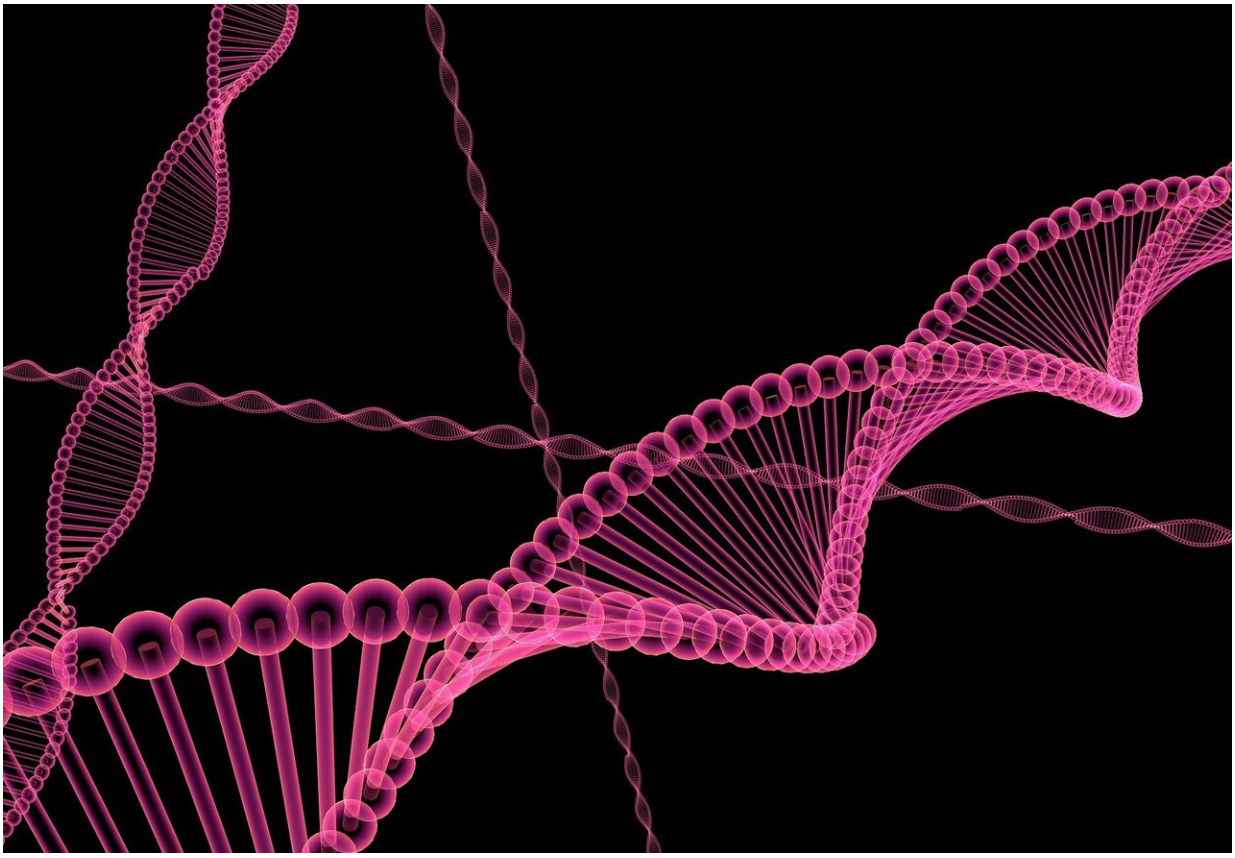
Gene mutation found to cause macrocephaly and intellectual deficits

November 13 2018, by Ellen Goldbaum



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The absence of one copy of a single gene in the brain causes a rare, as-yet-unnamed neurological disorder, according to new research that builds on decades of work by a University at Buffalo biochemist and his

colleagues.

First authors on the paper are Ina Schanze, Ph.D., from the Institute of Human Genetics at University Hospital Magdeburg and Jens Bunt, Ph.D., of the Queensland Brain Institute of the University of Queensland, Australia.

Co-author Richard M. Gronostajski, Ph.D., is a professor of biochemistry in the Jacobs School of Medicine and Biomedical Sciences at UB, director of its Genetics, Genomics and Bioinformatics Graduate Program and a researcher at UB's New York State Center of Excellence in Bioinformatics and Life Sciences. He has been studying the family of nuclear factor I (NFI) proteins, which play important roles in the differentiation of stem cells in the brain.

So far, the absence of some of the proteins has been found to cause several rare diseases from birth and could be implicated in autism spectrum disorder and bipolar disorder.

The new paper, published Nov. 1 in the *American Journal of Human Genetics*, reports for the first time that intellectual disability and macrocephaly, enlargement of the brain, are associated with the absence of nuclear factor I B (NFIB) in humans.

"This paper shows that a single point mutation in NFIB is responsible for these clinical characteristics, including mild intellectual disability, lack of muscle tone, speech delay, attention deficit disorder and other behavioral abnormalities, as well as macrocephaly," said Gronostajski.

The syndrome is extremely rare, having been identified in only 18 individuals so far worldwide.

Suspecting an important role

Gronostajski first became interested in the NFI protein in the 1980s because it was the first human site-specific DNA-binding protein shown to play a role in the replication of viral DNA in human cells. At the time, little was known about how viral or human DNA replication was regulated by host genes.

"Once we discovered that the protein was actually part of a gene family and that these genes were only present in multicellular eukaryotes, not bacterial, plant or single celled eukaryotes, I suspected that they would play an important role in animal and human development," Gronostajski said. "This turned out to be the case."

Gronostajski is responsible for developing the first genetically modified mice that were missing these proteins. Since 1999, his work has helped illuminate how mutations of NFIA, NFIX and, now, NFIB, affect physical and cognitive development.

Previous work

In 1999, while at Case Western Reserve University and the Lerner Research Institute at the Cleveland Clinic, Gronostajski and his colleagues discovered that mice lacking NFIA had severe brain abnormalities, including hydrocephalus and the complete or partial absence of the corpus callosum, the largest anatomical tract in the brain.

In 2007, human patients were discovered with a similar phenotype as the mouse model, which included callosum agenesis (the complete absence of this brain region) and hydrocephalus. Surprisingly, renal problems also were discovered in these patients, and similar defects were then found in the mouse model.

In 2008, Gronostajski co-authored another paper demonstrating that

NFIX is required for normal hippocampus development in the brain. Subsequent studies from his and collaborators' laboratories showed that NFIX is essential for normal neural stem cell, cerebellum and skeletal muscle development. These studies led to the discovery in 2010 that mutations of NFIX in humans result in the severe developmental disorders Malan syndrome and Marshall-Smith syndrome, each of which causes severe intellectual delays and aberrant muscle function.

Missing connection

While the syndrome caused by the NFIB mutation is extremely rare, Gronostajski said that the mutation may be clinically present in other types of intellectual and behavioral disabilities.

"Until you start looking for it, you don't know the frequency," he said.

The mouse model lacking NFIB that was developed by Gronostajski and colleagues has defects in the corpus callosum, a large anatomical tract that connects the right and left sides of the brain. Without it, he explained, certain activities can't be coordinated between two sides of the brain, resulting in intellectual issues, such as impairment of abstract reasoning and problem-solving abilities.

Some affected individuals were identified through the Global Alliance for Genomics & Health, an international organization through which researchers and clinicians share data about diseases and possible genomic causes. Gronostajski is hopeful that as more work is done with the mouse models where the NFI genes are deleted, therapies will be developed that aid patients with mutations in NFI genes.

More information: Ina Schanze et al. NFIB Haploinsufficiency Is Associated with Intellectual Disability and Macrocephaly, *The American Journal of Human Genetics* (2018). DOI: 10.1016/j.ajhg.2018.10.006

Provided by University at Buffalo