Variations in gene DHX9 underlie wide spectrum of human neurodevelopmental disorders and neuropathy

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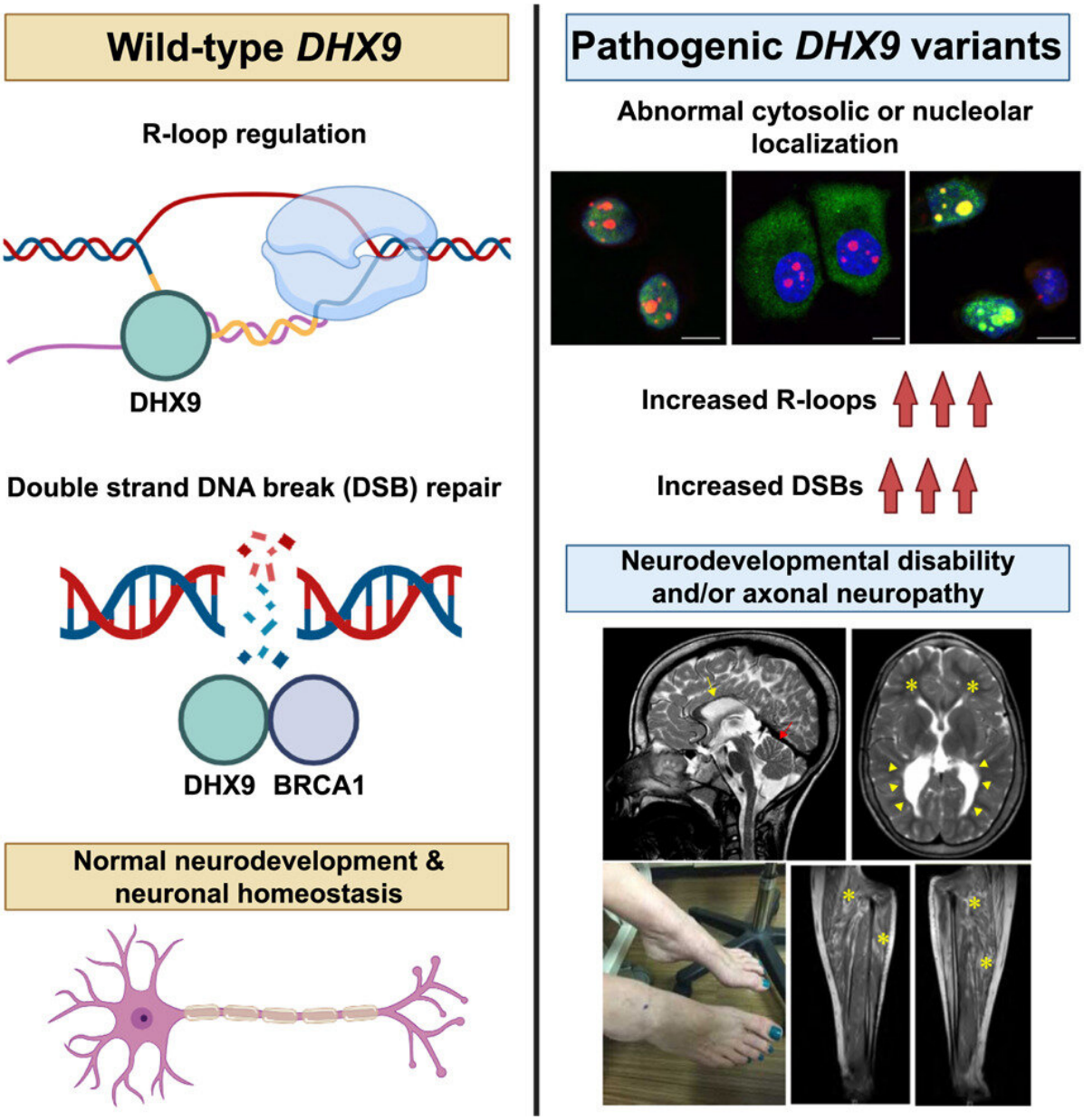

Graphical abstract. Credit: *The American Journal of Human Genetics* (2023). DOI: 10.1016/j.ajhg.2023.06.013

A group of 20 patients with undiagnosed neurodevelopmental disorders ranging from severe to mild has now received a genetic diagnosis thanks to an international team of researchers at the GREGoR Research Center at Baylor College of Medicine, the Chinese University of Hong Kong, the German Mouse Clinic and collaborating institutions.

The team analyzed the patients' genes and conducted family studies to detect genetic mutations related to their condition. They discovered that the patients had mutations of the gene DHX9, which disrupted the gene's normal function. This is the first time that this gene has been associated with a human disease. Studies in animal models showed a connection between defective variations of the gene and neurodevelopmental problems.

Altogether, the findings support that those variations of DHX9 underlie human neurodevelopment disorders and neuropathy. The study appears in *The American Journal of Human Genetics.*

"Our study started with two patients with remarkably different neurologic conditions for which they did not have a diagnosis despite extensive testing. Looking to find an answer to explain their condition, the patients joined our working group studying the genetic underpinnings or genomics of rare diseases," said first author Dr. Daniel Calame, instructor of pediatric neurology and developmental neurosciences and part of the GREGoR Research Center at Baylor.

"In the beginning, we did not have any reason to believe that these patients had a genetic diagnosis in common. It was after we analyzed the results of their genome sequencing that we realized that each had a distinct unusual variant of gene DHX9. This motivated us to expand our efforts to find more cases, ultimately the 20 we came upon."

One of the surprising aspects of this study is that the patients' conditions are remarkably diverse.

"Some patients have the most severe developmental disorders, including intellectual disability, seizures and movement disorders. Other patients have less severe conditions, for instance autism with normal IQ, while other patients have milder conditions—normal development but nerve degeneration leading to neuropathy, a condition typically causing numbness or weakness in adolescence or adulthood," Calame explained.

To begin to understand how variations in gene DHX9 can disturb neurodevelopment in such a variety of ways, the researchers conducted laboratory experiments in which the different DHX9 variants found in patients were introduced into cells and their functions compared to that of the DHX9 variant not associated with a condition.

"These cellular studies allowed us to distinguish quite clearly the functional alterations in the variants in the severe cases from those associated with the less severe or the mildest cases," said co-corresponding author Dr. Shen Gu, assistant professor in the School of Biomedical Sciences at the Chinese University of Hong Kong.

For instance, some variants associated with severe neurodevelopmental disorders were not located in the cell nucleus where the normal variant is typically located, but outside the nucleus in the surrounding cytoplasm.

"Another variant linked to severe neurodevelopmental disorders did not

affect DHX9 localization but instead increased double-stranded DNA breaks, a process that negatively affects the integrity of the DNA and can disrupt the normal function of the cell," Shen said.

In addition to cellular studies, the researchers explored the effect of eliminating the Dhx9 gene in animal models. "Without the Dhx9 gene, the animals were less active in new environments and had a reduced sense of hearing, indicating a connection between the gene and neural functions," Shen said. "Our study shows DHX9 is involved in regulating mammalian neurodevelopment and neuronal well-being."

"This is an amazing story of international collaborative science, the global nature of human genetics research and the insights that can be gleaned by the study of neurological disease from a gene and genomic variation viewpoint—and achievements possible by the joining of scientific forces from two of my favorite cities: Hong Kong and Houston," said Dr. James R. Luski, the Cullen Foundation Endowed Chair in Molecular Genetics, professor of pediatrics and molecular and human genetics and member of the Dan L Duncan Comprehensive Cancer Center at Baylor. Lupski also is co-corresponding author of this work and a principal investigator at GREGoR Research Center.

More information: Daniel G. Calame et al, Monoallelic variation in DHX9, the gene encoding the DExH-box helicase DHX9, underlies neurodevelopment disorders and Charcot-Marie-Tooth disease, *The American Journal of Human Genetics* (2023). DOI: 10.1016/j.ajhg.2023.06.013

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