Study identifies gene expression abnormalities in autism

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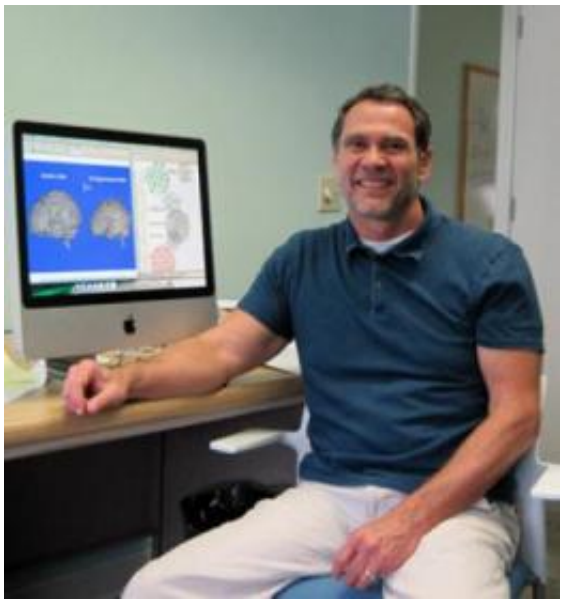

This is Eric Courchesne, Ph.D., of the UC San Diego Autism Center for Excellence. Credit: UC San Diego School of Medicine

A study led by Eric Courchesne, PhD, director of the Autism Center of Excellence at the University of California, San Diego School of Medicine has, for the first time, identified in young autism patients genetic mechanisms involved in abnormal early brain development and overgrowth that occurs in the disorder. The findings suggest novel genetic and molecular targets that could lead to discoveries of new prevention strategies and treatment for the disorder.

The study to be published on March 22 in PLoS Genetics uncovered differences in gene expression between brain tissue from young (2 to14 years old) and adult individuals with autism syndrome disorder, providing important clues why brain growth and development is abnormal in this disorder.

Courchesne first identified the link between early brain overgrowth and autism in a landmark study published by the Journal of the American Medical Association (JAMA) in 2003. Next, he tested the possibility that brain overgrowth might result from an abnormal excess of brain cells. In November 2011, his study, also published in JAMA, discovered a 67 percent excess of brain cells in a major region of the brain, the prefrontal cortex - a part of the brain associated with social, communication and cognitive development.

"Our next step was to see whether there might be abnormalities of genetic functioning in that same region that might give us insight into why there are too many cells and why that specific region does not develop normally in autism," said Courchesne.

In the new study, the researchers looked towards genes for answers, and showed that genetic mechanisms that normally regulate the number of cortical neurons are abnormal. "The genes that control the number of brain cells did not have the normal functional expression, and the level of gene expression that governs the pattern of neural organization across the prefrontal cortex is turned down. There are abnormal numbers and patterns of brain cells, and subsequently the pattern is disturbed," Courchesne said. "This probably leads to too many brain cells in some locations, such as prefrontal cortex, but perhaps too few in other regions of cortex as well."

In addition, the scientists discovered a turning down of the genetic mechanisms responsible for detecting DNA defects and correcting or removing affected cells during periods of rapid prenatal development.

Autism is a highly heritable neurodevelopmental disorder, yet the genetic underpinnings in the brain at young ages have remained largely unknown. Until now, few studies have been able to investigate whole-genome gene expression and genotype variation in the brains of young patients

with autism, especially in regions such as the prefrontal cortex that display the greatest growth abnormality.

Scientists - including co-first authors Maggie Chow, PhD, and Tiziano Pramparo, PhD, at UC San Diego - identified abnormal brain gene expression patterns using whole-genome analysis of mRNA levels and copy number variations from 33 autistic and control postmortem brain samples. They found evidence of dysregulation in the pathways that govern cell number, cortical patterning and cell differentiation in the young autistic prefrontal cortex. In contrast, in adult patients with autism, the study found that this area of the brain shows dysregulation of signaling and repair pathways.

"Our results indicate that gene expression abnormalities change across the lifespan in autism, and that dysregulated processes in the developing brain of autistic patients differ from those detected at adult ages," said Courchesne. "The dysregulated genetic pathways we found at young ages in autism may underlie the excess of neurons - and early brain overgrowth - associated with this disorder."

Provided by University of California - San Diego

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