Multiple genes implicated in autism

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(PhysOrg.com) -- By pinpointing two genes that cause autism-like symptoms in mice, researchers at MIT's Picower Institute for Learning and Memory have shown for the first time that multiple, interacting genetic risk factors may influence the severity of autistic symptoms.

The study, reported in the Feb. 9 advance online edition of the *Proceedings of the National Academy of Sciences (PNAS)*, lends support to researchers' long-suspected belief that in individuals whose autism is genetic in origin, more than one gene is implicated.

The work could lead to drugs targeting signaling mechanisms between the two interacting genes responsible for some autism spectrum disorders (ASDs) symptoms. The molecular intersection of the two genes' pathways in the brain may also serve as a diagnostic target or biomarker for a subset of individuals with ASDs.

"We found that two genetic risk factors for ASDs act cooperatively in mice to influence brain size and social behavior, both of which are altered in ASDs," said Damon T. Page, a Picower Institute postdoctoral fellow and lead investigator of the study.

Approximately 24 percent of humans with autism have macrocephaly — head circumference above the 98th percentile — and increased brain size. Studies in ASDs patients have shown that brain size is correlated with the severity of behavioral problems.

Individuals with ASDs show deficits in social interaction, impaired

communication and repetitive behaviors. According to the Centers for Disease Control, ASDs are the second most common serious developmental disability after mental retardation.

“Our results provide evidence that the severity of autistic symptoms may be the product of variations in DNA in multiple locations in the genome,” Page added.

“An important implication is that because the majority of instances of autism appear to involve multiple genes, specific gene combinations may worsen effects. New therapeutics may one day be developed that influence particular signaling mechanisms in the disorder,” said Mriganka Sur, the Newton Professor of Neuroscience and head of the MIT Department of Brain and Cognitive Sciences.

Page and colleagues found that mice carrying mutations in two different candidate autism susceptibility genes have more severe symptoms than those with only a single mutation.

The researchers studied the effects on mouse brain development and behavior of mutations in the PTEN gene, which encodes the phosphatase and tensin homolog protein, and the serotonin transporter gene.

Double whammy of symptoms

The researchers found that mice with a mutation in PTEN alone or in the serotonin transporter gene alone had brains that were larger than normal, while mice with simultaneous mutations in PTEN and serotonin transporter genes had even larger brains.

In female mice, a mutation in PTEN impaired sociability, while those that also had a mutation in serotonin transporter had worse symptoms.

The authors concluded that interaction between the two genes influences brain growth and sociability in mice, noting that mutations in serotonin transporter may be one of multiple risk factors that could modify the severity of autistic symptoms in individuals who previously developed mutations in PTEN. Future work will be aimed at characterizing how genetic, environmental and pharmacological manipulations impact these animals' autism-related traits.

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