

Gene Expression Profile Distinctions In Autistic Children Identified

Genomic analysis could add biological certainty to behavioral diagnosis

From a M.I.N.D. Institute announcement.

A group of genes with known links to natural-killer cells -- the first to attack viruses, bacteria and malignancies -- are expressed at high levels in the blood of children with autism when compared to children without the disorder, according to a new study from the UC Davis M.I.N.D. Institute. Researchers also found gene expression distinctions in children with early onset and regressive forms of the disorder. The outcomes, published in the January issue of *Genomics*, offer hope that gene expression analyses can provide biological evidence of autism, currently diagnosed only through behavioral assessments, in some children.

"What we found were 11 specific genes with expression levels that were significantly higher in the blood of children with autism when compared to the blood of typically developing children," said Frank Sharp, senior author of the study and professor of neurology with the M.I.N.D. Institute.

"Those 11 genes are all known to be expressed by natural-killer cells, which are cells in the immune system necessary for mounting a defense against infected cells. We were surprised by our results because we were not looking for these particular genes. And while a number of studies have shown immune system dysregulation to be an important factor in autism, ours is one of the first to implicate these particular cells."

In conducting the study, Sharp, molecular pathologist Jeff Gregg and their M.I.N.D. Institute colleagues used blood samples from 35 children diagnosed with autism, 14 with development delay but not autism and 12 typically developing children. The samples were subjected to gene expression analysis using microarrays and compared for common patterns. In addition to finding the 11 genes with natural-killer cell connections shared by all of the children with autism, they identified a pattern of 140 genes differentially expressed in children with the early onset form of the disorder and a pattern of 20 genes differentially expressed in children with the regressive form of the disorder. The team is the first to use genomic profiling of blood to observe differences in children with autism.

A serious and increasingly prevalent neurodevelopmental disorder, autism is characterized by language impairments, social deficits and limited, repetitive behaviors. While some parents report they knew something was wrong with their child close to birth, others report their children progressed just like others and then lost social and/or language skills later, usually between the ages of 1 and 2.

These separate experiences led clinicians to hypothesize that there are at least two types of autism -- early onset and regressive. This study offers biological evidence of those two subtypes.

Microarrays are used to examine the expression levels of thousands of genes simultaneously. Because of its accuracy, the technology may become an important diagnostic tool for a variety of neurological conditions, including ischemic stroke and

multiple sclerosis. To perform the analysis, RNA is isolated from cells in the blood. Complimentary strands of DNA (cDNA) are then created using the RNA as a template. Fluorescently labeled cRNA is next made from the cDNA and hybridized with the DNA on the array.

Scanners using laser technology then read the array, revealing which genes are expressed and at what levels.

In addition to being expressed by natural-killer cells, some of the 11 genes found to be expressed at higher levels in children with autism are also expressed by CD8+ T lymphocytes -- cells that target infected cells and, once bound to them, destroy them. It is not yet clear whether autism involves a primary problem in natural-killer cells, CD8+ lymphocytes or both.

"What we are seeing can reflect something in the environment that is triggering the activation of these genes or something genetic that the children have from the time they were conceived," Sharp explained. "Such an immune response could be caused by exposure to a virus, another infectious agent or even a toxin. Another possibility is that these changes represent a genetic susceptibility factor that predisposes children to autism when they are exposed to some environmental factor."

He added that the current study also does not identify whether or not the natural-killer cells are functioning abnormally, which further work by M.I.N.D. Institute immunologists will reveal.

"If the natural-killer cells are dysfunctional, this might mean that they cannot rid a pregnant mother, fetus or newborn of an infection, which could contribute to autism."

Gregg and Sharp consider the findings preliminary until they can be replicated, but still believe the study results point them in a new research direction that will shed light on the biological foundations of autism and eventually lead to new therapeutic targets.

The study, "Gene Expression Profiles in Children with Autism," was funded by the National Institutes of Environmental Health Sciences and the U.S. Environmental Protection Agency through the UC Davis Center for Children's Environmental Health and the UC Davis M.I.N.D. Institute. A copy can be downloaded at www.sciencedirect.com.