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CRY1 and *CRY2* genetic variants in seasonality: A longitudinal and cross-sectional study

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ABSTRACT

Cryptochromes are key components of the circadian clocks that generate and maintain seasonal variations. The aim of our study was to analyze the associations of *CRY1* and *CRY2* genetic variants with the problematicity of seasonal variations, and whether the problematicity of seasonal variations changed during the follow-up of 11 years. Altogether 21 *CRY1* and 16 *CRY2* single-nucleotide polymorphisms (SNPs) were genotyped and analyzed in 5910 individuals from a Finnish nationwide population-based sample who had filled in the self-report on the seasonal variations in mood and behavior in the year 2000. In the year 2011, 3356 of these individuals filled in the same self-report on the seasonal variations in mood and behavior. Regression models were used to test whether any of the SNPs associated with the problematicity of seasonal variations or with a change in the problematicity from 2000 to 2011. In the longitudinal analysis, *CRY2* SNP rs61884508 was protective from worsening of problematicity of seasonal variations. In the cross-sectional analysis, *CRY2* SNP rs72902437 showed evidence of association with problematicity of seasonal variations, as did SNP rs1554338 (in the *MAPK8IP1* and downstream of *CRY2*).

1. Introduction

For the majority of the human population, there are fluctuations in mood and behavior across seasons (Kasper et al., 1989). Among individuals having mood disorder these seasonal variations tend to be pronounced (Wehr and Rosenthal, 1989). Seasonal variations characterize the clinical picture of those with the seasonal pattern or seasonal affective disorder (SAD) (Rosenthal et al., 1984b). The winter type of SAD is the most common form (Partonen and Lonnqvist, 1998; Patten et al., 2016). Earlier, we have shown that, of the Finnish general population aged 30 and over, 85% which corresponds to the estimated number of 2,766,037 inhabitants followed a seasonal pattern in mood and behaviors, 38.9% (1,266,531 inhabitants) experienced routine seasonal variations to the extent of threshold-level SAD, and 2.6% (85,615 inhabitants) suffered from these symptoms to the extent equal to SAD (Grimaldi et al., 2009).

Physiological functions and behaviors demonstrate daily and seasonal variations that are generated and maintained by the circadian clocks responding to stimuli from the habitat (Meijer et al., 2007). Within cells on molecular level, cryptochromes guide a range of functions of the circadian clocks (Lamia et al., 2011), and they are necessary for the development of intercellular networks in the master circadian clock in the cells of the suprachiasmatic nucleus (Ono et al., 2013) that produces synchronizing signals throughout the organism (Evans et al., 2015). Environmental light and ambient temperature of the external 24-hour cycle act together to dictate the phase and to entrain circadian clocks (Boothroyd et al., 2007), but the change of seasons tends to challenge their functions (Stoleru et al., 2007). Since most biochemical reactions respond robustly to temperature, it might have been used as the original, universal time-giver to the organism (Buhr et al., 2010), and the evolution of mechanisms to buffer the effects of day-to-day (or season-to-season) changes in ambient temperature expected to favor adaptation (Francois et al., 2012). Concerning day-active animals, transcription of the cryptochrome genes that are key components of the circadian clocks is induced in the evening (Lincoln et al., 2002), and the heat-induced phase shifts of the circadian clock are severely reduced in the cryptochrome loss-of-function mutants (Kaushik et al., 2007). Thus, the cryptochrome proteins regulate the temperature entrainability, and if this were to hold for mammals as well, including humans, then dysfunction of cryptochrome proteins may contribute to the seasonal variations in mood and behavior being experienced as a problem.

Dysfunction of the circadian clocks has been hypothesized to play a role in the etiology of mood disorders (Bunney and Potkin,

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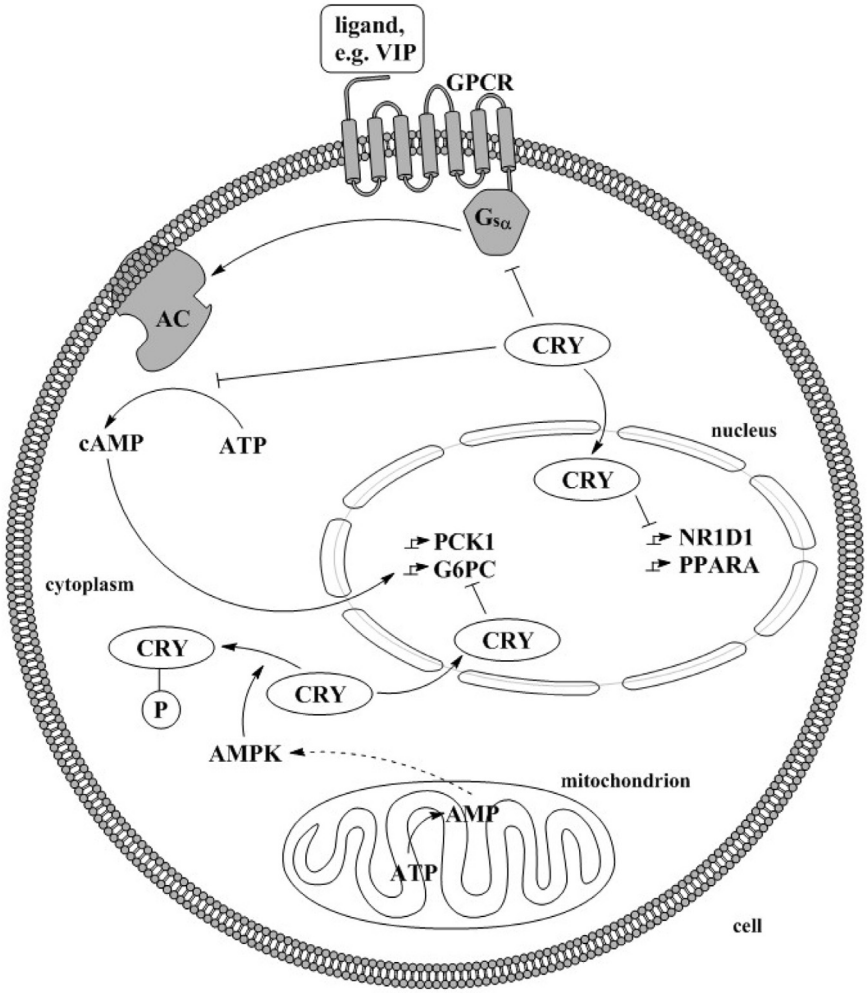

Fig. 1. Schematic of the key functions of cryptochromes in a cell. Cryptochromes (CRY2 and CRY1) are proteins that are repressors in the transcription-translation loops in the core of circadian clocks, and inhibitors of the cyclic adenosine monophosphate signal pathway. In the cytoplasm, CRY2 and CRY1 inhibit both the alpha-subunit of stimulatory guanosine-triphosphate-binding proteins coupled to transmembrane receptors and the activity of adenylyl cyclase. Adenylyl cyclase produces the second messenger cyclic adenosine monophosphate for intracellular signaling. In the nucleus, CRY2 and CRY1 repress the transcription of, e.g., *PCK1*, *G6PC*, *NR1D1* and *PPARA*. *PCK1* is a main control point for the regulation of gluconeogenesis, and *G6PC* encodes a key enzyme in glucose homeostasis. *NR1D1* encodes a ligand-sensitive transcription factor that negatively regulates the expression of core clock proteins, and *PPARA* encodes a key regulator of lipid metabolism for the peroxisomal beta-oxidation pathway of fatty acids and for the propagation of clock information to metabolic pathways. By these actions, CRY2 and CRY1 are involved in the functions of circadian clocks and in the metabolism of glucose and lipids, and they may contribute to mood regulation on daily basis as well as to seasonal variations in mood and behavior. Abbreviations: AC=adenylyl cyclase; AMP=adenosine monophosphate; AMPK=adenosine-monophosphate-activated protein kinase; ATP=adenosine triphosphate; cAMP=cyclic adenosine monophosphate; CRY=cryptochrome; GPCR=G protein–coupled receptor; G6PC=glucose-6-phosphatase, catalytic subunit; $G_{s\alpha}$=stimulatory guanosine-triphosphate-binding protein, alpha subunit; NR1D1=nuclear receptor subfamily 1, group D, member 1; P=phosphorus; PCK1=phosphoenolpyruvate carboxykinase 1 (soluble); PPARA=peroxisome proliferator-activated receptor alpha; VIP=vasointestinal peptide.

2008). Those genes which encode repressors of transcription are thought to be of key importance, since they are essential to the normal function of circadian clocks (Ukai-Tadenuma et al., 2011). Here, the cryptochrome circadian clock 2 (CRY2) and cryptochrome circadian clock 1 (CRY1) proteins are the key repressors in the core of the circadian clock (Dardente et al., 2007; Ozturk et al., 2007; Ye et al., 2011, 2014). However, CRY2 has a key role in balancing the expression of cryptochromes, as it not only acts as a general repressor, but also opposes in specific the actions of CRY1 and inhibits CRY1 from accessing to its targets too early (Anand et al., 2013). See Fig. 1 for a schematic of the key functions of cryptochromes in a cell.

CRY2 has been associated with depressive disorders (Lavebratt et al., 2010; Kovanen et al., 2013), bipolar disorders (Sjoholm et al., 2010), and greater chronicity of depressive symptoms in patients with major depressive or bipolar disorder (Fiedorowicz et al., 2012). On the other hand, *CRY1* has earlier been associated with depression (Soria et al., 2010; Hua et al., 2014) and nominally significant association has been observed with lithium treatment response for bipolar disorder (McCarthy et al., 2011). However, no association with bipolar disorder has been observed (Shi et al., 2008; Nievergelt et al., 2005). Thus, data from the very beginning to date are so far consistent with the hypothesis that CRY2 and CRY1 proteins modulate circadian and emotional responses, and therefore *CRY2* and *CRY1* are highly interesting and relevant target to study the seasonal variations in mood and behavior in humans. Here, we hypothesize that there is a variant of *CRY2* or *CRY1* which increases the odds for seasonal variations in mood and behavior being experienced as a problem.

Cryptochromes may be involved not only in regulation of mood and behavior, but also in that of metabolism of glucose, cholesterol and triglycerides. In a consortium meta-analysis of genome-wide association studies using the Homeostasis Model Assessment indices of insulin resistance and beta-cell function, the A-allele of *CRY2* SNP rs11605924 was found to associate with fasting glucose and beta-cell function, but not to play a major role in type