Journal of Affective Disorders 151 (2013) 748–755

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Preliminary communication

Heritability and linkage analysis of personality in bipolar disorder

Tiffany A. Greenwood [a,*], Judith A. Badner [b], William Byerley [c,d], Paul E. Keck [e], Susan L. McElroy [e,f], Ronald A. Remick [g], A. Dessa Sadovnick [h], John R. Kelsoe [a,i,j]

[a] Department of Psychiatry, University of California San Diego, 9500 Gilman Drive, Mail Code 0737, La Jolla, CA 92093, USA
[b] Department of Psychiatry, University of Chicago, Chicago, IL, USA
[c] Department of Psychiatry, University of California San Francisco, San Francisco, CA, USA
[d] San Francisco Department of Veterans Affairs Medical Center, San Francisco, CA, USA
[e] Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, Cincinnati, OH, USA
[f] Lindner Center of HOPE, Mason, OH, USA
[g] St. Paul's Hospital, Vancouver, Canada
[h] University of British Columbia, Vancouver, Canada
[i] San Diego Veterans Affairs Healthcare System, San Diego, CA, USA
[j] Institute for Genomic Medicine, University of California, San Diego, La Jolla, CA, USA

ARTICLE INFO

Article history:
Received 1 June 2013
Accepted 14 June 2013
Available online 22 August 2013

Keywords:
Bipolar disorder
Personality
TCI
Heritability
Genetic linkage

ABSTRACT

Background: The many attempts that have been made to identify genes for bipolar disorder (BD) have met with limited success, which may reflect an inadequacy of diagnosis as an informative and biologically relevant phenotype for genetic studies. Here we have explored aspects of personality as quantitative phenotypes for bipolar disorder through the use of the Temperament and Character Inventory (TCI), which assesses personality in seven dimensions. Four temperament dimensions are assessed: novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (PS). Three character dimensions are also included: self-directedness (SD), cooperativeness (CO), and self-transcendence (ST).

Methods: We compared personality scores between diagnostic groups and assessed heritability in a sample of 101 families collected for genetic studies of BD. A genome-wide SNP linkage analysis was then performed in the subset of 51 families for which genetic data was available.

Results: Significant group differences were observed between BD subjects, their first-degree relatives, and independent controls for all but RD and PS, and all but HA and RD were found to be significantly heritable in this sample. Linkage analysis of the heritable dimensions produced several suggestive linkage peaks for NS (chromosomes 7q21 and 10p15), PS (chromosomes 6q16, 12p13, and 19p13), and SD (chromosomes 4q35, 8q24, and 18q12).

Limitations: The relatively small size of our linkage sample likely limited our ability to reach genome-wide significance in this study.

Conclusions: While not genome-wide significant, these results suggest that aspects of personality may prove useful in the identification of genes underlying BD susceptibility.

1. Introduction

Bipolar disorder (BD) is a severe mood disorder that affects approximately 1% of the population and is characterized by episodes of major depression interspersed with periods of mania (bipolar I) or hypomania (bipolar II) (Goodwin and Jameson, 1990). Family, twin, and adoption studies, have suggested that BD is familial with a substantial genetic component and an estimated heritability of approximately 80% (Craddock and Jones, 1999; Taylor et al., 2002). Despite this high heritability, the many attempts that have been made over the last few decades to identify genetic variants contributing to BD susceptibility have met with limited success. Linkage and association studies have implicated numerous chromosomal regions and candidate genes with significant evidence for an involvement in BD, yet the causal variants have remained elusive (Serretti and Mandelli, 2008). Recent genome-wide association studies (GWAS) of BD and large meta-analyses of several thousand subjects have produced significant evidence for association to some interesting new candidates, yet these loci explain only 1–2% of BD susceptibility (Baum et al., 2008; Ferreira et al., 2008; Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Scott et al., 2009; Sklar

* Corresponding author.
E-mail address: tgreenwood@ucsd.edu (T.A. Greenwood).

0165-0327/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jad.2013.06.015

et al., 2008; Smith et al., 2009; Wellcome Trust Case Control Consortium, 2007).

While the difficulties in identifying genes for BD have generally been attributed to genetic heterogeneity and small gene effects, it is also likely that the categorical diagnostic systems (DSM and others) used in genetic studies are limited in their ability to capture the tremendous clinical heterogeneity observed in BD probands and their families (Gershon et al., 1982; Kelsoe, 2003; Price et al., 1985). Since traditional diagnostic systems are based on symptomatology, rather than etiology, they may not adequately reflect with the underlying pathology. As some have suggested BD, may be better conceptualized as part of a continuous distribution of clinical variation, ranging from very mild and subclinical to severe, consistent with a polygenic trait influenced by the interaction of many genes of small effect (Akiskal, 1983; Akiskal and Pinto, 2000; Kelsoe, 2003). Thus, the use of a quantitative phenotype to model this variation may be a powerful tool for elucidating the genetic architecture of BD.

The variation in the presentation, course, and underlying pathology that is observed among patients with BD and other mood disorders has been shown to be associated with personality traits, which may serve as useful endophenotypes in genetic studies (Lara and Akiskal, 2006; Lara et al., 2006; Loftus et al., 2008; Savitz et al., 2008a). Endophenotypes are quantitative phenotypes that relate to specific neurobiological functions associated with a disorder and demonstrate reliability, stability, and heritability (Gottesman and Gould, 2003). Several questionnaires evaluating personality are available, including the Temperament and Character Inventory, 125-question version (TCI-125), which is a self-administered true/false questionnaire that assesses personality according to Cloninger's psychobiological model (Cloninger et al., 1993). Temperament refers to automatic emotional responses to experience and is measured in four dimensions: novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (PS). Character refers to self-concepts and individual differences in goals and values and is measured in three dimensions: self-directedness (SD), cooperativeness (CO), and self-transcendence (ST). These temperament and character dimensions interact to form an individual's personality with certain interactions presumably leading to mood and other psychiatric disorders. Previous studies of the TCI in mood disorders have shown that subjects with BD score higher on the NS, HA, and ST dimensions than the general population (Harley et al., 2011; Loftus et al., 2008; Young et al., 1995), while subjects with major depressive disorder (MDD) score higher on NS and HA but lower on SD, CO, and ST (Bayon et al., 1996; Cloninger et al., 1994; Farmer et al., 2003; Hansenne et al., 1999; Harley et al., 2011; Marijnissen et al., 2002; Svrakic et al., 1993; Young et al., 1995). Thus, subjects with mood disorders appear to possess personality traits that are significantly different from non-ill individuals. Importantly, the TCI has been shown to have very good reliability, internal consistency, and stability over time (Cloninger et al., 1994, 1993; Heath et al., 1994; Keller et al., 2005), as well as evidence of heritability in the general population (Heath et al., 1994; Heiman et al., 2003; Keller et al., 2005).

Here we have used the TCI to assess the utility of personality dimensions as endophenotypes to aid in dissecting the underlying genetic architecture of BD. We evaluated personality dimension scores for subjects with BD, relatives with MDD, and their clinically unaffected relatives with comparison to an independent sample of control subjects. We have previously reported evidence for the familiality of personality in BD (Evans et al., 2005). We now report evidence for the heritability of five personality dimensions in 101 BD families and the results of a subsequent genetic linkage analysis of 51 families genotyped for a single nucleotide polymorphism (SNP) linkage panel. Even in this post-GWAS era, linkage remains a valuable tool for the detection of the aggregate effects of multiple rare and common variants within a gene or region.

2. Methods

2.1. Subjects

Subjects from BD families were selected from three different data sets collected for genetic studies of BD. The primary dataset (University of California San Diego, UCSD) was recruited at one of three sites (San Diego, Vancouver, and Cincinnati) as part of a collaborative genetic linkage study of BD (Kelsoe et al., 2001). The other two datasets were recruited at UCSD as part of the National Institute of Mental Health (NIMH) Genetics Initiative for Bipolar Disorder Waves 3 and 4 (Dick et al., 2003). Since the TEMPS-A was only administered at the San Diego site of the NIMH consortium, data was not available for the rest of the NIMH collection. Families were first identified through a proband diagnosed with bipolar I disorder or bipolar II disorder (UCSD sample) or a bipolar I sibling pair (Waves 3 and 4). Each subject was interviewed and diagnosed using either a modified version of the Structured Clinical Interview for DSM-III-R (SCID) or the Diagnostic Interview for Genetics Studies (DIGS) (Nurnberger et al., 1994; Spitzer et al., 1992). Interviewers were extensively trained and reliability was regularly tested. A panel of clinicians reviewed the interview, medical records, and information from family informants in order to make a final DSM-IV diagnosis. Control subjects were ascertained by advertising in the UCSD Mental Health Clinical Research Center and screened using the SCID for the absence of psychiatric illness. The TCI-125 was also administered to all subjects at the time of interview, and blood was drawn for the establishment of lymphoblastoid cell lines. All subjects provided written informed consent according to procedures approved by the local Institutional Review Board of each university.

The final sample included 670 subjects from 101 families with TCI data available for 428 subjects with the following diagnoses: 129 subjects (30.2%) with bipolar I (BDI), 39 (9.1%) with bipolar II (BDII), 9 (2.1%) with schizoaffective disorder, bipolar-type (SA-BP), 99 (23.2%) with recurrent major depression (MDD-R), 18 (4.2%) with a single episode of major depression (MDD-SE), 122 (28.6%) with no history of mood disorders, and 11 (2.6%) of unknown diagnoses. These data, along with the number of informative relative pairs, are summarized in Table 1. We also included an independent sample of 53 control subjects with no personal or family history of mental illness. This sample is approximately 62% female with an average age at interview of 45 ($\pm$ 17). All subjects were Caucasians of European ancestry.

2.2. Genotyping

Genotyping was performed by the Center for Inherited Disease Research (CIDR) using the Illumina Infinium HumanLinkage-12 panel containing 6090 SNP markers across the genome. A subset of the families and were genotyped as part of a larger study of 972 European ancestry families that were evaluated for linkage to BD (Badner et al., 2012). The 5670 autosomal and X-linked SNPs that passed the initial quality control assessments by CIDR were evaluated for missingness, allele frequency, and Hardy–Weinberg equilibrium, and families were further assessed for relatedness, Mendelian errors, unlikely genotypes, and ancestry, as described in detail in elsewhere (Badner et al., 2012). Cleaned genotypes were available for 261 subjects from 51 of our 101 UCSD and NIMH families (see Table 1). The remaining 5642 SNPs were ordered on the physical map according to Genome Build 36, and the deCODE genetic map was used to estimate genetic map distances (Kong