Scientists make progress in decoding genetics of insomnia

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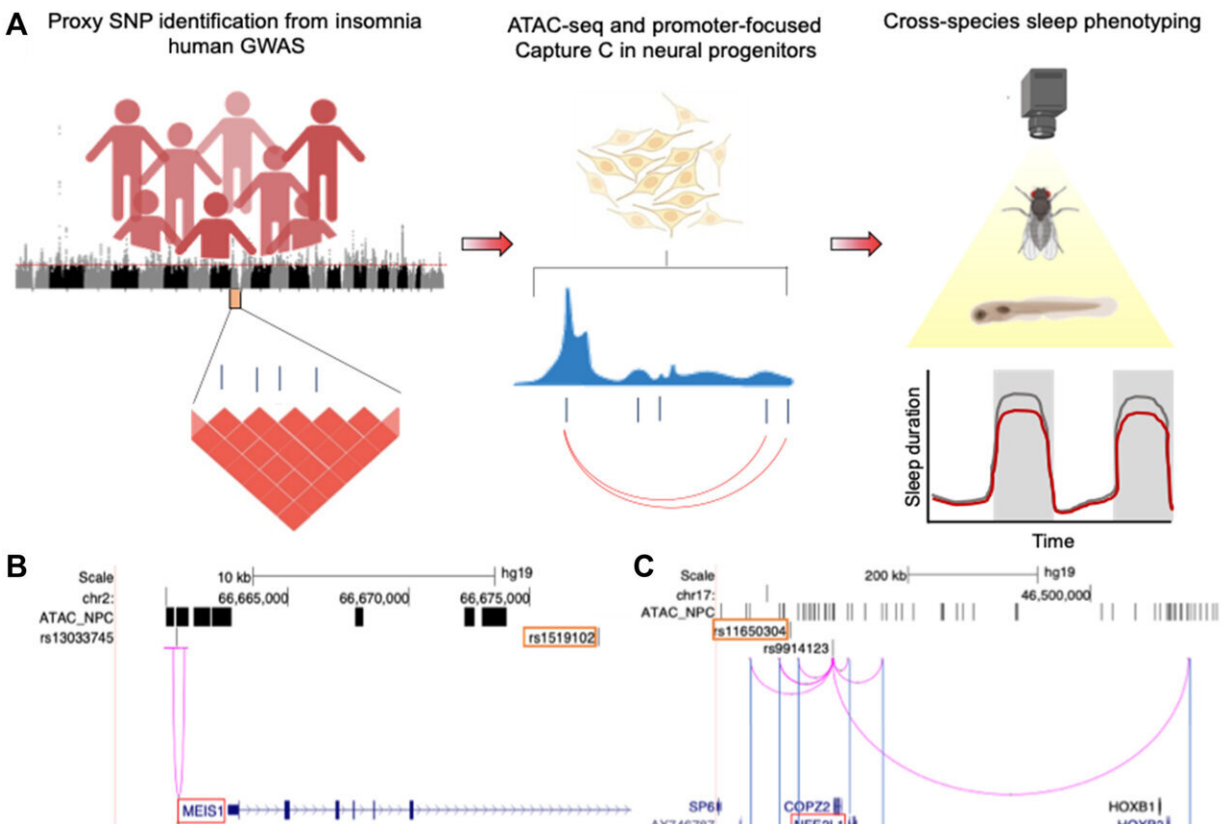

Translating human GWAS signals to functional outcomes with variant-to-gene mapping. (A) Leveraging existing insomnia human GWAS loci, we identified proxy SNPs in strong linkage disequilibrium with sentinel SNPs using both genome-wide ATAC-seq and high-resolution promoter-focused Capture C data from iPSC-derived NPCs and then performed high-throughput sleep and activity screening using Drosophila RNAi lines with confirmation in a vertebrate zebrafish (Danio rerio) model. (B to D) Three examples of chromatin loops linking insomnia associate SNPs to candidate effector genes in NPCs. (B)

rs13033745 [coefficient of determination (r^2) with sentinel SNP rs1519102 = 0.84] loops to the MEIS1 promoter region. (C) rs9914123 (r^2 with sentinel SNP rs11650304 = 0.76) loops to the promoters of SP2, PRR15L, CDK5RAP3, NFE2L1, CBX1, and HOXB3 in a ~700-kb region. (D) rs3752495, rs8062685, and rs9932282 (r^2 with sentinel SNP rs3184470 = ~1) loop to the promoters of PIG-Q, NHLRC4, and NME4. Orange box, sentinel SNP. Black bars, open chromatin peaks from ATAC-seq. Magenta arcs, chromatin loops from promoter-focused Capture C. Neuronal enhancer and promoter tracks are from. Credit: *Science Advances* (2023). DOI: 10.1126/sciadv.abq0844

A research effort involving researchers from Texas A&M University, the Perelman School of Medicine at the University of Pennsylvania and Children's Hospital of Philadelphia (CHOP) has used human genomics to identify a new genetic pathway involved in regulating sleep from fruit flies to humans—a novel insight that could pave the way for new treatments for insomnia and other sleep-related disorders.

Texas A&M geneticist and evolutionary biologist Alex Keene collaborated with Penn's Allan Pack and Philip Gehrman and CHOP's Struan Grant on the groundbreaking research, which is published in *Science Advances*.

"There have been enormous amounts of effort to use human genomic studies to find sleep genes," Keene said. "Some studies have hundreds of thousands of individuals. But validation and testing in animal models is critical to understanding function. We have achieved this here, largely because we each bring a different area of expertise that allowed for this collaboration's ultimate effectiveness."

Keene says the most exciting thing about the team's work is that they developed a pipeline starting not with a model organism, but with actual human genomics data.

"There is an abundance of human genome-wide association studies (GWAS) that identify genetic variants associated with sleep in humans," Keene said. "However, validating them has been an enormous challenge. Our team used a genomics approach called variant-to-gene mapping to predict the genes impacted by each genetic variant. Then we screened the effect of these genes in fruit flies.

"Our studies found that mutations in the gene Pig-Q, which is required for the biosynthesis of a modifier of protein function, increased sleep. We then tested this in a vertebrate model, zebrafish, and found a similar effect. Therefore, in humans, flies and zebrafish, Pig-Q is associated with sleep regulation."

Keene says the team's next step is to study the role of a common protein modification, GPI-anchor biosynthesis, on sleep regulation. In addition, he notes that the human-to-fruit flies-to-zebrafish pipeline the team developed will allow them to functionally assess not only sleep genes but also other traits commonly studied using human GWAS, including neurodegeneration, aging and memory.

"Understanding how genes regulate sleep and the role of this pathway in sleep regulation can help unlock future findings on sleep and sleep disorders, such as insomnia," said Gehrman, an associate professor of clinical psychology in psychiatry at Penn and a clinical psychologist with the Penn Chronobiology and Sleep Institute. "Moving forward, we will continue to use and study this system to identify more genes regulating sleep, which could point in the direction of new treatments for sleep disorders."

Keene's research within his Center for Biological Clocks Research-affiliated laboratory lies at the intersection of evolution and neuroscience, with primary focus on understanding the neural mechanisms and evolutionary underpinnings of sleep, memory formation

and other behavioral functions in fly and fish models. Specifically, he studies fruit flies (Drosophila melanogaster) and Mexican cavefish that have lost both their eyesight and ability to sleep with the goal of identifying the genetic basis of behavioral choices which factor into human disease, including obesity, diabetes and heart disease.

More information: Justin Palermo et al, Variant-to-gene-mapping followed by cross-species genetic screening identifies GPI-anchor biosynthesis as novel regulator of sleep, *Science Advances* (2023). DOI: 10.1126/sciadv.abq0844. www.science.org/doi/10.1126/sciadv.abq0844

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