Genes causing pediatric glaucoma contribute to future stroke

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(Edmonton, AB) Every year in Canada about 50,000 people suffer from a stroke, caused either by the interruption of blood flow or uncontrolled bleeding in the brain. While many environmental risk factors exist, including high blood pressure and smoking, stroke risk is also frequently inherited. Unfortunately, remarkably little is known regarding stroke's genetic basis.

A study from the University of Alberta, published in the *Journal of Clinical Investigation*, extends knowledge of stroke's genetic underpinnings and demonstrates that in some cases it originates in infancy.

The research identifies two genes (FOXC1 and PITX2) that cause cerebral small vessel disease, a "pre-stroke" condition that increases the risk of future stroke up to ten times. It was found the mutations result in cerebral small vessel disease in patients as young as one year of age. By inhibiting these genes in lab models, the researchers induced comparable brain vascular changes and gained key insights into the mechanisms involved.

The two genes are known to cause a type of pediatric glaucoma by affecting the normal migration of vital stem cells to the eye. These same stem cells also play a pivotal role in the formation of brain blood vessels, forming the smooth muscle in artery walls that is essential for structural integrity. A reduction in the number of these cells impairs vascular stability, and leads to cerebral small vessel disease. This in turn

substantially increases the long term risk of stroke.

By demonstrating for the first time that a proportion of stroke has a developmental basis, the research has identified a very wide timeframe (five decades or more) between the onset of cerebral small vessel disease and a stroke occurring. This discovery provides ample opportunity for therapeutic intervention—currently with improved blood pressure control, statins, etc.—and the expectation that the findings will stimulate research to develop treatments targeting potential solutions.

Equally, the findings may provide novel insights in eye disease where the research originated. Some patients with pediatric glaucoma caused by the genes FOXC1 and PITX2 suffer gradual visual deterioration despite excellent surgical control of intraocular pressure. It has always been assumed that ongoing damage to the eye was responsible. However, the identification of extensive brain vascular changes provides an alternative explanation, and is expected to influence clinical management for these patients.

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