Histone protein influences both neurological disorder and cancer

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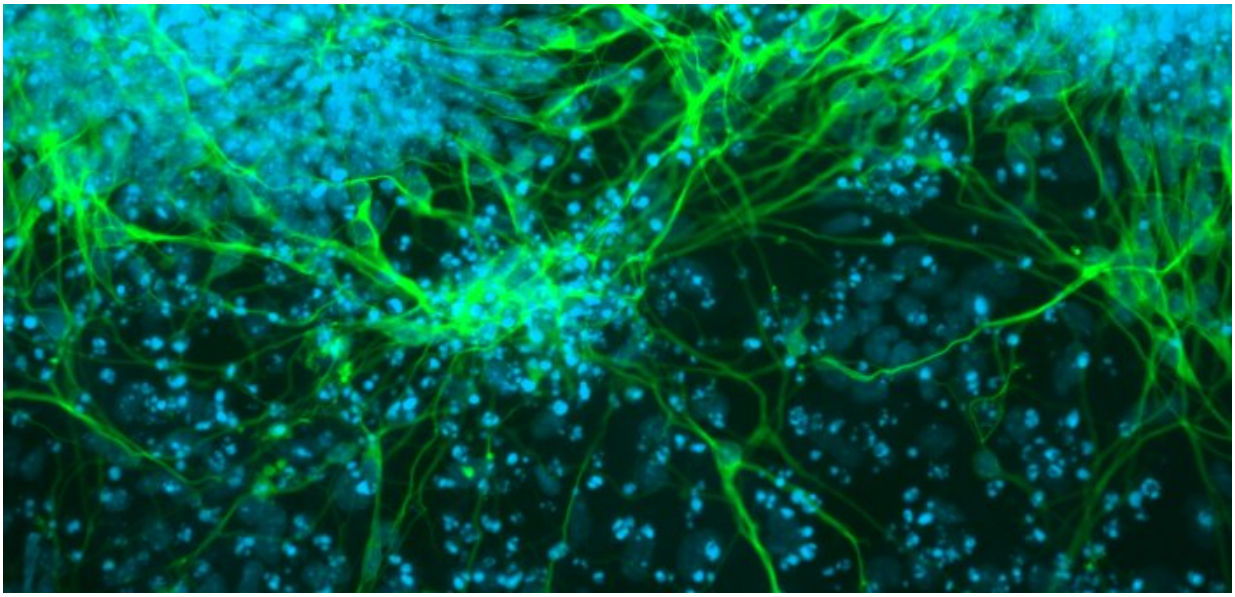

Mutations in a histone regulator protein are linked to both a rare neurodevelopmental disorder and to some cancers, according to a study published in the journal Genes and Development. The protein, PHIP/BRWD2, binds to three different histone modifications that are associated with active gene expression, which explains it's two-sided impact, according to Marc Morgan, DPhil, research assistant professor of Biochemistry and Molecular Genetics and lead author of the study. Credit: Northwestern University

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The protein, PHIP/BRWD2, binds to three different histone modifications that are associated with active gene expression, which explains it's two-sided impact, according to Marc Morgan, DPhil, research assistant professor of Biochemistry and Molecular Genetics and lead author of the study.

"If you have too little of this protein, it leads to a neurodevelopmental disorder called Chung-Jansen syndrome, but too much of this protein has been linked to cancer cell proliferation," Morgan said.

"This is a superb discovery by Dr. Morgan, which not only identified a groundbreaking mechanism for chromatin interactions, but also could have major implications for the treatment of neurodevelopmental disorders and cancers," said Ali Shilatifard, Ph.D., the Robert Francis Furchgott Professor, chair of Biochemistry and Molecular Genetics, a professor of Pediatrics, director of the Simpson Querrey Institute for Epigenetics, a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University and senior author of the study.

Histones—the protein spools around which DNA is looped—often have modifications which can influence gene expression. The combination of DNA loops and histone spools are referred to as nucleosomes and gene-promoting modifications of nucleosomes increase gene expression, while gene silencers reduce expression.

Mutations in the gene that codes for PHIP/BRWD2 have been linked to both neurodevelopmental disorders and cancers, but the specific mechanisms underlying these associations were previously unknown, according to Morgan.

In collaboration with Michael Keogh, Ph.D., chief scientific officer of

Epicypher, the investigators screened dozens of synthetic nucleosomes with specific modifications for an interaction with PHIP/BRWD2, essentially introducing PHIP into an array of purified nucleosomes and seeing with which PHIP actually bound. The study showed that three histone modifications—all associated with cell proliferation—were bound by PHIP.

Next, the investigators examined actual cells, using ChIP-sequencing to analyze protein interactions with DNA. They found that PHIP/BRWD2 interacted with locations where the same three histone modifications exist.

"This is one of the first demonstrations of a simultaneous and cooperative triple-binding domain," Morgan said.

What happens after this interaction is less clear, however. PHIP/BRWD2 binds to these sites and recruits another complex called CRL4, but how that complex affects cell proliferation, both in the cases of too much and too little PHIP, remains unknown.

However, these findings open up new avenues of research, both for this specific pathway and for other histone-protein-related neurodevelopmental disorders.

"PHIP-associated Chung-Jansen syndrome appears to be fairly rare, but as diagnostic human genome sequencing becomes more widespread, new patients are being identified," Morgan said. "Overall, mutations of histone regulator proteins are the cause of a large number of neurodevelopmental disorders. It's possible that some of these syndromes are affecting similar pathways, and if there are pathways in common, we might be able to design a therapy. The first step towards that goal is to understand the underlying molecular biology in precise detail."

More information: Marc A.J. Morgan et al, A trivalent nucleosome interaction by PHIP/BRWD2 is disrupted in neurodevelopmental disorders and cancer, *Genes & Development* (2021). DOI: 10.1101/gad.348766.121