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Research report

A missense variant (P10L) of the melanopsin (*OPN4*) gene in seasonal affective disorder☆

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Abstract

Background: Melanopsin, a non-visual photopigment, may play a role in aberrant responses to low winter light levels in Seasonal Affective Disorder (SAD). We hypothesize that functional sequence variation in the melanopsin gene could contribute to increasing the light needed for normal functioning during winter in SAD.
Methods: Associations between alleles, genotypes, and haplotypes of melanopsin in SAD participants ($n=130$) were performed relative to controls with no history of psychopathology ($n=90$).
Results: SAD participants had a higher frequency of the homozygous minor genotype (T/T) for the missense variant rs2675703 (P10L) than controls, compared to the combined frequencies of C/C and C/T. Individuals with the T/T genotype were 5.6 times more likely to be in the SAD group than the control group, and all 7 (5%) of individuals with the T/T genotype at P10L were in the SAD group.
Limitations: The study examined only one molecular component of the non-visual light input pathway, and recruitment methods for the comparison groups differed.
Conclusion: These findings support the hypothesis that melanopsin variants may predispose some individuals to SAD. Characterizing the genetic basis for deficits in the non-visual light input pathway has the potential to define mechanisms underlying the pathological response to light in SAD, which may improve treatment.

Keywords: Melanopsin; Seasonal affective disorder; OPN4

☆ The opinions and assertions expressed herein are those of the authors and are not to be construed as expressing the views of the USUHS or the United States Department of Defense.

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1. Introduction

Seasonal affective disorder (SAD) is characterized by recurrent depressions in fall and winter (Rosenthal et al., 1984a). Aberrant responses to light in SAD are suggested by the seasonality of depressive episodes, the favorable antidepressant response to light therapy (Golden et al., 2005), and a lengthened melatonin release profile in winter (Wehr et al., 2001), and may be mediated by abnormal retinal phototransduction (Wehr et al., 1987).

Twin studies measuring seasonal variation in mood and behavior indicate that 29%–69% of seasonality is heritable (Jang et al., 1997; Madden et al., 1996). Most candidate gene studies for SAD have focused on the serotonin transporter (Johansson et al., 2001, 2003a; Rosenthal et al., 1998; Sher et al., 2000; Thierry et al., 2004; Willeit et al., 2003), the serotonin receptor 2A (Enoch et al., 1999; Johansson et al., 2001; Lee et al., 2006), the D4 dopamine receptor (Levitan et al., 2004a, b), and circadian clock genes (Johansson et al., 2003b; Paik et al., 2007; Partonen et al., 2007). Positive findings in these studies account for only a small proportion of the estimated heritability of SAD.

We hypothesize that the light input pathway that mediates non-visual responses to light may modulate the symptoms of SAD through genetic variations in molecular components of this pathway. A key signaling component of the human non-visual light input pathway, the photopigment melanopsin (Provencio et al., 2000, 2002; Rollag et al., 2003), is found in retinal ganglion cells projecting to non-visual centers of the brain including the suprachiasmatic nucleus (Hattar et al., 2006). Intrinsically photosensitive, melanopsin-containing retinal ganglion cells have been implicated in functions including circadian photoentrainment (Hattar et al., 2003; Panda et al., 2002, 2003; Ruby et al., 2002), negative masking (Mrosovsky and Hattar, 2003), and the pupillary light reflex (Hattar et al., 2003; Lucas et al., 2003; Panda et al., 2003). Although no data have yet linked melanopsin variations to human physiological responses to light, circadian photoentrainment, negative masking, and pupillary light reflex from mice suggest that melanopsin may be important in similar functions in humans.

A role for abberant phototransduction in SAD would be supported by evidence of diminished retinal sensitivity in patients with SAD. Research on whole-retina measurements of sensitivity in SAD have had mixed findings, some showing subsensitivity (Hebert et al., 2002; Lam et al., 1991; Ozaki et al., 1995), no difference in sensitivity (Murphy et al., 1993), or supersensitivity (Terman and Terman, 1999) in SAD patients compared to healthy controls. However, melanopsin-containing cells comprise only 2% of one type of cell in the retina, ganglion cells (Provencio et al., 2002). Therefore, deficits in the sensitivity of this one type of cell would not be observable in whole-retina measurements of sensitivity.

Each photoreceptor in the retina has a unique peak of the visible spectrum of light at which it is most sensitive. The wavelength of light that is optimal for inducing a specific biological response can help identify which photoreceptor is most important in conveying light information to the brain for that response. Melanopsin is maximally sensitive to blue light near 480 nm (Qiu et al., 2005), when expressed in human embryonic kidney cells. Melanopsin-containing ganglion cells in primates have nearly the same peak spectral sensitivity of 482 nm (Dacey et al., 2005). Meta-analysis findings indicate that green, blue, and yellow wavelengths of light and full-spectrum light yield larger treatment effects in SAD than red wavelengths of light (Lee et al., 1997), although the wavelengths of light used in these studies, emitted by fluorescent bulbs, is variable and includes peaks at multiple different wavelengths (Glickman et al., 2006). More recently, a study using narrow-bandwidth LEDs indicated that blue (468 nm) light is more effective in reducing symptoms of SAD than dim red (654 nm) light (Glickman et al., 2006), although it is still unknown how narrow-bandwidth blue light would compare to full-spectrum or white light, the standard in light therapy for SAD. Regardless, the similarity of the maximal sensitivity of melanopsin (480 nm) and light effective for treating SAD indicate that melanopsin may be involved in the mechanism of action of light therapy for SAD.

It is possible that sequence variations in the melanopsin gene may affect light input to the brain, increasing vulnerability to SAD. The present study uses a candidate gene approach to investigate the potential involvement of haplotypes in the melanopsin gene, in addition to specific single nucleotide polymorphisms (SNPs) that result in coding variants of the melanopsin protein.

2. Methods

SAD participants volunteered for SAD research at the National Institute of Mental Health in response to community advertising. Inclusion criteria for the SAD group included a mood disorder with seasonal pattern, and no history of other Axis I disorders established using the Structured Clinical Interview for DSM-III Axis I Disorders (SCID; Spitzer et al., 1990). Control participants were recruited from the NIH Healthy