We have conducted a rigorous observational research study in suspected delayed sleep-wake phase disorder (DSWPD) patients. The objective was to measure sleep-wake patterns and to conduct exploratory genetic analyses to delineate the genetic landscape of the DSWPD phenotype.

We measured the sleep-wake patterns (self-reported bed time, wake time, midpoint of sleep, and sleep latency) of participants by daily post-sleep diaries for 10 weeks. Participants completed questionnaires on demographics, medical and surgical history, sleep history, and concomitant medications. Altogether, 119 participants were consented and 76 participants provided samples for whole genome sequencing. Seventy-eight participants were females and the mean age was 44 years.

Principal component analysis defined ancestry as 29.3% AFR, 17.3% AMR, and 53.4% EUR.

We observed a significant enrichment of the minisatellite 54bp (1: 7829913-7829966 (GRCh38)) variable number of tandem repeat (VNTR) PER3 rs57875989 4 allele. We observed significantly higher frequencies of the 4/4 variant, 59.2% when compared to the super control population frequency of 42.2% (n = 315; recessive: OR 1.9, CI 1.07 to 3.65, p = 0.03). This variant is of particular interest as it is located in the coding region of VNTR (exon 18). Functionally, PER3 is phosphorylated by casein kinase 1 (CK1) and translocates to the nucleus to inhibit CLOCK/BMAL1 in the presence of PER1. The VNTR motif contains clusters of potential phosphorylation sites for CK1. Given the VNTR PER3 variant could change protein phosphorylation levels in addition to tertiary protein structure and also have interactions with binding partners, it is hypothesized that the VNTR would cause functional changes in PER3. The observed accumulation of the PER3 VNTR 4/4 supports prior literature describing evening-types and DSWPD patients as having greater frequencies of PER3 4/4 homozygotes; this effect can be as high as 75% homozygotes in DSWPD.

These results demonstrate that, on average, DSWPD individuals are more likely to harbor variants within their core clock genes with particular enrichment of the VNTR variant, potentially leading to a pronounced delay in sleep period. This variant can further impact the response to treatment across carriers of the 4/4.