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Research report

Identification of circadian gene variants in bipolar disorder in Latino populations

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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.
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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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[1] These authors contributed significantly to the conceptualization, data analysis, and writing of the manuscript so as to be considered first authors.

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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%)

GoldenGate Custom Genotyping Assay (96-plex) and run on the BeadExpress System (Illumina Inc., San Diego, CA). Genotyping was blinded to subject diagnosis and characteristics. The SNP panel consisted of variants from circadian genes selected from the literature based on previous association with BD in other studies (Benedetti et al., 2003, 2004a, 2004b; Mansour et al., 2006, 2009; McGrath et al., 2009; Nievergelt et al., 2006; Severino et al., 2009; Shi et al., 2008; Soria et al., 2010; Szczepankiewicz et al., 2006). These included SNPs in the following genes: Aryl Hydrocarbon Receptor Nuclear Translocator-Like 1 (ARNTL), Circadian Locomotor Output Cycles Kaput (CLOCK), Casein Kinase 1 Epsilon (CSNK1E), Cryptochrome 1 (CRY1), Cryptochrome 2 (CRY2), Glycogen Synthase Kinase 3-beta (GSK3β), Neuronal PAS Domain Protein 2 (NPAS2), Nuclear Receptor Subfamily 1, Group D, Member 1 (NR1D1), Period 1 (PER1), Period 2 (PER2), Period 3 (PER3), RAR-Related Orphan Nuclear Receptor Beta (RORβ), and Timeless (TIM), Casein Kinase 1 Epsilon (CSNK1E), and Peroxisome Proliferator-Activated Receptor Gamma, Coactivator 1 Beta (PPARGC1B). Additional SNP selection was designed to cover the circadian genes of interest (ARNTL, CLOCK, CSNK1E, CRY2, GSK3β, PER2, RORβ, and TIM) and was based on a Tagging SNP approach ($r^2 \geq 0.9$) using SNPbrowser™ software version 4.0 (Applied Biosystems) using a minimum minor allele frequency of 0.1 and was based on data from CEU, YRI, and CHB HapMap populations.

Genotype data was assessed for quality using the plink software. Individuals with $>10\%$ missing genotype data and SNPs with excessive missingness ($>10\%$), minor allele frequencies <0.01, or exhibiting deviations from Hardy–Weinberg Equilibrium (HWE <0.01) were removed prior to analysis. Genotypes were checked for Mendelian errors, with inconsistent genotypes set to missing.

2.3. Statistical analysis

Family based single marker and haplotype association testing was performed using the FBAT ver 2.0.4 software package (Horvath et al., 2001) which is able to test for association using data from nuclear families, sibships, pedigrees, or any combination (with or without founder genotypes), is adjusted for population admixture, and it is not biased due to pedigree relationships or population. All SNPs were subjected to FBAT analysis in the initial stage. A second analysis, using haplotypes, was conducted only for SNPs showing evidence of association in stage 1. Haploview version 4.2 (Barrett et al., 2005) was used to visualize LD relationships between genotyped variants and to define the LD blocks following the D' method described by Gabriel et al. (2002). Haplotype analyses were performed using the Haplotype-Based Association Testing (HBAT) assessment in the FBAT ver 2.0.4 program (Horvath et al., 2004). Haplotype specific and global permuted *P*-values were calculated for individual haplotype tests in haplotype FBAT, assuming an additive genetic model. In order to maximize power in the statistical analyses, permutation procedures were implemented to calculate the empirical *p*-values derived from 10,000 permutations.

The power calculations for family designs for binary traits and multiple family-types were done in PBAT (v3.3) using Monte-Carlo simulations (Lange et al., 2004) based on actual sample pedigree structures. Type I error was set at 0.05. The additive inherited model was assumed using the average minor allele frequency of 0.27 and population prevalence 0.01.

3. Results

3.1. Sample characteristics

Four SNPs and 14 individuals were removed for excessive missingness (>0.1). All remaining SNPs ($N=92$) passed minor allele frequency and HWE thresholds (MAF >0.01; HWE >0.01, respectively). The total successful genotyping rate in the remaining individuals was 0.958. After quality control filtering, there were 92 SNP genotypes for 870 individuals (465 BD phenotype, 405 unaffected relatives). Of these, 341 (39.2%) were male and 529 (60.8%) were female. Within the 207 pedigrees, there were 533 nuclear families consisting of 147 affected offspring with both parents and 318 affected individuals without both parents (but with a minimum of 2 first degree relatives). The Mendelian error rate was 5.22E−05, with 4 Mendel errors detected in total which were set to missing. Power calculations by PBAT estimated that the study had $<99\%$ power to detect odd ratios of 2.0 (major effect), 71% power to detect odd ratio of 1.5 (modest effect) and 20% power to detect odd ratio of 1.2 (low effect).

3.2. Single marker results

Nominal associations between several of the circadian gene SNPs and BD were noted. These included variants in CSNK1E (rs1534891, $p=0.00689$), ARNTL (rs3789327, $p=0.0212$), CSNK1D (rs4510078, $p=0.0228$), and CLOCK (rs17777927, $p=0.0317$). Individually, none of the SNPs were significantly associated with BD after correction for multiple testing (critical $p=5.43\text{E}-4$). We then selected genes with nominal evidence of association in the FBAT analysis (CSNK1E, ARNTL, and CLOCK), for further haplotype analysis. CSNK1D was excluded from further analysis, as rs4510078 was the only marker genotyped within the gene.

3.3. Haplotype results

The LD relationships between genotyped variants were define following the D' method in Haploview. Haplotype based-association test results are shown in Table 2. Three additional SNPs (rs2075983; rs6001093; rs135757) were found to be in strong LD with the rs1534891 SNP in CSNK1E (Fig. 1). The whole marker permutation test of the CSNK1E haploblock was significantly associated with BD (X^2 sum; $P=5.91\times10^{-3}$). A specific 4-locus CSNK1E haplotype (AAGA) showed a significant association with BD (*Z*-score$=2.685$, permuted $P=7.62\times10^{-3}$). A second haplotype (AGAA) was significantly under-transmitted in BD (*Z*-score$=-2.829$, permuted $P=5.45\times10^{-3}$).

The rs3789327 SNP was part of a 3-locus haploblock (rs1868049; rs3789327; rs11022778) in the ARNTL gene (Fig. 2). The global ARNTL haploblock permutation test was significantly associated with BD (X^2 sum; $P=2.99\times10^{-3}$). A 3-locus ARNTL haplotype (GAA) showed a significant association with BD (*Z*-score$=3.269$, permuted $P=1.06\times10^{-3}$). A second haplotype (GGA) was significantly undertransmitted in BD (*Z*-score$=-2.49$, permuted $p=0.0148$).

Nine additional markers (rs10462028; rs1801260; rs3805148; rs3736544; rs11932595; rs4340844; rs4864542; rs2070062; rs13132420) were in the same LD block with rs17777927 within the CLOCK gene (data not shown). No statistically significant associations were noted between CLOCK haplotypes and BD.

4. Discussion

In the study presented, we conducted a family-based association test examining the relationships between circadian gene SNP

Table 2
Haplotype-Based Association Test for CLOCK, ARNTL, and CSNK1E variants.

CLOCK **Haplotype**	**Freq**	**Families**	***Z***	***P***	**P_2side**	**Global *P***
h1: GACGCACGAA	0.409	105	−0.756	0.449	0.446	0.162
h2: GAAACAACAG	0.253	101	1.043	0.297	0.238	
h3: AGAGCGACCG	0.174	84	0.816	0.414	0.439	
h4: GACGCGCGAA	0.085	45	−0.434	0.664	0.709	
h5: AGAGGGACCG	0.035	21	−1.911	0.056	0.058	
h6: AACGCACGAA	0.021	15	−0.737	0.461	0.432	
ARNTL						
Haplotype	**Freq**	**Families**	***Z***	***P***	**P_2side**	**Global *P***
h1: GGC	0.342	107	−0.404	0.686	0.651	**2.99E−03**
h2: GGA	0.267	95	−2.419	**1.56E−02**	**1.48E−02**	
h3: GAA	0.253	97	3.269	**1.08E−03**	**1.06E−03**	
h4: AAA	0.137	73	−1.06	0.289	0.304	
CSNK1E						
Haplotype	**Freq**	**Families**	***Z***	***P***	**P_2side**	**Global *P***
h1: GGAG	0.718	112	0.61	0.542	0.519	**5.91E−03**
h2: AGAA	0.206	91	−2.829	**4.67E-03**	**5.45E−03**	
h3: AAGA	0.043	36	2.685	**7.25E-03**	**7.62E−03**	
h4: AGGA	0.029	38	0.316	0.752	0.840	

884 individuals from 207 pedigrees were evaluated, using an additive model and biallelic tests. Haplotype = linkage disequilibrium blocks consisted on the following single-nucleotide polymorphisms: **CLOCK**: rs10462028, rs1801260, rs3805148, rs3736544, rs17777927, rs11932595, rs4340844, rs4864542, rs2070062, and rs13132420; **ARNTL**: rs1868049, rs3789327, and rs11022778; **CSNK1E**: rs2075983, rs1534891, rs6001093, and rs135757; Freq = frequency of the haplotype; Families = number of informative families; P_2side = two-sided *p*-values using permutation test based on 10,000 permutations. Bold denotes statistical significance after Bonferroni correction for multiple testing.

markers and BD in a Latino sample. In our sample, we found nominal associations with 4 SNPs and BD. Relationships between BD and three of these four SNPs have been previously reported. These include CSNK1E rs1534891, which has been reported as a component of a multi-locus interaction associated with BD (Shi et al., 2008), CSNK1D rs4510078, which has been associated with BD (Kripke et al., 2009), and ARNTL rs3789327, which has been associated with depression as a quantitative trait in BD (Maciukiewicz et al., 2014). In addition, other SNPs located within the haploblocks of interest have been associated with BD (Dmitrzak-Weglarz et al., 2014; Shi et al., 2008; Soria et al., 2010) and other clinical aspects of the illness including sleep disturbances (Dmitrzak-Weglarz et al., 2014; Serretti et al., 2003, 2005), depression (Maciukiewicz et al., 2014), appetite disturbances (Maciukiewicz et al., 2014), increased recurrence rates (Benedetti et al., 2003), rapid cycling (Shi et al., 2008), and diurnal preference for daily activities (Lee et al., 2010).

While the aforementioned SNP association did not demonstrate significant associations after corrections for multiple testing, the analyses did identify a four-locus CSNK1E haplotype that was associated with BD. In addition, another four-locus CSNK1E haplotype was identified which was under-transmitted in BD. In ARNTL, we also identified a 3-locus haplotype that was significantly associated with BD as well as a second haplotype that was under-transmitted in the illness. These findings suggest that some variants in CSNK1E and ARNTL may confer increased susceptibility for developing the disorder while others may provide a protective effect against the development of the illness.

The central mechanism of molecular clocks revolves around the expression of circadian genes and the interactions of their mRNA and protein products that function as interconnected transcriptional and translational feedback loops (Reppert and Weaver, 2002). The phase, period, and amplitude of endogenous clocks are determined by the protein products of circadian genes. In essence, the molecular clock is comprised of positive and negative arms that function in a similar fashion to gears in a clock providing the pushes and pulls that keep the clock ticking.

Our findings are interesting in that the haplotypes found to be in significant association with BD were in two genes encoding integral components of endogenous molecular clocks. ARNTL, located on chromosome 11 (11p 15.2), encodes for a basic helix-loop-helix-PAS domain transcription factor. Arntl forms a heterodimer with Clock. It is this complex that makes up the positive arm of the transcriptional–translational feedback loop. The Clock:Arntl complex binds to E-box elements in promoter regions of other core circadian genes such as the PER and CRY genes that comprise the negative arm of molecular clocks. The timing of the endogenous clock is able to be fine tuned by certain clock modifying factors. CSNK1E, located on chromosome 22 (22 q13.1), encodes for a kinase which functions to phosphorylate clock proteins thus affecting their function and stability (Reppert and Weaver, 2002). Csnk1e phosphorylates the Per and Cry proteins, thus, regulating the stability and subcellular localization of these core molecular clock proteins (Akashi et al., 2002; Camacho et al., 2001; Keesler et al., 2000; Lee et al., 2001; Schlosser et al., 2005). Phosphorylated Per and Cry proteins are translocated back into the cytoplasm and inhibit the transcriptional activity of Clock:Arntl. This causes a decrease in the transcription of PER and CRY and decreases the levels of these proteins thus resetting the molecular clock. The functional role that Csnk1e exerts on the functioning of molecular clocks (Vanselow and Kramer, 2007) may play a significant role in the expression of biological rhythms as well as the physiological processes influenced by this system (Liu et al., 2007).

While possibly conferring risk for the development of rhythm disturbances in BD, variations in these genes may have other possible physiological consequences related to the illness. CSNK1E has been associated with phenotypic variants of circadian phase (Lowrey et al., 2000; Toh et al., 2001; Vanselow et al., 2006), dopamine regulation (Li et al., 2011), and a sensitivity to substances of abuse (Bryant et al., 2012; Levran et al., 2008; Perreau-Lenz et al., 2012; Veenstra-VanderWeele et al., 2006). These areas may be germane to BD as phase disturbances (Linkowski et al., 1985a, 1985b, 1994; Nurnberger et al., 2000; Salvatore et al., 2008; Wehr et al., 1980; Wood et al., 2009), substance abuse in BD (Levin and

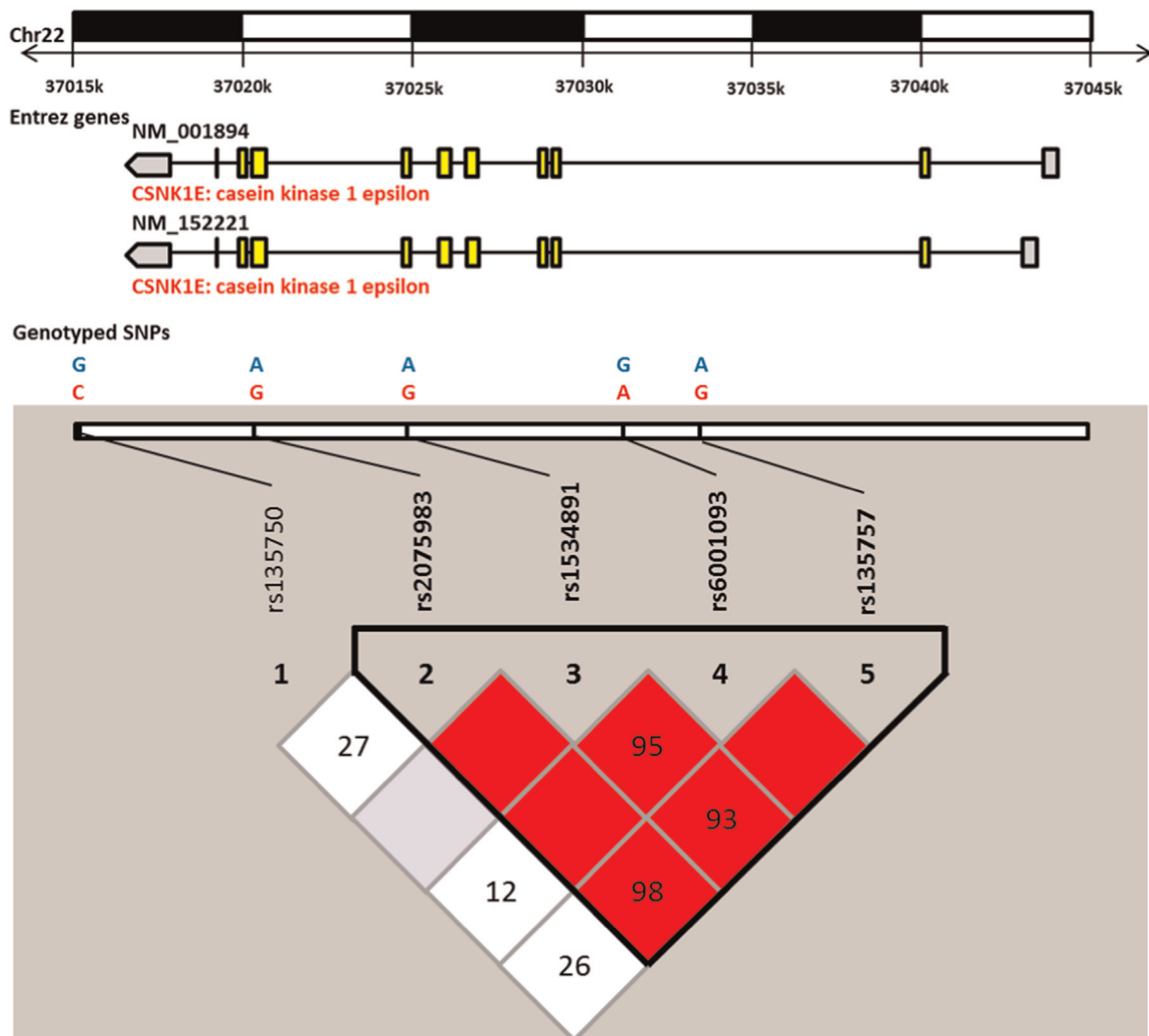

Fig. 1. Casein kinase 1 epsilon (CSNK1E) haplotype block. A linkage disequilibrium plot of the CSNK1E gene (shown as a black line) and adjacent regions with respect to the 5 genotyped SNPs is presented. The data visualized here using Haploview V4.2 are based on the current genotyping data from the Latino population. Squares indicate pairwise r^2 values on a red-scale with $D'=1$ (red) through to $D'=0$ (white). Linkage disequilibrium block, as defined in Haploview, are represented by the triangular lines. The nominally associated single marker rs1534891 is part of a 4-locus haploblock spanning 12 kilobases across introns 2–8. Order of haploblock SNPs (SNPs in bold) from left to right: rs2075983; rs1534891; rs6001093; rs135757.

Hennessy, 2004), and dopamine functioning (Ishikawa et al., 2007) have been related to the illness. In a similar fashion as with Clock, Arntl forms heterodimer with Npas2. NPAS2, a paralog of CLOCK is expressed in the forebrain, basal ganglia and limbic system (Reick et al., 2001) and may play a role in processing sensory stimuli (Dudley et al., 2003). ARTNL has also been associated with seasonal affective disorder (Partonen and Lonnqvist, 1996) and metabolic regulation (Gomez-Abellan et al., 2008; Kennaway et al., 2013; Lee et al., 2011; Rudic et al., 2004; Shimba et al., 2011; Young et al., 2014). These are of interest in bipolar disorder since seasonality (Cassidy and Carroll, 2002; Hakkarainen et al., 2003; Shin et al., 2005; Silverstone et al., 1995; Thompson et al., 1988), metabolic abnormalities (Fagiolini et al., 2005), and cognitive dysfunction (Arts et al., 2008; Bora et al., 2009; Glahn et al., 2010) have been associated with BD.

Some have suggested that examining the functioning of molecular clocks may yield advances in the phenotypic characterization of various illnesses (Saini et al., 2015). With respect to BD, polymorphisms in circadian genes have demonstrated associations with recurrence rates and cycling patterns (Benedetti et al., 2003; Shi et al., 2008), insomnia (Serretti et al., 2003; Shi et al., 2008), age at illness onset (Benedetti et al., 2004b), diurnal patterns of mood expression (Shi et al., 2008), and response to treatments such as sleep deprivation (Benedetti et al., 2004b) and lithium (Benedetti et al., 2005). While bipolar disorder is a complex trait disorder with evidence supporting a polygenic risk susceptibility (Craddock and Sklar, 2013), variations in circadian genes may be related to heritable phenotypic variants of the illness. These associations will need to be explored further to better characterize possible phenotypes and heritable variants of the disorder.

Emerging literature suggests that certain pharmacological treatments for bipolar disorder may affect functioning of molecular clocks. Mood stabilizers such as lithium (Osland et al., 2011; Padiath et al., 2004) and valproic acid (Johansson et al., 2011; Li et al., 2002) have been shown to influence the rhythmic expression of circadian genes and the rhythmic properties of molecular clocks. The effects of lithium on circadian gene may work to modify functioning of the dopaminergic system (Roybal et al., 2007). It has also been suggested that the rapid acting antidepressant response associated with both sleep deprivation and low dose ketamine may be associated with the modulation of the biological timing system (Benedetti et al., 2014; Bunney and Bunney, 2013; Bunney et al., 2015). Ketamine has been shown to alter circadian gene expression in neuronal cell culture (Bellet

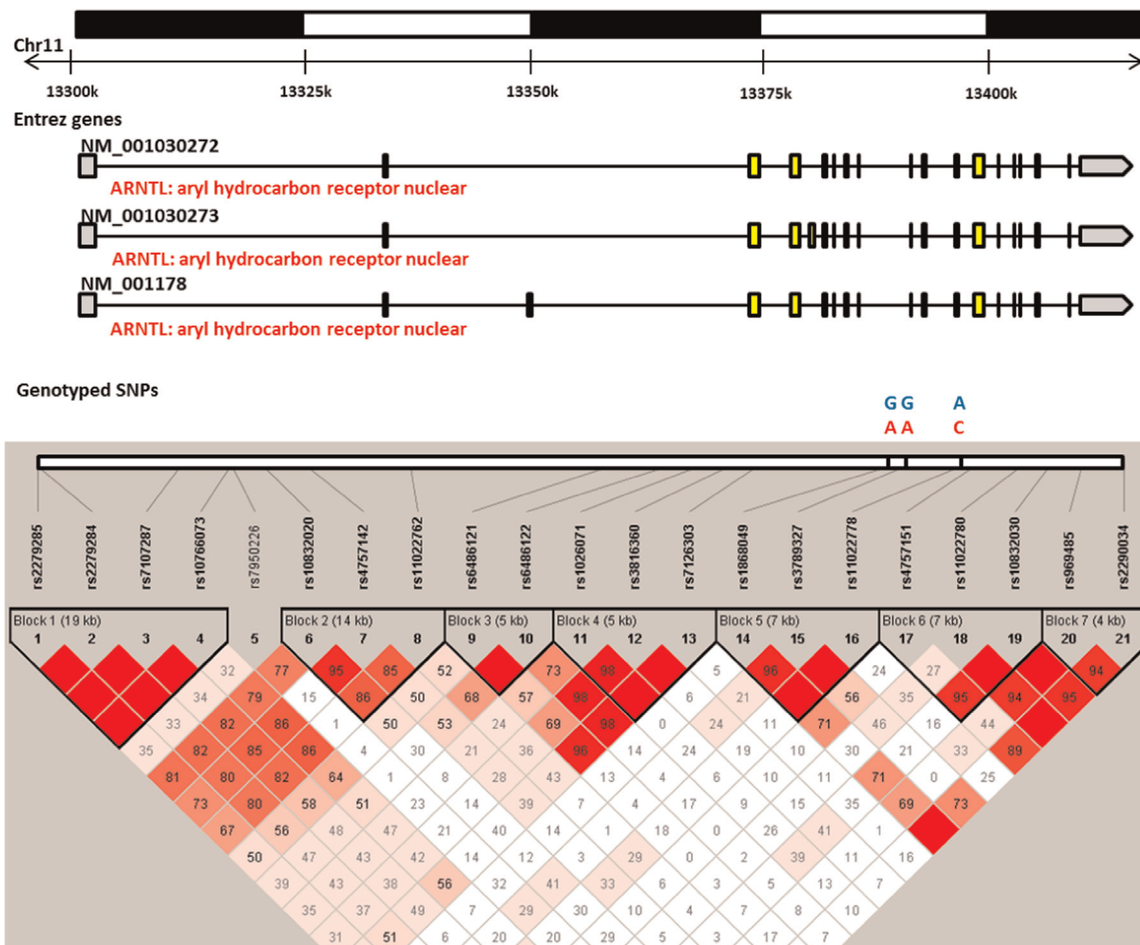

Fig. 2. Aryl hydrocarbon receptor nuclear (ARNTL) haplotype blocks. The intermarker linkage disequilibrium pattern across the ARNTL gene (shown as a black line) was generated by Haploview V4.2 based on 21 SNPs genotyped in the Latino population. Squares indicate pair-wise r^2 values on a red-scale with $D'=1$ (red) through to $D'=0$ (white). Linkage disequilibrium blocks are represented by the triangular lines. The nominally associated single marker rs3789327 is part of a 3-locus haploblock (Block 5). Major and minor alleles of Block 5 are in blue and red, respectively. Order of SNPs (haploblock SNPs in bold) from left to right: Block 1 (19 kb): rs2279285, rs2279284, rs7107287, rs10766073, and rs7950226; Block 2 (14 kb): rs10832020, rs4757142, and rs11022762; Block 3 (5 kb): rs6486121, rs6486122; Block 4 (5 kb): rs1026071, rs3816360, and rs7126303; Block 5 (7 kb): rs1868049, rs3789327, and rs11022778; Block 6 (7 kb): rs4757151, rs11022780, and rs10832030; Block 7 (4 kb): rs2290034, rs2290034.

et al., 2011). Sleep deprivation has been shown to alter circadian gene expression in animal models (Thompson et al., 2010; Wisor et al., 2002, 2008) and in humans (Ackermann et al., 2013; Archer et al., 2008; Moller-Levet et al., 2013). It is hypothesized that these rapid antidepressant effects may be secondary to resetting abnormalities in molecular clocks and therefore stabilizing circadian rhythmicity (Bunney and Bunney, 2013; Bunney et al., 2015).

Our study has some strengths and some limitations. In terms of testing for association at the genetic level, our analysis uses family based association, which is robust to population stratification which can lead to false positive or negative results in genetic association studies. Another strength of the study is that bipolar patients were carefully diagnosed, using multiple sources of diagnostic information and a unified consensus approach and came from families with high genetic loading for BD. The primary limitation of the study is the sample size. Although the positive association found is a significant association, failure of association in the other SNPs may be due to the small sample size and insufficient power to detect association of low to moderate effect (OR 1.2–1.5). Larger samples would need to be studied within this population to definitively rule out association between these other genes and BD in Latinos.

In conclusion, the results of this family-based association study of circadian genes and BD in a Latino population noted some nominal associations between circadian gene SNPs and statistically significant associations between CSNK1E and ARNTL haplotypes and BD. These findings support previous literature suggesting that genetic variations in CSNK1E and ARNTL may confer an increased susceptibility to the development of BD. It should be noted that the current study focused solely on assessing the relationships between SNPs and circadian genes and BD. Following up these results using mapping and sequencing will be required to define the genetic architecture of CSNK1E and ARNTL and any specific variants “tagged” by this haplotype that might confer the increased risk of BD in the Latino population. Replication of the haplotype finding in Latino and non-Latino populations would be useful to better understand the particular haplotype markers associated with BD in different populations. Future studies focusing on intermediate phenotypes and examining quantitative traits are warranted to define the functional role that CSNK1E and ARNTL variations may play on the pathophysiology of BD. Given their functioning, further research is warranted to ascertain the relationships between circadian gene variants and physiological mechanisms that may be related to BD.

Disclosures

Contributors

Robert Gonzalez – project design, analysis, and manuscript preparation.

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Erika Villa – data cleaning and analysis.

Mercedes Ramirez – performed best estimation consensus diagnoses.

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Conflicts of interest

The authors have no conflicts of interest to disclose in regards to this manuscript.

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