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Perturbed Genes Regulating White Blood Cells Linked to Autism Genetics and Severity

Degree of dysregulation in gene network correlated to severity of autism symptoms in male toddlers

Researchers at University of California San Diego School of Medicine say they are getting closer to identifying the mechanisms of autism spectrum disorder (ASD) and biomarkers that can aid in early diagnosis and predictions of symptom severity.

A team of scientists analyzed blood gene expression data from 302 one- to four-year-old boys with and without the diagnosis of ASD. They uncovered a critical gene network that is disrupted in ASD, noting that the perturbed gene network is related to fetal brain development and also dysregulated in ASD cellular models.

The findings, published online September 23, 2019 in *Nature Neuroscience*, suggest genetic factors influencing brain development during pregnancy are a primary cause of ASD.

“The genetics of ASD are extremely heterogeneous,” said co-senior author Nathan E. Lewis, PhD, associate professor of pediatrics and bioengineering. “Hundreds of genes have been implicated, but the underlying mechanisms remain murky. These findings identify how ASD genetics dysregulate a core network that influences brain development at fetal and in the very early years of life and, consequently, the severity of later ASD symptoms.”

The findings could form the basis for early diagnosis and prediction of symptom severity of ASD, wrote the authors. Early intervention is known to enhance the quality of life of individuals with ASD by improving symptoms, such as cognitive and learning impairments.

However, current diagnosis methodologies rely heavily upon clinical identification of tell-tale behavioral symptoms, such as abnormal facial expressions, limited communications skills and inappropriate social interactions — all of which can be unstable at early ages, making diagnosis and predicted outcomes very difficult. No reliable, practical and objective markers of prognosis currently exist.

“There is an urgent need for robust tests that can identify the disorder and its expected severity at very early ages so that treatment can start early, enabling a better outcome for each child,” said co-senior author Eric Courchesne, PhD, professor of neuroscience and co-director of the UC San Diego Autism Center of Excellence.

First author Vahid H. Gazestani, PhD, said data from the boys’ blood gene expression, combined with neuron models, revealed dysregulation of a common gene network containing key signaling pathways with roles in fetal brain development. “We found that many of the known ASD risk genes regulate this core network and hence their mutations can disrupt this developmentally critical network.”

The worse the network dysregulation, the scientists found, the more severe the symptoms experienced later on by affected boys. Although the authors cautioned that the findings need to be replicated in larger studies, they said the data are consistent with previous studies by the Courchesne and Lewis labs and other groups, which have shown the diagnostic and prognostic power of blood gene expression for ASD.

“Increasingly, evidence indicates that ASD is a progressive disorder that, at prenatal and early postnatal stages, involves a cascade of molecular and cellular changes, such as those resulting from dysregulation of signaling pathways and networks,” said Courchesne.

“Our evidence suggests that abnormal signals from known ASD risk genes may be channeled through this important gene network,” added Gazestani, “and that, in turn, sends signals that alter fetal and postnatal brain formation and wiring patterns.”

The researchers hope to create a framework in which physicians and others can systematically diagnose, classify and prognostically stratify patients with ASD at much earlier ages, based upon genetic or molecular markers, expediting treatment.

“The study shows that through analyses of gene expression from ordinary blood samples, it is possible to study aspects of ASD’s fetal molecular origins, uncover the functional impact of hundreds of ASD risk genes that have been discovered over the years, and develop clinical tests of ASD diagnosis and severity prognosis,” said Lewis.

Additional co-authors include: Tiziano Pramparo, Srinivasa Nalabolu, Benjamin P. Kellman, Sarah Murray, Linda Lopez and Karen Pierce, all at UC San Diego.

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MEDIA CONTACT

Scott LaFee, 858-249-0456, slafee@ucsd.edu

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