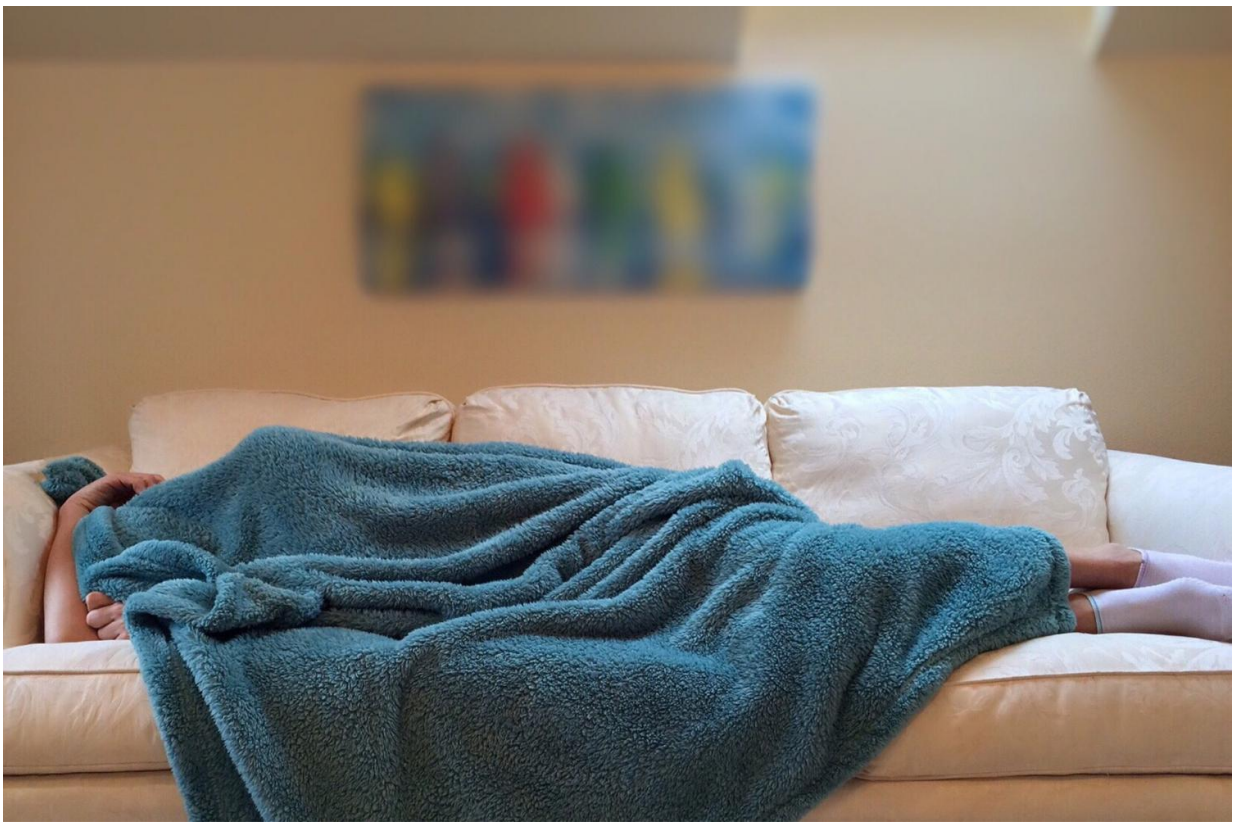
Shared genetic links between sleep and neuropsychiatric conditions may lead to new treatments

June 4 2024



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Disturbed sleep is very common in almost all neuropsychiatric and neurodevelopmental conditions (NDPCs), such as autism, attention

deficit and hyperactivity disorder, schizophrenia, and bipolar disorder.

While it is understandable that the symptoms of such conditions would lead to sleep disruption and also that sleep disruption would worsen symptoms in these conditions, Irish researchers have now found new genetic associations between some of these conditions and chronotype, the behavioral manifestations of an individual's circadian rhythm ("night owl" or "early bird)".

These findings may point the way to the development of new therapies for patients.

Presenting the results of the study to the annual conference of the European Society of Human Genetics, Dr. Laura Fahey, a postdoctoral researcher in the Family Genomics Research Group, Maynooth University, Republic of Ireland, says that sleep disturbances are known to predate the onset of major depressive disorder and bipolar disorder, and that polygenic score analysis can identity whether these conditions and sleep traits share genetic variation.

The researchers therefore used polygenic risk score analysis on large-scale genetic studies of NDPCs to test their ability to predict chronotype and insomnia in over 409,000 participants in the UK Biobank.

Their findings strengthen known genetic correlation results in that they show that polygenic scores for autism and schizophrenia are associated with an evening chronotype, while polygenic scores for attention-deficit/hyperactivity disorder, schizophrenia, and bipolar disorder are associated with insomnia.

"We also identified novel associations between bipolar disorder and chronotype, as well as insomnia and autism," says Dr. Fahey. "These are interesting insights into the genetic basis of sleep disruption, and may

open new research avenues for the treatment of sleep and circadian rhythm disturbances in these patients."

"The finding that shared genetic variation between bipolar disorder and chronotype was enriched (overrepresented) in a pathway called NRF2-KEAP1 was interesting to us, as the NRF2 pathway was previously linked to the pathology of bipolar disorder and schizophrenia. Additionally, NRF2 has previously been shown to be rhythmically regulated by circadian clock genes.

"However, it was surprising that there was no enrichment of shared genetic variation in any biological pathway for the other sleep-NDPC phenotype pairs investigated. This was particularly surprising for ADHD and insomnia, as we found these two phenotypes to have the strongest genome-wide correlation.

"A reason for this could be that the shared genetic variation is highly polygenic, affecting all biological pathways somewhat equally. It could also be that this shared genetic variation is enriched in cell- or tissue-specific pathways, which we did not explore," Dr. Fahey says.

The researchers also intend to test polygenic scores from more diverse populations, the UK Biobank data used in their study being on individuals of white British ancestry.

"We need to know whether this work can be applied to other population groups, since we hope that our work may contribute to the development of predictive and preventive interventions in the future," says Dr. Fahey.

Further research could also investigate the impact of the genetic variation found in the biological pathways identified by the scientists as influencing circadian rhythm; for example, whether there are specific subsets of patients with these changes where it would be useful to look

for differences in gene expression.

"However, the next stage of my research project will take a broader perspective and aim to better understand the genetic architecture using different methods and investigating both rare and common genetic variations underlying sleep and circadian rhythm disturbances in NDPCs," Dr. Fahey says.

Professor Alexandre Reymond, from the Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland, and chair of the conference, said, "It is interesting to see that perturbations of the same molecular pathways are associated with distinct phenotypes (bipolar disorder/schizophrenia and chronotype), a phenomenon called pleiotropy. It is tantalizing to think that, if we are in presence of 'direct pleiotropy' where one trait influences the other trait, we may have some hints about possible treatments."

More information: Abstract no. C30: Shared genetic links between sleep, neurodevelopmental, and neuropsychiatric conditions: a genome-wide and pathway-based polygenic score analysis

Provided by European Society of Human Genetics

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