PER1 circadian gene functional polymorphism rs3027172 moderates risk for problematic alcohol use in the context of early life stress via negative urgency and ventral striatal reward reactivity

David A. Baranger1, Chloé Ifrah1, Ryan Bogdan1, Emily M. Drabant2, and Ahmad R. Hariri3

1. BRAINLab, Department of Psychology, Washington University in St. Louis, St. Louis, MO, USA; 2. 23andMe, Mountain View, CA, USA; 3. Laboratory of Neurogenetics, Department of Psychology & Neuroscience, Institute for Genome Sciences & Policy, Duke University, Durham, NC, USA

Background

• **PER1:**
  - Codes for the human Period 1 CLOCK gene. Expressed in the suprachiasmatic nucleus of the hypothalamus, as well as throughout peripheral tissues. Is integral to the establishment and maintenance of circadian rhythms.1
  - mPER1 knock-out mice: increased alcohol intake both with free-access and during social-defeat.3,4
  - Glucocorticoids: directly up-regulate PER1 expression via the Snai1 transcription factor.3,6
  - rs3027172: Located in the PER1 promoter region. The C allele reduces Snai1 affinity for the PER1 promoter region, thereby reducing glucocorticoid-driven expression four-fold.1 Has also been shown to predict increased incidence of adolescent alcohol abuse in the context of high early-life psychosocial adversity. Predicts increased risk of alcohol dependence in adults.3

• Ventral striatum (VS): critical for reward processing; decreased BOLD activation has been associated with addiction and MDD.8

• **Impulsivity:** Increased negative urgency impulsivity (tendency to act rashly when experiencing negative mood) is predictive of problematic drinking.2

• **Aims:**
  1. Replicate the previously-reported interaction between the risk (C) allele, early-life stress, and increased risk for alcohol abuse (Dong).
  2. Test for novel associations between rs3027172 and reward-related VS reactivity.
  3. Test whether reward-related VS reactivity and negative urgency impulsivity mediates the relationship between PER1 rs3027172 and risk for alcohol dependence.

Methods

• **Participants:** Undergraduates who completed the ongoing Duke Neurogenetics Study (DNS): reward-related ventral striatum: n = 338

• **Genetic Data:** rs3027172 was only available for a subset of participants (n=219). However, a close proxy, 3027160 was present for all 338 (R²=0.954, D′=1.00). This SNP was used for all analyses.

• **Statistical analyses:** Main effect of task were first isolated in SPM and extracted via bilateral ventral striatal ROIs. All further analyses were conducted in SPSS using these extracted values. Linear regression models with PER1 genotype, gender, and self-reported ethnicity as independent variables, and ventral striatum reactivity as the dependent variable. Following significant results, moderated regression analyses were conducted with the same models and CTQ a moderator. A factor analysis was used to generate a Negative Urgency Impulsivity Factor. A linear regression model with ventral striatum reactivity, gender, and self-reported ethnicity as independent variables, and the negatve urgency impulsivity factor as the independent variable was tested. Finally, a post-hoc mediation model with all variables was tested.

**Reward-related ventral striatum task:** n=338, A
Number-guessing paradigm with positive and negative feedback (Panel A).

Results

**Figure 1:** Early-life stress (CTQ) moderates the relationship between PER1 genotype (t=2.45, p=0.0145). The effect is significant at values CTQ>40 and at trend-level significance at 35<CTQ<40.

**Figure 2:** Early-life stress (CTQ) moderates the relationship between left ventral striatal reward reactivity and PER1 genotype (t=2.623, p=0.0091). The effect is significant at values CTQ>45 and at trend-level significance at 40<CTQ<45.

**Figure 3:** The reward task reliably activated the ventral striatum across participants.

**Figure 4:** Factor analysis was used to create a negative impulsivity factor from the NEO-Pi-R impulsiveness scale, the Barrat attentional impulsivity scale, and the Bicope coping with substance scale. The factor explained 55% of shared variance.

**Figure 5:** Schematic representation of the mediation model. Both the direct and full indirect paths are significant (BootLLCI= -0.0167; BootULCI= -0.0011; does not pass through zero).

**Figure 6:** Schematic representation of a mediation model. The direct path is only significant in PER1 minor allele carriers (BootLLCI= 0.0076; BootULCI= 0.0463) the indirect path is only significant in PER1 major homozygotes (BootLLCI= 0.00; BootULCI= 0.0058)

Conclusions

• Consistent with previous reports, **PER1** rs3027172 predicted risk for alcohol abuse, moderated by early life stress.

• As hypothesized, **PER1** rs3027172 predicted ventral striatal (VS) reward reactivity, moderated by early life stress, though in the opposite direction as hypothesized.

• As hypothesized, a post-hoc mediation model, with VS reward reactivity and negative urgency impulsivity, was significant.

• A further mediation model revealed that while minor allele carriers have increased reward reactivity, this effect does not appear to mediate increased negative urgency impulsivity and increased risk for problematic drinking.

• Circadian rhythms are critical, not only for the establishment and maintenance of sleeping patterns, but also for the regulation of homeostatic processes, such as body weight, temperature, and hormone production.5 The results of this study suggest that perturbing the system’s ability to properly adapt to the environment leads to an exaggerated stress-response over time, possibly causing individuals to self-medicate in times of stress.

• Further work will extend this study to other reward regions, such as the OFC, and will examine the effects of mutations in other circadian genes on this and other phenotypes, such as anhedonia.

Acknowledgements

We extend thanks to the participants of the Duke Neurogenetics Study, as well as to the researchers and staff at the Washington University BRAINLab and the Duke University Laboratory of NeuroGenetics.

References