INTRODUCTION

- Persistent posttraumatic stress symptoms (PTSS) are common after motor vehicle collision (MVC) and major thermal burn injury (MTHB).

**Previous literature suggests that alterations in circadian rhythm (CR) signaling influence PTSS vulnerability. For example, blunted rhythmicity of sleep/wake cycle indicators and core circadian rhythm genes/gene regulators (e.g., RORA, CLOCK, and TEF) have been shown to predict PTSS severity.**

**Previously literature also suggests that CR pathway influence depends on stress severity and/or vulnerability.** A well-studied genetic factor contributing to stress vulnerability is FKBPs rs3800373 allele.

HYPOTHESES

- Genetic variants in CR pathway genes predict PTSS severity following MVC and MTHB.

- The influences of CR genes on PTSS depends on level of individual periatomic distress and individual FKBPs rs3800373 allele.

METHODS

**African American men and women ≥18 and ≤65 years of age presenting to one of 13 different emergency department (EDs) within 24 hours of MVC who did not have a serious fracture or other injury requiring hospital admission were enrolled (n = 967). This MVC cohort served as the discovery cohort. For the replication cohort, African American and European American men and women ≥18 and ≤61 years of age were enrolled after MTHB (n = 68). DNA samples were (PAxGene) collected in the immediate aftermath of trauma. PTSS was assessed using the Impact of Events Scale Revised (IES-R, MVC cohort) or Post-traumatic Stress Symptom Interview (PSSI, MTHB cohort) 6 weeks, 6 months, and 1 year following trauma.**

**Periatomic distress was assessed using the Periatomic Distress Inventory (PDI). Samples were genotyped using the MEGA platform (Illumina). Repeated measure mixed modeling adjusted for age, sex, study site, and time following trauma was used to evaluate associations between PTSS severity following MVC and 31 common genetic across 9 CR-pathway genes (PER3, NPAS2, PER2, CLOCK, RORB, BMAL1, TIMELESS, RORA, and TEF). Potential SNP sex, SNP*distress, and SNP*PKBPS SNP interactions were also evaluated. To account for multiple comparisons, we adjusted p values using the False Discovery Rate. RNA samples (RNA PAXgene tubes) were collected in the ED. To evaluate influence of TEF variant on gene expression, total RNA was library prepared using Ovation Human Blood RNA-Seq Library System kit (NuGen) and sequenced on a HiSeq 2500. Raw sequencing reads were aligned to hg19 using STAR, quantified using RSEM, and normalized to the overall upper quartile. RNA*SNP*PKBPS interactions were assessed using linear regression models adjusted for age, sex, and study site.**

**TABLE 1. Study participant characteristics.**

**TABLE 2. Five genetic variants from four circadian rhythm-associated genes predict posttraumatic stress symptom (PTSS) severity following motor vehicle collision.**

**FIGURE 1. The core circadian rhythm pathway.**

**FIGURE 2. TEF SNP rs5758324 interacts with stress to predict PTSS severity following MVC. This finding replicated in a second cohort of individuals experiencing major thermal burn injury (MTHB).**

**FIGURE 3. Association between SNPs in the TEF genomic region and PTSS severity following MVC.**

**FIGURE 4. Among individuals with high distress in the early aftermath of MVC who may develop substantial PTSS severity, TEF mRNA expression levels are lower in individuals with the rs5758324 major allele and higher in individuals with the rs575832 minor allele.**

**FIGURE 5. SNP rs5758324 is located in Intron 2 of the TEF gene.**

**REFERENCES**


