Journal of Affective Disorders 186 (2015) 367–375

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research report

Identification of circadian gene variants in bipolar disorder in Latino populations

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ARTICLE INFO

Article history:
Received 23 May 2015
Received in revised form
23 June 2015
Accepted 8 July 2015
Available online 31 July 2015

Keywords:
Circadian
Bipolar disorder
Casein Kinase 1 Epsilon
Aryl Hydrocarbon Receptor Nuclear Translocator-Like
Latino
Family-based association test

ABSTRACT

Background: Variations in circadian genes can impact biological rhythms. Given the rhythm disturbances that characterize bipolar disorder (BD), genes encoding components of molecular clocks are good candidate genes for the illness.
Methods: A family based association analysis of circadian gene single nucleotide polymorphisms (SNPs) and BD was conducted in Latino pedigrees. 884 individuals from 207 pedigrees (473 BP phenotype and 411 unaffected family members) were genotyped. Family based single marker association testing was performed. Ancestral haplotypes (SNPs found to be in strong LD defined using confidence intervals) were also tested for association with BD.
Results: Multiple suggestive associations between circadian gene SNPs and BD were noted. These included CSNK1E (rs1534891, $p=0.00689$), ARNTL (rs3789327, $p=0.021172$), CSNK1D (rs4510078, $p=0.022801$), CLOCK (rs17777927, $p=0.031664$). Individually, none of the SNPs were significantly associated with BD after correction for multiple testing. However, a 4-locus CSNK1E haplotype encompassing the rs1534891 SNP (Z-score$=2.685$, permuted $p=0.0076$) and a 3-locus haplotype in ARNTL (Z-score$=3.269$, permuted $p=0.0011$) showed a significant association with BD.
Limitations: Larger samples are required to confirm these findings and assess the relationship between circadian gene SNPs and BD in Latinos.
Conclusions: The results suggest that ARNTL and CSKN1E variants may be associated with BD. Further studies are warranted to assess the relationships between these genes and BD in Latino populations.

1. Introduction

Rhythm disturbances have long been recognized as significant features of bipolar disorder (BD). As such, disturbances of biological rhythms have been hypothesized to play a fundamental role in the etiology of the disorder (Gonzalez, 2014). BD is a complex trait disorder (Craddock and Sklar, 2013). A substantial amount of evidence suggests that genetic factors confer a significant risk to the development of BD and possibly to the phenotypic expression of the illness (Craddock and Sklar, 2013; Kieseppa et al., 2004).

Given that there are now a number of genes known to

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http://dx.doi.org/10.1016/j.jad.2015.07.014

influence circadian patterns, variations in these circadian genes may contain variants that are associated with susceptibility to bipolar disorder.

The precision of the circadian timing system is in large part dictated by the expression of circadian genes and the interactions of their protein products (Edery, 2000; Reppert and Weaver, 2002). Alterations in these core circadian genes can change the expressed circadian period and phase (Ralph et al., 1990) and disrupt normal circadian rhythmicity (Herzog et al., 1998).

Circadian gene variants have been associated with BD (Benedetti et al., 2004b; Benedetti et al., 2005; Kishi et al., 2008; Kripke et al., 2009; Lamont et al., 2010; Lee et al., 2010; Mansour et al., 2009; Mansour et al., 2006; McGrath et al., 2009; Nievergelt et al., 2006; Pickard et al., 2008; Serretti et al., 2003, 2005; Severino et al., 2009; Shi et al., 2008; Soria et al., 2010; Szczepankiewicz et al., 2006) and clinical signatures of the illness (Lamont et al., 2010). Preliminary studies also suggest that a less robust molecular clock may be associated with the disorder (Yang et al., 2009). In addition, emerging literature suggests that certain pharmacological treatments (Benedetti et al., 2005; Johansson et al., 2011; Li et al., 2002; Osland et al., 2011; Padiath et al., 2004) and biologically based treatments (Benedetti et al., 2004b) for the illness may exert some of their therapeutic action through molecular clocks. Preclinical models also suggest physiological relationships between circadian gene functioning, BD, and pathophysiological mechanisms previously implicated in the illness (Roybal et al., 2007).

While there have been studies examining the relationship between circadian gene markers and BD, to the best of our knowledge none have been conducted in Latino populations. We, therefore, conducted a family based association study in a Latino population to examine the relationship between circadian gene single nucleotide polymorphisms (SNPs) and BD. Hispanics are the largest and fastest growing ethnic group in the United States, representing 16 percent of the US population (Ennis et al., 2011). This decade, the Hispanic population has grown by 43% and individuals with Mexican origin increased by 54% (Ennis et al., 2011). Despite this growth, there is a tremendous paucity of psychiatric genetic research focused on this population. Hispanics are an admixed population resulting from interbreeding between individuals from different continental populations, in which ancestral genomes have diverged over time due to genetic drift and/or natural selection (Dries, 2009). The mixture of ancestral genomes in Hispanics makes genetic studies susceptible to population stratification issues, in which spurious associations of allele frequencies between cases and controls are due to systematic differences in ancestry rather than association of genes with disease state (Freedman et al., 2004). Most investigators have circumvented population stratification issues by focusing their efforts on more homogenous populations, namely Caucasians of European descent. However, concerns regarding population stratification should not lead to exclusion of admixed groups such as Hispanics, as observed differences in prevalence rates, disease presentation, and treatment outcomes for BD may be explained by ethnic specific genetic variation (Oquendo et al., 2010). We, therefore, conducted a family based association study in a Latino population to examine the relationship between circadian gene single nucleotide polymorphisms (SNPs) and BD, as family based studies are robust against population stratification issues (Horvath et al., 2001).

2. Methods

2.1. Study sample

Study procedures were approved by the institutional review board at Texas Tech University Health Science Center as well as by the institutional review boards of all participating research sites. All subjects signed institutional review board approved consent forms prior to enrolling in the study. Research was performed in accordance with the Helsinki Declaration of 1975.

Latino subjects were recruited from the United States (Texas, New Mexico, and California), Mexico (Mexico City, Monterrey), Costa Rica (San Jose), and Guatemala (Guatemala City) as part of a multi-site study to identify genes associated with bipolar disorder in persons of meso-American Latino ancestry (Gonzalez et al., 2014). Previous genetic structure analysis has shown that these populations are closely related, with high levels of admixture consisting of three major ancestral populations (Caucasian, Native American, and African) (Campos-Sanchez et al., 2013). Families recruited for this study were families with presumed multiplex cases of Bipolar Type I Disorder or Schizoaffective Bipolar Disorder, with ancestry (at least two of the four grandparents of BD proband) from Mexico or Central America. For the current analysis of circadian gene variants, we utilized a sample consisting of subjects from 207 of these pedigrees.

Diagnoses were made according to DSM-IV criteria. A best-estimation consensus procedure using the Diagnostic Interview for Genetic Studies (DIGS), the Family Interview for Genetic Studies (FIGS), and a review of available psychiatric records was used to confirm diagnoses as previously described (Gonzalez et al., 2013). Of the total of 884 individuals included in the present analyses, 473 met best estimation criteria for lifetime diagnosis of either Bipolar Disorder, Type I or Schizoaffective Disorder, Bipolar Type, by DSM IV criteria.

2.2. Genotyping

A total of 884 individuals from 207 pedigrees (473 with BD phenotype: 257 Bipolar Disorder Type I with psychosis, 200 Bipolar Disorder Type I without psychosis, 16 Schizoaffective, Bipolar Type and 411 additional family members) were genotyped for these analyses of circadian gene variants. For each BD subject, we genotyped the subject and both parents if DNA was available. If both parents were not available, we genotyped the BD subject, one parent, and additional siblings. Table 1 shows the sample characteristics of pedigrees by country of origin.

DNA was isolated from lymphoblastoid cell lines established and stored for each study participant at the NIMH Center for Collaborative Genetic Studies. SNPs were genotyped using

Table 1
Sample characteristics of pedigrees by country of origin.

	United States	Guatemala	Costa Rica	Mexico
Pedigrees	**56**	**17**	**39**	**95**
Individuals with BD	122	41	105	205
Affected parents	17	4	10	34
Trios	27	6	35	88
1 parent 1 sibling	37	10	10	51
1 parent 2 siblings	33	9	5	16
1 parent 3 siblings	7	2	24	13
1 parent 4 siblings	1	5	4	3
1 parent 5 siblings	–	–	5	1
1 parent 6 siblings	–	5	7	2
1 parent 7 siblings	–	–	2	–
1 parent 8 siblings	–	–	3	–
Total (% female)	**220** (66.4%)	**70** (64.3%)	**210** (56.7%)	**384** (59.4%)