Genetic variant, auto-antibodies linked to autism

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(Medical Xpress) -- A study by researchers at UC Davis has found that pregnant women with a particular gene variation are more likely to produce auto-antibodies to the brains of their developing fetuses and that the children of these mothers are at greater risk of later being diagnosed with autism.

The finding is the first to demonstrate a genetic mechanism at play in the development of the neurodevelopmental disorder among some children — offering the possibility of a genetic test for some women at risk for having a child with autism, said Judy Van de Water, an immunologist and the study's co-principal investigator.

"Association of a MET genetic variant with autism-associated maternal autoantibodies to fetal brain proteins and cytokine expression," is published online today in the journal *Translational Psychiatry*, a Nature publication.

"Our study gives strong support for the idea that, in at least some cases, autism results from maternal immunity gone overboard," said Judy Van de Water, a professor of internal medicine and a researcher affiliated with the UC Davis MIND Institute. "This is the first time that a genetic factor known to be important in autism and its effects have been demonstrated."

Autism is a neurodevelopmental disorder that affects a child's ability to learn and communicate socially. It affects an estimated 1 in 110 children

in the United States, according to the U.S. Centers for Disease Control and Prevention.

For the study, Van de Water and her colleagues examined the action of the MET gene, which has a known association with autism, among 200 mothers of children with autism and 150 mothers of typically developing children enrolled in the Northern California-based Childhood Autism Risks from Genetics and the Environment (CHARGE) Study. All of the study participants were between 24 and 60 months of age at the time of study enrollment, lived with one biological parent, and spoke either English or Spanish.

The researchers found that the C-allele of the MET gene is more common in mothers with several immunologic abnormalities that might contribute to the development of autism. Analysis of the MET C-allele is a method of determining susceptibility for immune dysregulation in the mothers.

One abnormality they attributed to the MET C allele is the presence of antibodies against fetal brain proteins in the blood of the mothers. These brain-attacking antibodies occur in some mothers with an autistic child, but are not found in mothers of typically developing children. It is believed that these antibodies somehow injure the developing brain of the fetus, and in some instances may cause autism.

Researchers do not yet know when or how the antibodies are formed, or precisely what happens to the brain tissue exposed to them, but based on a collaborative paper with Loren Martin at Azuza Pacific University, they appear to have pathologic significance, or a functional effect on brain development, changing the way the brain develops. Van de Water and her group are still working on the precise effect of these maternal antibodies on the developing brain.

The investigators also found that MET protein levels are reduced in cells from mothers with one C allele and one normal allele, and were even lower in those with two C alleles. Lower MET protein on the cell surface may increase susceptibility to a more intense and prolonged immune response when the cells are activated, like exposure to a bacteria or virus. This, in turn, could make these individuals more prone to forming antibodies against 'self' proteins, such as those found in the fetal brain.

In addition, the investigators evaluated the functional polymorphism in the study participants' immunological cytokines, molecules that tell other cells what to do. The cytokine IL-10, an important anti-inflammatory marker, was reduced in women with the MET C allele. IL-10 is a well-studied immunosuppressive molecule that is important for preventing autoimmunity. A reduction in IL-10 would increase the chances that an inflammatory response would continue unchecked.

"The convergence of these two distinct associations with autism risk — that of maternal antibodies to fetal brain proteins and the MET C allele — provides the first link between an autism susceptibility gene and its effects," Van de Water said.

Daniel B. Campbell, assistant professor of psychiatry and the behavioral sciences at the Zilkha Neurogenetic Institute of the University of Southern California, is co-principal investigator of the study.

"The presence of maternal antibodies to fetal blood proteins is one of the best markers known for autism, accounting for about 12 percent of cases. In contrast, genetic factors previously identified in children with autism account for only 2 or 3 percent of cases," Campbell said.

"Now we not only have a marker, but we are starting to understand the actual mechanisms of what causes autism," Campbell said. "These findings can greatly enhance our understanding of the origins of some

cases of autism and may directly lead to screening tests and treatments to prevent it."

Why women with the C allele form antibodies against fetal brain proteins is another important area of interest, according to Van de Water, because it suggests a hyper-responsive immune system. Proteins associated with the MET gene function as key blockers of immune activity.

"Our study has found that a kind of safety switch that regulates the immune system and prevents it from targeting the brain of the developing fetus is defective in some mothers of children who later develop autism," Van de Water said.

Van de Water said the relationship between autism and aberrations in the immune system, once a radical notion in the scientific community, is now becoming a well-accepted and very fruitful focus of research.

"While it is not known how the antibody response against fetal brain proteins arise, it may be possible to one day treat susceptible women to reduce the likelihood of having an autistic child," Van de Water said.

Provided by UC Davis