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Gene responsible for three forms of childhood neurodegenerative diseases found

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A Montreal-led international team has identified the mutated gene responsible for three forms of leukodystrophies, a group of childhood-onset neurodegenerative disorders. Mutations in this gene were identified in individuals from around the world but one mutation occurs more frequently in French-Canadian patients from Quebec. Published in the September issue of the *American Journal of Human Genetics* and selected for the Editors' Corner of the journal, the findings are crucial to the development of diagnostic tests and genetic counseling for families, and provide insights into a new mechanism for these disorders of the brain.

Currently, there are no cures for leukodystrophies which are a group of inherited neurodegenerative disorders affecting preferentially the white matter of the brain. White matter serves to cover nerve cell projections called axons, allowing nerve impulses to be correctly transmitted. Many children with a leukodystrophy appear normal at birth with very little or no indication that they have the disorder. Symptoms such as walking difficulties, falls or tremor gradually appear. As they grow older they lose mobility, speech and develop swallowing difficulties, and as teenagers are often wheelchair bound or bed ridden. The majority of patients die prematurely. The evolution and symptoms vary according to the specific type of leukodystrophy. It is estimated that at least 30-40% of individuals with a leukodystrophy remain without a precise diagnosis despite extensive investigations.

The study identified the first mutations in the POLR3A gene in families

from Quebec. Mutations in the same gene were found in patients from the USA, Syria, Guatemala, France, and other European countries. The international team was led by Drs Bernard Brais and Geneviève Bernard and included scientists from Montreal, Washington D.C., Dallas, Beirut, Paris, Clermont-Ferrand, and Bordeaux. The group was able to demonstrate that mutations in the same POLR3A gene localized on chromosome 10 were responsible for three clinically different forms of leukodystrophies: Tremor-Ataxia with Central Hypomyelination (TACH) first described in Quebec cases, Leukodystrophy with Oligodontia (LO), and 4H syndrome or Hypomyelination, Hypodontia and Hypogonadotropic Hypogonadism syndrome.

"We identified many different mutations in the POLR3A gene which codes for a key subunit of RNA Polymerase III (Pol III), a highly conserved protein complex with a crucial role in gene expression, and many other important pathways," explains Dr. Brais. "This finding is surprising considering the fundamental role of Pol III. It is also an encouraging discovery because if we can identify which targets of Pol III, when decreased, lead to the disease, we could develop therapeutic strategies to replace them." The research was conducted in the laboratory of Dr Brais at the Centre de recherche du Centre hospitalier de l'Université de Montréal (CRCHUM). Dr. Brais is now a clinician-scientist at The Montreal Neurological Institute and Hospital, The Neuro at McGill University, and Dr. Geneviève Bernard has recently been recruited as a clinician-researcher at The Montreal Children's Hospital, McGill University Health Centre.

Provided by McGill University