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Protecting against aging at the molecular level

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Research from Western University and Lawson Health Research Institute sheds new light on a gene called ATRX and its function in the brain and pituitary. Children born with ATRX syndrome have cognitive defects and developmental abnormalities. ATRX mutations have also been linked to brain tumors. Dr. Nathalie Bérubé, PhD, and her colleagues found mice developed without the ATRX gene had problems in in the forebrain, the part of the brain associated with learning and memory, and in the anterior pituitary which has a direct effect on body growth and metabolism. The mice, unexpectedly, also displayed shortened lifespan, cataracts, heart enlargement, reduced bone density, hypoglycemia; in short, many of the symptoms associated with aging. The research is published in the *Journal of Clinical Investigation*.

Ashley Watson, a PhD candidate working in the Bérubé lab and the first author on the paper, discovered the loss of ATRX caused DNA damage especially at the ends of chromosomes which are called telomeres. She investigated further and discovered the damage is due to problems during DNA replication, which is required before the onset of cell division. Basically, the ATRX protein was needed to help replicate the telomere.

Working with Frank Beier of the Department of Physiology and Pharmacology at Western's Schulich School of Medicine & Dentistry, the researchers made another discovery. "Mice that developed without ATRX were small at birth and failed to thrive, and when we looked at the skeleton of these mice, we found very low bone mineralization. This

is another feature found in mouse models of premature aging," says Bérubé, an associate professor in the Departments of Biochemistry and Paediatrics at Schulich Medicine & Dentistry, and a scientist in the Molecular Genetics Program at the Children's Health Research Institute within Lawson. "We found the loss of ATRX increases DNA damage locally in the forebrain and anterior pituitary, resulting in systemic defects similar to those seen in aging."

The researchers say the lack of ATRX in the anterior pituitary caused problems with the thyroid, resulting in low levels of a hormone called insulin-like growth factor-one (IGF-1) in the blood. There are theories that low IGF-1 can deplete stores of stem cells in the body, and Bérubé says that's one of the explanations for the premature aging. This research was funded by the Canadian Institutes of Health Research.

More information: Atrx deficiency induces telomere dysfunction, endocrine defects, and reduced lifespan, *J Clin Invest.* doi:10.1172/JCI65634

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