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SHANK3 Puts Autism to Sleep

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Editor's Choice Summary

Issue date: (we will complete)
DOI: 10.1126/scitranslmed.axyXXXX (we will complete)
Volume: (we will complete)
E-locator: (we will complete)

Overline: Autism Spectrum Disorder

Title: *SHANK3* Puts Autism to Sleep

One-sentence summary: Mutation in the autism gene *SHANK3* leads to sleep problems in mice and humans.

Your name: Emily K. Osterweil

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Text of summary

Disruptions in social communication and language are well-known symptoms of Autism Spectrum Disorders (ASD), however the sleep difficulties plaguing up to 80% of patients are less appreciated. These sleep disturbances are significantly detrimental to patients and caregivers, and often correspond to a worsening of behavioral problems.

Not much is known about the cause of disrupted sleep in ASD. To investigate this issue, Ingiosi et al. examined sleep patterns in humans and mice with mutations in *SHANK3*, a high-confidence autism gene associated with the neurodevelopmental disorder Phelan-McDermid Syndrome (PMS). Using records from the PMS International Registry (PMSIR), the authors verify a significant increase in sleep problems in patients with *SHANK3* mutations versus typically developing controls. To examine the mechanisms linking *SHANK3* deficiency to altered sleep, the authors performed a series of behavioral experiments using the *Shank3^{ΔC}* mutant mouse model. The results show that *Shank3^{ΔC}* mutants not only sleep less, they take longer to fall asleep after being deprived. This corresponds to a deficit in electroencephalographic (EEG) spectra associated with deep Rapid Eye Movement (REM) sleep. When kept in the dark *Shank3^{ΔC}* mutants showed an unusual decline in wheel running that became more disorganized over time, a behaviour that indicates alteration of circadian rhythms.

In order to see whether there were changes in gene expression that might provide clues, the authors performed RNA sequencing on prefrontal cortex isolated from sleep-deprived *Shank3^{ΔC}* mutant versus WT mice. This revealed changes in genes involved in the MAP kinase (MAPK) signaling pathway and transcription factors that regulate circadian rhythms. The important suggestion here is that there is an identifiable molecular basis for the observed sleep disturbances. Now researchers can perform mechanistic experiments to identify which molecular pathways can be therapeutically targeted to alleviate disrupted sleep in *Shank3^{ΔC}* mutants, and potentially other models of ASD.

More studies will be needed to confirm the changes seen in the *Shank3^{ΔC}* mouse model, and further sleep studies in PMS patients will be important for validating the translational potential for patients. However, the insights here are an important step towards understanding the nature of disrupted sleep in ASD.

Highlighted Article

Ingiosi AM, Schoch H, Wintler T, Singletary KG, Righelli D, Roser LG, Medina E, Risso D, Frank MG, Peixoto L. **Shank3** modulates **sleep** and expression of circadian transcription factors. *Elife*. 8. pii: e42819. doi: 10.7554/eLife.42819 (2019).

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