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DIFFERENTIAL EARLY BRAIN RESPONSES TO SPEECH IN TODDLERS WITH AUTISM AND POOR LANGUAGE DEVELOPMENT ARE LINKED TO WIDESPREAD GENE EXPRESSION ACTIVITY IN BLOOD LEYKOCYTE CELLS.

Researchers identify molecular underpinnings of different brain responses to speech in toddlers with autism and poor early language development and outcome

An international team of scientists, led by researchers at the University of Cyprus and the University of California San Diego (UCSD) School of Medicine, have identified a previously unknown large-scale association between patterns of gene expression in blood leukocyte cells and widespread functional neural responses to speech measured with functional magnetic resonance imaging (fMRI). This large-scale association occurs differently in toddlers diagnosed with autism spectrum disorder (ASD) and who have poor language development, compared to toddlers with ASD and good language development or typically developing toddlers. The identified important genes are numerous, comprising several thousands of genes working together in a coordinated fashion. These genes are known to be active across many tissues throughout the body, including the brain, and are accessible for study in blood leukocyte cells. Many of these key genes were also dysregulated in brain tissue of patients with autism and are important during prenatal periods of brain development. Many key genes were also those that are differentiated in human versus non-human primate brain and appear to be important for component processes of language such as vocal learning. The study underscores that there are different molecular biological mechanisms changing brain development in a subtype of ASD toddlers with poor language outcome and this biological difference is present well before poor language outcomes manifest.

The findings were published online November 26, 2018 in the journal *Nature Neuroscience*.

“Early language development in autism is highly variable,” said first author Michael Lombardo, PhD, assistant professor of psychology at the University of Cyprus. “Some toddlers with autism are minimally verbal, while at the other extreme, many individuals develop language like typically developing toddlers. An important and long-standing question has been whether these very different language profiles in autism are subtype distinctions that point to different biological underpinnings. We need to better understand the biological underpinnings of different early language development in autism because early language ability is one of the most important predictors of early intervention response and later-life outcomes. If we can understand the biology, this may have high impact in future work examining how to best facilitate change to the biology that can then substantially improve longer term outcomes for patients.”

At UCSD, the research team led by senior authors Eric Courchesne, PhD, and Karen Pierce, Ph.D., professors of neurosciences and co-directors of the UCSD Autism Center of Excellence, collected blood samples from 118 toddlers with an average age of 29 months and measured transcriptional activity of all protein coding genes in the genome. The UCSD team additionally collected fMRI data during natural sleep from toddlers while they were passively stimulated with speech stimuli. Using behavioral clinical assessment data collected repeatedly each year from 1-4 years of age the team was able to split toddlers with autism into subtypes that showed poor or good language outcome by 3 to 4 years of age.

Using advanced biostatistical methods, Dr. Lombardo lead analyses that clustered genes into highly correlated 'gene modules' and then assessed how the activity of gene modules were related to the whole-brain neural response to speech. Gene module activity linked to neural responses to speech were widespread across the genome, encompassing several thousand genes that work together in a coordinated fashion. This primary finding that large-scale coordinated gene expression activity in blood is highly linked to in vivo fMRI response in living patients is a methodological advance that could help further research hone in on how to best assess which individuals will respond to different kinds of treatment.

"One of the biggest challenges in advancing understanding of ASD," said senior author Eric Courchesne, "has been the absence of a method to identify what gene activity differences underlie the initial brain differences and clinical symptoms in living toddlers with ASD. This is because the living toddler's brain is inaccessible to the direct measurement of gene activity. As such, gene activity differences underlying emerging brain dysfunction and clinical symptoms has remained completely unknown – until now. Our novel method takes advantage of the fact that a large number of ASD-relevant and prenatal brain-relevant genes and gene networks broadly express in easily accessible non-brain tissues such as leukocytes as well as in brain. By carefully analyzing such early-age gene activity, it is possible to advance understanding of this key biology better in living toddlers with ASD. This unique method not only has huge impact on understanding the molecular bases of ASD, but also how to monitor changes in the biology as a function of early intervention. We think this method for linking molecular mechanisms in available peripheral samples like blood with in vivo measures of the brain with neuroimaging helps us substantially in this regard."

The team plans to extend this work into clinically relevant directions such as monitoring treatment response in ASD subtypes and potentially leveraging the information from gene expression, fMRI and clinical measures to develop tools that can better predict language outcomes for toddlers with ASD at very early ages.