

# Autism gene study finds widespread impact to brain's growth signaling network

April 8 2021



Neuroscientist Damon Page, PhD, has identified a new mechanism underlying brain undergrowth seen in individuals with Dyrk1a mutations, linked to autism. Graduate student Jenna Levy is the study's first author. Credit: Scripps Research

Damage to the autism-associated gene Dyrk1a, sets off a cascade of



problems in developing mouse brains, resulting in abnormal growthfactor signaling, undergrowth of neurons, smaller-than-average brain size, and, eventually, autism-like behaviors, a new study from Scripps Research, Florida, finds.

The study from neuroscientist Damon Page, Ph.D., describes a new mechanism underlying the <u>brain</u> undergrowth seen in individuals with Dyrk1a mutations. Page's team used those insights to target the affected pathway with an existing medicine, a growth hormone. It restored normal brain growth in the Dyrk1a mutant mice, Page says.

"As of now, there's simply no targeted treatments available for individuals with <u>autism spectrum disorders</u> caused by DYRK1A mutations," Page says. "This represents a first step in evaluating a potential treatment that could be used in the clinic."

Their study appears Thursday in the journal Biological Psychiatry.

To track the effects of missing Dyrk1a genes, Jenna Levy, the paper's first author and a graduate student in Page's lab, engineered mice to have one or two broken copies of Dyrk1a in their developing brain tissue. The brains of both sets of mice developed abnormally, she found, displaying decreased brain size and number of neurons, as well as reduced number of other brain cells.

## **Downstream effects**

The scientists also conducted "unbiased" proteomic studies, to see if the mutant mice had abnormally high or low levels of other unknown proteins that might impact brain development. Using a technique called "high-resolution tandem mass spectrometry coupled to liquid chromatography," they found that the Dyrk1a <u>mutant mice</u> had reduced levels of 56 cellular proteins, and increased levels of 33. Many of those



were known <u>autism</u> risk genes, some implicated in sending growth signals, Levy says.

"The specific signaling cascades we found altered in Dyrk1a mutants are implicated in multiple causal mechanisms of autism," Levy says.

A computational biology technique called Ingenuity Pathway Analysis helped them find altered proteins. There were changes to those involved in nerve signaling, creation of synapses, and growth of axons, the long, insulated extensions that give neurons their distinct shape. Also, multiple forms of the protein Tau were depleted in the Dyrk1a mice.

"These data implicate signaling cascades that were previously not known to be altered by Dyrk1a mutations," Page says.

#### Many autism genes

At least 200 different high-confidence risk genes for autism spectrum disorders have been identified, Page says, but little has been known about their roles and relationships, complicating diagnosis and treatment development efforts.





A side-by-side look at the brains of a normal newborn mouse and one lacking the autism and intellectual disability risk gene Dyrk1a. Mice without the gene display profound microcephaly, along with undergrowth of pyramidal neurons in the cerebral cortex. Credit: Image courtesy of the Page laboratory at Scripps Research

Page estimates that fewer than 1 percent of people diagnosed with autism spectrum disorder carry Dyrk1a mutations. Half of those show autistic behavioral traits, and about 70 percent have short stature. But many more people with autism diagnoses display microcephaly, or smaller-than-average head circumference, around 1 in 20, he says.

"Importantly for treatment considerations, this study suggests there may be a point of convergence for multiple autism causes," Page says. "Abnormal activity of this pathway appears to be shared across various genetic causes of autism, pointing to the possibility of common molecular target for therapeutics."



Previously, Page's lab has found autism-linked mutations to a gene called Pten can cause an opposite effect, brain overgrowth, or macrocephaly.

"What we didn't know before is that the signaling disruptions that cause microcephaly, brain undergrowth, appear to be the flip side of the coin of the signaling disruptions that cause macrocephaly, brain overgrowth," Page says.

Because of that, they hypothesized that restoring growth signaling at a high level, using a known growth hormone, might rescue the brain undergrowth.

"We thought that treating with insulin-like growth factor 1, IGF-1, should increase the activity of the downstream signaling cascade, which should result in increased growth," Levy says. After treating Dyrk1a mice from birth to day 7, she found that was the case. The observed microcephaly improved, and under the microscope, the brain tissue showed normalized neuron growth.

### **Toward targeted treatments**

Based on those results, more investigation is warranted on the potential for <u>growth hormone</u> treatment to benefit a minority of children with autism, those with Dyrk1a mutations, or related downstream mutations and manifestations, including microcephaly, Page says.

Many questions remain. Whether IGF-1 treatment in the newborn Dyrk1a mice might also improve autism-like behaviors in the mice is still under investigation, Levy adds. Also, it's still unclear whether there is a critical treatment window during mouse brain development, and if so, how large that window may be.

In humans, neural progenitor cells begin forming in the third week of



pregnancy. By the seventh week, actual neuron production starts. It's a short window—neuron production in the billions is mostly finished by around the 20th week of gestation. As neurons are made, each migrates to its final destination in the forming brain. Once there, it starts making connections with other neurons, elongating and branching out, literally wiring the developing brain. Rapid brain development continues with experience and growth after birth.

Autism is a constellation of disorders with multiple causes, meaning that targeted, individualized treatments will be needed to assist people who seek them, Page says. Prevalence of autism diagnoses has been rising steeply since the 1990s. Research from the U.S. Centers for Disease Control and Prevention now estimates 1 in 59 children have an autism spectrum disorder. The mutations to Dyrk1a that cause autism appear to be sporadic, meaning they aren't typically inherited, but rather appear randomly, Page says.

Page stresses that the study is preliminary, not grounds for off-label use of IGF-1 as a possible autism treatment. He's often asked by families what they can do for their children diagnosed with autism. He suggests asking their doctor for a genetic testing as a first step.

"It helps with understanding of what's going on, it allows them to connect and find support, and also to be aware if clinical trials begin," Page says. "It's too soon for affected families to go to their pediatrician and say, 'Give my child this.' This is a first step in evaluating whether a potential treatment could be used in the clinic."

**More information:** Jenna A. Levy et al, Dyrk1a Mutations Cause Undergrowth of Cortical Pyramidal Neurons via Dysregulated Growth Factor Signaling, *Biological Psychiatry* (2021). <u>DOI:</u> <u>10.1016/j.biopsych.2021.01.012</u>



#### Provided by The Scripps Research Institute

Citation: Autism gene study finds widespread impact to brain's growth signaling network (2021, April 8) retrieved 7 May 2024 from <u>https://medicalxpress.com/news/2021-04-autism-gene-widespread-impact-brain.html</u>

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