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March 09, 2015 | By Scott LaFee

Blood-Based Genetic Biomarkers Identify Young Boys with Autism

Proof-of-principle method suggests much-earlier diagnoses could be done with clinic test

In a study published in the current online issue of *JAMA Psychiatry*, an international team of scientists, led by researchers at the University of California, San Diego School of Medicine, report finding a highly accurate blood-based measure that could lead to development of a clinical test for autism spectrum disorder (ASD) risk in males as young as one to two years old. The test could be done in community pediatric settings. The degree of accuracy, they said, out performs other behavioral and genetic screens for infants and toddlers with ASD described in literature.

The causes of ASD are complex and diverse, making it difficult to conclusively diagnose the disease much before a child's fourth year of life. Indeed, the median age of diagnosis in the United States is 53 months.

"A major challenge is the difficulty of accurately diagnosing ASD, which is very heterogeneous, at an early enough age to implement the most effective treatment," said principal investigator Eric Courchesne, PhD, professor of neurosciences and director of the Autism Center of Excellence at University of California, San Diego School of Medicine.

In the proof-of-principle study, Courchesne, first author Tiziano Pramparo, PhD, and colleagues identified blood-based genomic biomarkers that differentiated toddlers with ASD, ranging in age from one to four years old, from a control group of toddlers without ASD. Blood samples were taken at the child's initial clinical intake. Importantly, the control group consisted of a mix of young boys commonly seen in community clinics, with typical development, mild language delay, transient language delay and global developmental delay. Against this control group, the researchers identified a genetic signature that identified 83 percent of ASD toddlers.

The study used an unbiased systems biology-based method to search for genes and gene pathways in blood samples that best distinguished ASD infants and toddlers from typically developing toddlers and toddlers with non-autism developmental delays. Specifically, the researchers measured leukocyte (white blood cell) RNA expression levels.

“Ideally, biomarkers come from tissue affected, but in ASD this is the brain, which is obviously an inaccessible tissue,” said Courchesne. “Peripheral blood of living ASD infants and toddlers is an important alternative, and obtaining blood samples is routine and safe and, thus, is a preferable and accessible tissue for identifying signatures of ASD that could be used in clinical screening and follow-up evaluations.”

Pramparo, an associate research scientist at the UC San Diego Autism Center of Excellence, said blood is expected to carry autism-relevant molecular signatures that can be used to detect the disorder at very young ages. It might also reflect aspects of the disrupted biology underlying neural defects.

In fact, the researchers found gene expression differences between ASD and non-ASD in genes related to translation and immune/inflammation functions, as well as cell adhesion and cell cycle. These “ASD signature classifier” genes are among those that can have effect on early brain development.

“New studies point to autism beginning in the womb,” said Courchesne, who, with colleagues, published one such widely reported study last year detailing disrupted brain development in post-mortem brains of autistic children. “Our present study shows examination of the gene expression profiles at the very early age of initial clinical detection reveals both strong evidence of early biological processes in ASD and abnormal signals with the potential to serve as an early, practical biomarker of risk for the disorder in general pediatric settings.”

The scientific team conducted two different analyses of blood samples involving two cohorts of study participants: 147 toddlers (91 with ASD, 56 control) in the first group, 73 toddlers (44 ASD, 29 control) in the second group. The first assay identified an ASD genomic signature 83 percent of the time; the second had a 75 percent accuracy rate.

Young male toddlers with autism were the focus of the study because autism is far more prevalent in males. “The genetics and molecular bases of autism may differ somewhat in affected males and females,” said Pramparo. “We reasoned, therefore, that different signatures might need to be discovered and developed in each gender in ASD.”

It was simpler to begin with boys. “Autism is four times more common in males,” said Courchesne, “and so we were able to more quickly recruit and test samples of autism males than autism females. Our current work is aimed at recruiting sufficiently large samples of females to begin work to discover possible gene expression markers for them.”

Courchesne emphasized that this was a first step toward a possible means of diagnosing autism much earlier than current methodologies, one that would greatly boost the efficacy of intervention and remedial treatments.

Though only proof-of-principle, Courchesne said the findings are encouraging. Next steps involve further refinement of the process and identification of diagnostic risk markers for females.

“As we write in the paper, our study showed that a blood-based clinical test for at-risk male infants and toddlers could be refined and routinely implemented in pediatric diagnostic settings.”

Co-authors include Karen Pierce, Cynthia Carter Barnes, Steven Marinero, Clelia Ahrens-Barbeau and Linda Lopez, UC San Diego Autism Center of Excellence; Michael V. Lombardo, University of Cambridge and University of Cyprus; Sarah S. Murray, Scripps Translational Sciences Institute; and Ronghui Xu, UCSD.

Funding for this research came, in part, from the National Institutes of Health (grants P50-MH081755, R01-MH036840, R01-MH080134, 1U54RR025204, 1UL1RR031980-01) and UC San Diego (grant KL2T00099).

Disclosure: Pramparo and Courchesne have a patent application pending that includes data from this study.

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