2	[PTPRD]
22	rs5993665	2.04E-05	14	[UFD1L,MRPL40,HIRA,CLDN5,CDC45L,C22orf39]
3	rs6809127	2.22E-05	6	[]
3	rs10513787	2.42E-05	17	[]

Table 3

Loci showing strongest evidence of association with PCS.

Chromosome	SNP	p	Additional SNPs (p<.0001), r^2>.25	Nearest Genes (within 50kb)
5	rs16875288	5.87E-08	4	[ADAMTS16]
17	rs7221595	4.53E-06	32	[ZZEF1,CYB5D2,ANKFY1]
3	rs9877870	1.28E-05	30	[LPP]
4	rs6848750	2.05E-05	7	[MGC48628]
8	rs2737327	2.38E-05	1	[WRN]
11	rs10890798	2.43E-05	7	[RAB39,CUL5,ACAT1]
4	rs17015692	2.63E-05	1	[]
8	rs10095012	2.91E-05	6	[]
18	rs550139	3.30E-05	6	[MAPRE2]
20	rs6095959	3.67E-05	3	[PTPN1]