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Genome-wide association study of personality traits in bipolar patients

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Abstract

Objective—Genome-wide association study was carried out on personality traits among bipolar patients as possible endophenotypes for gene discovery in bipolar disorder.

Methods—The subscales of Cloninger's Temperament and Character Inventory (TCI) and the Zuckerman–Kuhlman Personality Questionnaire (ZKPQ) were used as quantitative phenotypes. The genotyping platform was the Affymetrix 6.0 SNP array. The sample consisted of 944 individuals for TCI and 1007 for ZKPQ, all of European ancestry, diagnosed with bipolar disorder by Diagnostic and Statistical Manual of Mental Disorders-IV criteria.

Results—Genome-wide significant association was found for two subscales of the TCI, rs10479334 with the 'Social Acceptance versus Social Intolerance' subscale (Bonferroni P = 0.014) in an intergenic region, and rs9419788 with the 'Spiritual Acceptance versus Rational Materialism' subscale (Bonferroni P = 0.036) in *PLCE1* gene. Although genome-wide significance was not reached for ZKPQ scales, lowest P values pinpointed to genes, *RXRG* for Sensation Seeking, *GRM7* and *ITK* for Neuroticism Anxiety, and *SPTLC3* gene for Aggression Hostility.

Conclusion—After correction for the 25 subscales in TCI and four scales plus two subscales in ZKPQ, phenotype-wide significance was not reached.

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Keywords

bipolar; genome-wide association study; *GRM7*; personality; *RXRG*; Temperament and Character Inventory; Zuckerman–Kuhlman Personality Questionnaire

Introduction

A large number of family, twins, and adoption studies support the heritability of bipolar disorder (BD) (Kendler *et al.*, 1993; Berrettini, 1998), but genome-wide association studies (GWAS) have detected only one significant and two suggestive weak-effect associations, and that detection required meta-analysis of multiple studies (Wellcome Trust Case Control Consortium, 2007; Sklar *et al.*, 2008; Smith *et al.*, 2009). A possible explanation is that BD is a genetically heterogeneous disorder and that studies of its genetic basis will not be tractable until the major endophenotypic dimensions reflecting that genetic heterogeneity are identified. Several theorists have proposed that there is significant variation in the presentation, course, and underlying pathophysiology among patients with BD, and even among mood disorders that are associated with personality traits, which may serve as endophenotypes in genetic association studies (Lara and Akiskal, 2006; Lara *et al.*, 2006; Loftus *et al.*, 2008; Savitz *et al.*, 2008). Some previous studies have reported association of personality traits in bipolars with candidate gene polymorphisms (Serretti *et al.*, 2008; Serretti and Mandelli, 2008).

We report here on GWAS of personality traits that might function as endophenotypes of BD. The term endophenotype was coined by John and Lewis (1966) as an internal phenotype not obviously part of the disease definition, and used by Gottesman and Shields (1973) to refer to simpler traits in schizophrenia that could be heritable and measured. A related research strategy was developed by Rieder and Gershon (1978). An endophenotype was expected to offer a more defined and quantifiable measure than diagnosis and to involve fewer genes (Gottesman and Gould, 2003).

In this study, we report on two personality scales: the Temperament and Character Inventory (TCI) (Cloninger *et al.*, 1993; Cloninger, 1994), and the Zuckerman–Kuhlman Personality Questionnaire (ZKPQ; Zuckerman, 2002), which were administered to a large proportion of patient participants in National Institutes of Health/National Institute of Mental Health (NIH/NIMH) bipolar genetics studies. GWAS was used to test for quantitative trait associations with these scales in patients with BD.

Methods

Patients

Diagnosis—All included patients are BD cases from the NIMH Genetics Initiative (http://nimhgenetics.org). All are of European ancestry to increase homogeneity of allele frequencies. Patients' self-reported ethnicity was later confirmed in the course of analysis with their genotypes. Diagnosis of BD was determined for each individual using the Diagnostic Interview for Genetic Studies versions 3 and 4 (Nurnberger *et al.*, 1994), information from relatives, and review of the patient's medical records. Then, a best-estimate diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders-IV criteria (American Psychiatric Association, American Psychiatric Association, and Task Force on DSM-IV, 2000) was assessed by two senior clinicians in a blind procedure, with discrepancies referred to a third senior clinician and to a consensus discussion.

Genotyping

Two genotyping batches were created, one at the Broad Institute (http://www.broad.mit.edu) under the aegis of the Genetic Association Information Network (GAIN; http://www.genome.gov/19518664) with NIH and other support, and the other at the Translational Genomics Research Institute (TGEN; http://www.tgen.org), under an NIMH grant (5R01MH078151; John Kelsoe, PI) and designated here as TGEN1. Analysis of disease association was carried out by a consortium of investigators known as the Bipolar Genome Study group (Smith *et al.*, 2009). As described by Smith *et al.* (2009), the genotyping platform used was Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetryx Inc., Santa Clara, California, USA; McCarroll *et al.*, 2008). Genotype quality control measures done as part of an earlier publication included sex check, Hardy–Weinberg Equilibrium ($P<0.01$, minor allele frequency (MAF) >0.01, and call rate of more than 0.985, as reported elsewhere (Smith *et al.*, 2009). The final genotype dataset used for our analyses consisted of 702 866 single nucleotide polymorphisms (SNPs).

Phenotypes: personality scales

Cloninger's TCI version 9 (125 items) and the ZKPQ (99 items) (see Supplementary Tables 1 and 2, http://links.lww.com/PG/A12) are self-administered scales submitted to patients participating in BD studies from NIH/NIMH (Smith *et al.*, 2009). Individuals who had one or more missing answers on these scales were discarded from the sample; in addition, ZKPQ contains an 'Infrequency' scale intended to measure validity/reliability, and scores higher than 3 were discarded as suggested by the investigators. The final group for the TCI consisted of 944 patients, and 1007 individuals for the ZKPQ.

Genome-wide association study methods

Genome-wide association analyses were carried out using PLINK 1.06 (http://pngu.mgh.harvard.edu/purcell/plink/; Purcell *et al.*, 2007) and Golden Helix SVS 7 (Golden Helix Inc., Bozeman, Montana, USA; HelixTree Software, 2008), using one scale at a time as a quantitative phenotype.

For the TCI, we carried out an association analysis for all its 25 subscales, in which the six main scales were removed to avoid redundancy, and for the ZKPQ, association analyses were carried out with four scales and two subscales, as only one of the five main scales contains subscales. Empirical significance levels (EMP) were obtained by permutation procedures (mperm and aperm) using PLINK, and Bonferroni correction of the permuted *P* values by the total number of acceptable quality SNPs was used for multiple test correction.

Principal components analysis was used to assess population structure and possible admixture in the sample. This procedure was performed using Golden Helix SVS 7, by the method described in the study by Price *et al.* (2006). This analysis showed only one major component in this European-American sample (Supplementary Fig. 1, http://links.lww.com/PG/A9). A comparison made against another sample collected and genotyped in the same study (GAIN-AA, African Ancestry Americans), showed good consistency and independence of our study sample (Supplementary Fig. 2, http://links.lww.com/PG/A11).

A post-hoc analysis for statistical power using Quanto (Gauderman and Morrison, 2006) showed that for this sample with allele frequencies varying from 0.01 to 0.5, the estimated power is more than 0.99 for a quantitative genetic effect (R^2_G) greater than 0.1.

Results

Genome-wide association studies of Temperament and Character Inventory

The smallest *P* value was found for the C1 subscale 'Social Acceptance versus Social Intolerance' (TCI-C1) for rs10479334 (nominal *P*=2.094E-9; MAF=0.078) located on chromosome 5q21.3, no gene has been identified in this region. Additional analyses carried out for this specific SNP using Adaptive Permutation (aperm) in PLINK, gave an empirical significance value EMP1= 2.025E-8 (after 98 771 000 permutations), which represents *P*=0.0142 after Bonferroni multiple-test correction for 702 866 SNPs, which is genome-wide significant. However, this does not reach phenome-wide significance after correction for the 25 phenotypes studied in the TCI (Table 1, Fig. 1).

A second significant *P* value was found related to the Self-Transcendence 1 subscale 'Spiritual Acceptance versus Rational Materialism' for rs9419788, located on chromosome 10q23.33 (nominal *P*=4.26E-8; MAF=0.354). This SNP is located in PLCE1 (Table 1, *P*Fig. 2). After 38 926 000 adaptive permutations, EMP1=5.138e-008, which gives a =0.0361 after Bonferroni correction. The association reached genome-wide but not phenome-wide significance.

The most significant associations with each scale are in Table 1. Results from associations for all the scales are available from the investigators.

Genome-wide association studies of Zuckerman-Kuhlman Personality Questionnaire

Genome-wide significance was not reached for any scale of the ZKPQ. The lowest *P* values were found for these SNPs: rs285480 (retinoid X receptor gene, *RXRG*; nominal *P*=3.83E-07, Bonferroni=0.2694) with the Sensation-Seeking subscale; rs13080594 (glutamate receptor metabotropic 7 gene, *GRM7*; nominal *P*=7.68E-07) and rs411174 (IL2-inducible T-cell kinase gene, *ITK*; nominal *P*=1.47E-06) with the Neuroticism Anxiety, and rs17190927 (serine palmitoyltransferase, long-chain base subunit 3 gene, *SPTLC3*; nominal *P*=7.99E-07) with the Aggressiveness-Hostility scale.

Discussion

The test of association yielding the lowest *P* value was for a SNP in a noncoding region (rs10479334) associated with the TCI-C1 subscale, which is a quantitative measure of anger expression in social interactions. Anger and fear have been hypothesized to be the two personality traits most closely related to BD (Lara *et al.*, 2006). Therefore, rs10479334 deserves further research on possible functions in linkage disequilibrium with it. This SNP is in a 200-kb region with strong linkage disequilibrium inside, but within 1MB distance no known gene exists. Only a few expressed sequence tags have been identified so far.

We also found genome-wide significance for the TCI Self-Transcendence 1 subscale. For this trait, rs9419788 located in the *PLCE1* gene achieved a genome-wide significant *P* value. This gene is regulated by the M3 muscarinic cholinergic receptor (*CHRM3*; Evellin *et al.*, 2002).

The lowest *P* level for a subscale of the ZKPQ was found for the Sensation-Seeking subscale. This scale has been widely studied and linked to bipolar traits, and the noted SNP, rs285480 (unadjusted *P*=3.83E-07) is in the region of the *RXRG* gene (Kent *et al.*, 2002); this has been identified as one of the circadian top candidate genes for BD (Le-Niculescu *et al.*, 2009).

For Neuroticism-Anxiety ZKPQ scale the lowest *P* value found was 7.68E-07 for rs13080594, a SNP located in *GRM7* gene; this gene is a major candidate gene found in previous associations with BD (Wellcome Trust Case Control Consortium, 2007), depression (Shyn *et al.*, 2009; Muglia *et al.*, 2010; Saus *et al.*, 2010), schizophrenia (Ohtsuki *et al.*, 2008), and panic disorder (Otowa *et al.*, 2009), linked to the phenomenon of fear extinction, as well (Callaerts-Vegh *et al.*, 2006; Fendt *et al.*, 2008).

The associations here shown are product of the differences found in a bipolar case samples only. But the findings of genetic association with personality traits may not be specific to BD. A study of normal controls would be illuminating.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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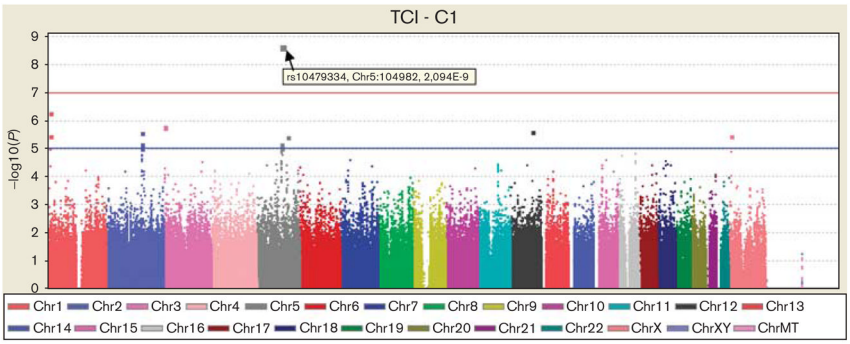

Fig. 1.

Manhattan plot of Temperament and Character Inventory subscale for Social Acceptance vs. Social Intolerance (TCI-C1) genome-wide association studies.

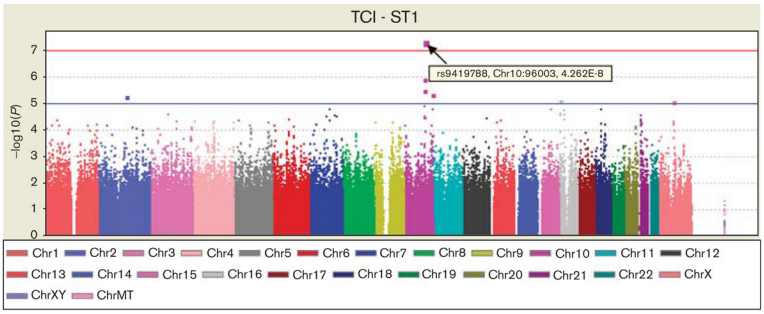

Fig. 2.

Manhattan plot of Temperament and Character Inventory-Self-Transcendence 1 (TCI-ST1) subscale genome-wide association studies.

Table 1

Top genome-wide association study results

Scale (phenotype)	SNP	Location	Gene	Unadjusted *P* value	EMP1	BONF
TCI-C1	rs10479334	5q21.3	–	2.094e-9	2.025e-8	0.0142
Social Acceptance vs. Social Intolerance						
TCI-ST1	rs9419788	Chromosome 10q23.33	*PLCE1*	4.26e-8	5.138e-8	0.0361
Spiritual Acceptance vs. Rational Materialism						
TCI-C3	rs9846232	Chromosome 3p25.1	*BC039529*	1.18e-8	8.831e-7	NS
Helpfulness vs. Unhelpfulness	rs9830807	Chromosome 3p25.1	*BC039529*	2.36e-8	3.888e-6	NS
ZKPQ-Sensation Seeking	rs285480	Chromosome 1q23.3	*RXRG*	3.83e-7	5.094e-6	NS
ZKPQ-Neuroticism Anxiety	rs13080594	Chromosome 3p26.1	*GRM7*	7.68e-7	2.614e-6	NS
	rs411174	Chromosome 5q33.3	*ITK*	1.47e-6	3.541e-5	NS
ZKPQ-Aggression Hostility	rs17190927	Chromosome 20p12.1	*SPTLC3*	7.99e-7	1.022e-5	NS

BONF, EMP1 *P* value after Bonferroni correction for 702 866 single nucleotide polymorphisms (SNPs); EMP1, empirical significance levels, adaptive permutation-calculated *P* value (max permutation =100 000 000 000); NS, not significant; TCI, Temperament and Character Inventory; Unadjusted *P*, unadjusted (nominal) genome-wide association study *P* value; ZKPQ, Zuckerman–Kuhlman Personality Questionnaire.