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Strain Differences of Molecular Circadian Rhythms in Primary Fibroblasts Derived from Founders of Collaborative Cross and Diversity Outbred Mice

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Disruption of circadian rhythms is commonly observed in addiction and increases vulnerability to drug abuse. However, it still remains to be elucidated the specific genetic mechanisms underlying the link between circadian rhythms and addiction. Powerful tools for investigating the genetics of complex traits are the Collaborative Cross (CC) and Diversity Outbred (DO) mouse populations. The DO genome harbors more than 45 million unique polymorphisms and allelic combinations providing expansive genetic and phenotypic variation, which enables high-precision genetic analyses. High-throughput cell-based screening of circadian rhythms in these mouse populations may be valuable for discovering potential genetic variants influencing molecular clock. Therefore, we used primary fibroblasts from the founders of CC and DO mice composed of 5 inbred (A/J, C57BL/6J, 129S1/SvlmJ, NOD/ShiLtJ and NZO/HiLtJ) and 3 wild-derived strains (CAST/EiJ, PWK/PhJ and WSB/EiJ) to identify variations in circadian phenotypes that associate with addiction-related traits. Following transfection with *Bmal1-dLuc* reporters, their rhythms were compared among strains. In comparison with C57BL/6J, the period of *Bmal1-dLuc* rhythms was significantly shorter in 129S1/SvlmJ, WSB/EiJ and CAST/EiJ in females and CAST/EiJ in males, but significantly longer in A/J, NOD/ShiLtJ and PWK/PhJ in males. Moreover, we also observed that the amplitude of *the* rhythms was significantly higher in 129S1/SvlmJ and WSB/EiJ in both females and males relative to C57BL/6J. These circadian phenotypes were consistent across cohorts. Heritability estimates were 65% for the period and 91% for the amplitude, indicating that circadian parameters were attributed to strains. Interestingly, these circadian parameters were correlated with addiction-related behaviors in cocaine self-administration.