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Finding may aid diagnosis of learning disabilities linked to brain tumor syndrome

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New insight into one of the most common inherited causes of brain tumors may help physicians diagnose and treat the learning disabilities that often accompany the condition.

Studying patients' skin samples and novel strains of mice, researchers at Washington University School of Medicine in St. Louis found that genetic mutations that cause neurofibromatosis 1 (NF1) can have varying effects on levels of dopamine, a signaling molecule in the brain associated with learning and attention. Some mutations dramatically decreased dopamine levels, while others had little to no effect on dopamine.

"The surprising findings, made using patient-derived skin cells, have changed the way we think about how NF1 mutations cause learning problems," said senior author David H. Gutmann, MD, PhD, the Donald O. Schnuck Family Professor of Neurology. "This may help us identify which patients are most likely to benefit from approved medications that increase dopamine levels in the brain, such as Ritalin."

The findings are available online in *Human Molecular Genetics*.

Scientists estimate that NF1 affects one in every 2,500 people. Although rarely fatal, it is among the most common inherited pediatric brain cancer syndromes. Over half of all NF1 patients also have significant learning and attention problems.

NF1 is caused by mutations in the gene that makes a protein called neurofibromin. In studies using brain nerve cells generated from NF1 patient skin cell-derived stem cells, Gutmann and his colleagues found that different NF1 gene mutations caused these nerve cells to produce either slightly reduced levels of neurofibromin or dramatically lower neurofibromin levels. Importantly, the amount of neurofibromin correlated with the levels of dopamine.

"Although the specific NF1-causing mutations varied among the patients, there was no middle ground—they either had near-normal levels of dopamine or more than 75 percent reductions in dopamine," Gutmann said.

The scientists then generated mice to mimic these differences in neurofibromin levels. One group had dramatically reduced levels of the protein in dopamine-producing nerve cells, while the other had only slightly reduced levels.

Testing showed that only mice with the lowest neurofibromin levels had memory problems. In contrast, those with more mild decreases in neurofibromin performed as well as control mice.

The mice with the lowest levels of neurofibromin also had the greatest reductions in dopamine compared with the mice with more neurofibromin.

"We were surprised to find that not all NF1 mutations have the same effects on the brain," Gutmann said. "We're working with colleagues to see if we can develop a blood test to help us predict learning disabilities in patients with NF1. We hope that this will lead to improved ways to diagnose and treat children with these cognitive challenges."

More information: "Elucidating the impact of neurofibromatosis-1

germline mutations on neurofibromin function and dopamine-based learning." *Human Molecular Genetics*, June 15, 2015 DOI: 10.1093/hmg/ddv103