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Chryptochrome 2 Variants, Chronicity, and Seasonality of Mood Disorders

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Objectives

Chryptochrome 2 (CRY2) establishes day-night rhythms and has a common variant rs10838524 that has been linked with winter depression (Lavebratt, Sjoholm et al. 2010) and rapid cycling in bipolar disorder (Sjoholm, Backlund et al. 2010). We sought to determine the relationship between rs10838524 and chronicity and seasonality of illness in a small but well-characterized sample with mood disorders.

Methods

A total of 35 Caucasian individuals with major depression and bipolar disorder from the Collaborative Depression Study (CDS), followed for a mean (SD) of 26.8 (1.2) and up to 30 years were included based on proximity to Iowa City from a total of 59 active participants at two sites: Iowa City, IA and St. Louis, MO. This study was approved by the University of Iowa IRB.

During prior prospective follow-up in the CDS, participants completed the Longitudinal Interval Follow-up Evaluation, which categorized the weekly severity of affective psychopathology every 6 months for five years and then yearly (Keller, Lavori et al. 1987). From weekly ratings of symptoms, the proportion of weeks with clinically significant depressive symptoms was estimated using established methods (Fiedorowicz, Solomon et al. 2009) over the course of follow-up and by estimated calendar month.

Genotyping for the CRY2 SNP rs10838524 was done using Pyrosequencing technology (Marsh, King et al. 2005). Genetic material from one participant could not be reliably genotyped. Regression models (SAS; proc glm) determined if presence of the A allele was associated with a more chronic course with more winter symptoms. No other polymorphisms were tested for this seasonality hypothesis, however, the serotonin transporter polymorphism (5HTTLPR) and CACNA1C:rs1006737 were examined in

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relation to chronicity. Given our small sample, variants were selected based on prior results and common alleles.

Results

Participants had a mean (SD) age of 61 (8) years at assessment and spent 30% (27%) of CDS follow-up with clinically significant depressive symptoms. A slight majority (56%) carried a diagnosis of bipolar disorder and 82% were female. Allele frequencies were well-balanced: AA (24%), GA (50%), GG (26%) and did not vary by gender, age, presence of bipolar disorder, or likelihood of receiving antidepressants in any statistically or clinically meaningful fashion.

A dose response relationship between chronicity of depressive symptoms (percent of follow-up weeks with depression) and number of CRY2rs10838524 A alleles demonstrated a significant linear trend (t=2.43, df=2, p=0.02): GG (12.9%), GA (30.9%), and AA (43%). In multivariate models, this linear trend (t=2.10, df=2, p=0.045) was independent of gender (p=0.54) and diagnosis (bipolar II p=0.54, bipolar I p=0.01, unipolar=reference). The percent of time with clinically significant depressive symptoms in Dec/Jan compared to June/July was not significantly higher for those with higher A allele burden: GG (−0.1%), GA (1.9%), AA (3.1%). Chronicity was not related to serotonin transporter gene and CACNA1C:rs1006737 variants.

Conclusion

We found the *CRY2* rs10838524 A allele to be associated with greater chronicity of depressive symptoms in a well-characterized sample with mood disorders although were unable to establish a clear seasonal pattern. Replication of our findings in larger, well-characterized samples is warranted.

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