Researchers identify specific fetal antigens attacked by maternal antibodies

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Judy Van de Water, MIND Institute, is in her lab with a colleague. Credit: UC Regents

UC Davis MIND Institute researchers have identified the specific antibodies that target fetal brain proteins in the blood of a subset of women whose children are diagnosed with autism. The finding is the first to pinpoint a specific risk factor for a significant subset of autism cases, as well as a biomarker for drug development and early diagnosis. The researchers have named autism related to these antibodies "Maternal Autoantibody-Related," or MAR autism.

The study found that the mothers of children with autism were more than 21 times as likely to have the specific MAR antibodies in their systems that reacted with fetal brain proteins, or antigens, than were the mothers of children who did not have autism. In fact, specific combinations of MAR antibodies were not found in the blood of mothers whose children were typically developing.

The research, "Autism-specific maternal autoantibodies recognize critical proteins in developing brain," is published online today in *Translational Psychiatry*, a *Nature* journal.

The study was led by principal investigator and immunologist Judy Van de Water, a researcher affiliated with the MIND Institute. Earlier studies by Van de Water and her colleagues found that women with certain antibodies in their bloodstreams are at greater risk of having a child with autism and that their children exhibited more severe language delays, irritability and self-injurious behaviors than did the autistic children of mothers whose blood did not have the antibodies.

"Now we will be able to better determine the role of each protein in brain development," said Van de Water, professor of internal medicine. "We hope that, one day, we can tell a mother more precisely what her antibody profile means for her child, then target interventions more effectively."

To identify the exact antigens targeted by the mothers' antibodies, Van de Water and her colleagues conducted the research in Northern California using blood samples from 246 mothers of children with autism and of a control group of 149 mothers of children without autism to examine their reactivity with the candidate antigens.

Seven antigens were significantly more reactive to the blood of mothers of children with autism than to that of the control mothers. The study

found that the mothers with antibodies that reacted with any one of these antigens, either individually or in combination with other antigens, were more than three times as likely to have a child with autism spectrum disorder.

Several combinations of antibodies in the blood from mothers of children with autism were not found in the control mothers' blood. Nearly 23 percent of mothers of children with autism had certain combinations of autoantibodies against the target antigens, compared with less than 1 percent of mothers of children without the disorder.

The specific antigens identified in the study are lactate dehydrogenase A and B, cypin (guanine deaminase), stress-induced phosphoprotein 1, collapsing response mediator proteins 1 and 2, and Y-box binding protein. All are found throughout the body, but also are expressed at significant levels in the human fetal brain and have established roles in neurodevelopment. For example, cypin is an enzyme that plays an important role in normal neurite branching, a fundamental function in the developing brain, whereas the CRMP proteins are critical later in neuron development for axon outgrowth.

Maternal antibodies are known to cross the placenta during pregnancy and can be detected in a fetus as early as 13 weeks. By 30 weeks, maternal antibody levels in the fetus are about half that of the mother, and at birth, the concentration is even greater in the newborn than in the mother herself. The maternal antibodies stay in the baby's bloodstream for about 6 months after birth, after which the baby's own immune system takes over.

Once in the fetal bloodstream, the antibodies then may enter the brain and attack cells that have corresponding proteins that act as antigens. This antigen-antibody response is an important defense against foreign invaders, such as bacteria or viruses, but is not normally directed against

oneself. When directed against one's own tissue, the antibodies are known as autoantibodies.

"It is important to note that women have no control over whether or not they develop these autoantibodies, much like any other autoimmune disorder," Van de Water said. "And, like other autoimmune disorders, we do not know what the initial trigger is that leads to their production."

Understanding which proteins and which pathways are implicated in MAR autism can help elucidate the causes of autism and possibly lead to new therapies, such as administering 'antibody blockers' to the mother during pregnancy to prevent damage to the developing fetal brain, Van de Water said.

These findings are leading to the development of a MAR diagnostic test for autism, which would be available to the mothers of young children who are showing signs of developmental delay. If the test were positive, the child would be a candidate for early behavioral intervention.

"These findings are incredibly important because they establish a cause for a significant portion of autism cases, thereby opening up new lines of inquiry into possible biological treatments," said MIND Institute Director Leonard Abbeduto. "In addition, the findings demonstrate that a diagnostic test is within reach. This test would be invaluable for women who are considering becoming pregnant and could lead to earlier and more accurate diagnosis of children with developmental challenges and help get them into behavioral interventions at younger ages."

A MAR diagnostic test also would assess a mother's risk of having a child with autism prior to conception, which is particularly important for women who already have a child with the disorder. UC Davis has patented this technology and licensed the exclusive worldwide rights to develop it for commercial purposes to Pediatric Bioscience, Inc.

"We know that early behavioral interventions for autism are critical," said Isaac Pessah, professor and chair of the Department of Molecular Biosciences in the UC Davis School of Veterinary Medicine and former director of the UC Davis Center for Children's Environmental Health. "Developing a predictive test for autism before symptoms become obvious could have an enormous impact on treating children with the condition."

Study participants were from the CHARGE (Childhood Autism Risks from Genetics and the Environment) study, an ongoing study that was launched in 2001 by the MIND Institute and the UC Davis Center for Children's Environmental Health, of which Van de Water now is director. Children with autism spectrum disorder, children with developmental delay and typically developing children between the ages of 2 and 5 years are studied with the goal of better understanding the causes of autism.

A related study is the MARBLES (Markers of Autism Risk in Babies ? Learning Early Signs) study, also being conducted at the MIND Institute and the Center for Children's Environmental Health. This study follows pregnant women who already have a child with autism. Multiple factors related to genetics and the environment is under study in an effort to uncover predictors for having a child with autism.

Van de Water said knowing the specific protein targets of the maternal antibodies enables researchers to develop more precise animal models of autism.

Provided by UC Davis