Researchers identify genetic variations linked to oxygen drops during sleep

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Researchers have identified 57 genetic variations of a gene strongly associated with declines in blood oxygen levels during sleep. Low oxygen levels during sleep are a clinical indicator of the severity of sleep

apnea, a disorder that increases the risk of heart disease, dementia, and death. The study, published today in the *American Journal of Human Genetics*, was funded by the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health.

"A person's average blood oxygen levels during sleep are hereditary, and relatively easy to measure," said study author Susan Redline, M.D., senior physician in the Division of Sleep and Circadian Disorders at Brigham and Women's Hospital, and professor at Harvard Medical School. "Studying the genetic basis of this trait can help explain why some people are more susceptible to sleep disordered breathing and its related morbidities."

When we sleep, the oxygen level in our blood drops, due to interruptions in breathing. Lung and sleep disorders tend to decrease those levels further, and dangerously so. But the range of those levels during sleep varies widely between individuals and, researchers suspect, is greatly influenced by genetics.

Despite the key role blood oxygen levels play in health outcomes, the influence of genetics on their variability remains understudied. The current findings contribute to a better understanding, particularly because researchers looked at overnight measurements of oxygen levels. Those provide more variability than daytime levels due to the stresses associated with disordered breathing occurring during sleep.

The researchers analyzed whole genome sequence data from the NHLBI's Trans-Omics for Precision Medicine (TOPMed) program. To strengthen the data, they incorporated results of family-based linkage analysis, a method for mapping genes that carry hereditary traits to their location in the genome. The method uses data from families with several members affected by a particular disorder.

"This study highlights the advantage of using family data in searching for rare variants, which is often missed in genome-wide association studies," said James Kiley, Ph.D., director of the Division of Lung Diseases at NHLBI. "It showed that, when guided by family linkage data, whole genome sequence analysis can identify rare variants that signal disease risks, even with a small sample. In this case, the initial discovery was done with fewer than 500 samples."

The newly identified 57 variants of the DLC1 gene were clearly associated with the fluctuation in oxygen levels during sleep. In fact, they explained almost 1% of the variability in the oxygen levels in European Americans, which is relatively high for complex genetic phenotypes, or traits, that are influenced by myriad variants.

Notably, 51 of the 57 genetic variants "influence and regulate human lung fibroblast cells, a type of cell producing scar tissue in the lungs," said study author Xiaofeng Zhu, Ph.D., professor at the Case Western Reserve University School of Medicine. This is important, he said, because "Mendelian Randomization analysis, a statistical approach for testing causal relationship between an exposure and an outcome, shows a potential causal relationship between how the DLC1 gene modifies fibroblasts cells and the changes in oxygen levels during sleep."

This relationship, Kiley added, suggests that a shared molecular pathway, or a common mechanism, may be influencing a person's susceptibility to the lack of oxygen caused by sleep disordered breathing and other lung illnesses such as emphysema.

More information: Jingjing Liang et al, Sequencing Analysis at 8p23 Identifies Multiple Rare Variants in DLC1 Associated with Sleep-Related Oxyhemoglobin Saturation Level, *The American Journal of Human Genetics* (2019). DOI: 10.1016/j.ajhg.2019.10.002

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