Gene's newly explained effect on height may change tumor disorder treatment

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A mutation that causes a childhood tumor syndrome also impairs growth hormone secretion, researchers at Washington University School of Medicine in St. Louis have found.

The discovery provides new insights into an old mystery, revealing why patients with neurofibromatosis type 1 are frequently shorter than their peers. The surprising details have led scientists to consider modifying their search for treatments for the inherited disorder, which is caused by a mutation in the neurofibromin 1 (NF1) gene and is characterized by an increased risk of cancer.

"We've learned that the NF1 gene affects stature through a different pathway than the one we've previously focused on to understand cancers in patients with neurofibromatosis type 1," says Washington University neurologist David H. Gutmann, M.D., Ph.D., a Washington University neurologist who treats individuals with neurofibromatosis at St. Louis Children's Hospital. "Given that this second pathway has been linked to cancer in other contexts, we may need to consider the possibility that it is contributing to these tumors and alter our treatment goals accordingly."

The results appear online in the journal *Human Molecular Genetics*.

Neurofibromatosis 1 affects more than 100,000 people in the United States and is one of the most common tumor predisposition syndromes. The severity of the condition varies.

The NF1 protein, called neurofibromin, influences a number of different growth control pathways. Until now, much research focused on neurofibromin's effects on RAS protein activity, which is linked to cell growth, proliferation and cancer. Normally, NF1 deactivates RAS proteins. In its absence, scientists believe unchecked RAS can promote cancer development.

To learn more, Gutmann's lab created a line of mice in which stem cells in the brain do not make the NF1 protein. They found that these mice were significantly smaller than normal and failed to grow and gain weight after birth.

Balazs Hegedus, Ph.D., a postdoctoral researcher in Gutmann's laboratory, noticed that the pituitary glands, which produce growth hormone, also were unusually small in these mice. The amount of a second hormone that triggers growth hormone release was also greatly reduced.

"We wanted to know if we could blame this on RAS protein activity, so we generated new mice with normal levels of neurofibromin expression, but increased levels of RAS activation in brain stem cells," says Gutmann, the Donald O. Schnuck Family Professor of Neurology, and director of Washington University Neurofibromatosis Center. "However, those mice were normal."

NF1 also increases brain levels of cyclic AMP (cAMP), an important signaling molecule. Working with the same line of mice where stem cells in the brain do not make the NF1 protein, researchers fed pregnant mice and their newborns an agent that increased cAMP levels. The baby mice were closer to normal size, even though they still lacked neurofibromin in brain stem cells. Gutmann suspects the mice didn't completely return to normal because dietary supplementation of cAMP levels cannot match the natural ability of neurofibromin to control cAMP levels.

Gutmann is intrigued by the connection to cAMP. Research in other disorders has begun to build a number of associations between cAMP and tumor formation. Gutmann's laboratory and others have treatments in the works for neurofibromatosis 1 that restore the inhibitory effect neurofibromin normally has on RAS, but the new results may mean treatments are also needed to restore neurofibromin's effects on cAMP levels.

"What we've learned also may help us gain insight into other disease processes," Gutmann notes. "There are a number of other rare genetic abnormalities that cause short stature, and this same pathway may be involved."

To follow up, Gutmann plans additional studies to explore the role of the NF1 gene in the pituitary gland and the hypothalamus, a brain region that controls pituitary gland production of growth hormone.

Source: Washington University