Study finds regions of DNA that appear linked to autistic spectrum disorders

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Using an innovative statistical approach, a research team from Washington University School of Medicine in St. Louis and the University of California, Los Angeles, has identified two regions of DNA linked to autism. They found the suspicious DNA with a much smaller sample of people than has been used traditionally in searches for autism genes.

Autism — a disorder that involves social deficits, language problems and repetitive, stereotyped behaviors — affects around one in 1,000 children. And the combined incidence of autism spectrum disorders, which include Asperger syndrome and pervasive developmental disorder, brings the total number of affected children to one in every 150 births. Boys are affected three to four times more often than girls.

There's clearly a genetic component to autism, according to John N. Constantino, M.D., associate professor of psychiatry and pediatrics at Washington University School of Medicine and a co-principal investigator on this latest study. If one child in a family is autistic, there's a 10 percent chance a sibling also will have autism. Past research has isolated a few regions of DNA linked to autism, but very few of those studies have been replicated, so no specific autism genes have yet been identified.

"Those older studies used what's called an 'affected sib pair' design that looks for genetic markers in siblings with autism," says Constantino. "That approach has worked well for single-gene disorders, but autism is a complex disease that may involve many genes that each make very small contributions. When that's the case, it's harder to find genetic markers."

So Constantino's group, in collaboration with the other co-principal investigator, Daniel H. Geschwind, M.D., Ph.D., and neuropsychiatric and genetics researchers at UCLA, is using a different approach. They report their findings in the April issue of the *American Journal of Psychiatry*.

"Although we once believed you either had this condition or you didn't, we now know that there's a continuous distribution of autism symptoms from very mild to very severe," Constantino says.

That means in families where a child is autistic, parents and unaffected siblings may have very subtle communication impairments or behavioral tendencies that would be considered autistic only in their most severe forms. Those traits may indicate genetic tendencies that contribute to autism and now can be measured with a diagnostic interview tool called the Social Responsiveness Scale (SRS), which Constantino developed with his colleague Richard D. Todd, Ph.D., M.D., at Washington University.

Using the SRS to gather data about both children with autism and their unaffected parents and siblings allowed the researchers to take a more quantitative approach to find subtle symptoms of autism that aggregate in families. In all, they used the SRS to study members of 99 families who were part of the Autism Genetic Resource Exchange (AGRE).

"We characterized everyone using the quantitative measures that the Social Responsiveness Scale provides," Constantino explains. "With the SRS, we looked not just at whether a person has autism but more systematically at the degree of autistic impairment. Then we analyzed their genetic material and found significant linkage to these symptoms on regions of chromosomes 11 and 17."

Older survey methods also had flagged those regions of DNA, but those studies used samples more than three times larger than this study. Constantino and Geschwind believe the fact that they identified the same areas of DNA means that their quantitative method can find genes related to

autism and that if used in bigger samples, it may be able isolate other suspicious regions of DNA that studies using traditional methods can't find.

The researchers now have begun to make more detailed maps of the chromosome regions related to autism. They're also using the SRS to study more families.

In theory, the greater statistical power of their method will be magnified as the researchers study larger numbers of people. They say that power may help them isolate many more genes that might contribute to autism spectrum disorders. They'll also continue to look closely at genes in the suspicious DNA regions identified so far and try to figure out what's going on at the genetic level to make some children autistic.

"We know that the dopamine D4 receptor gene is in the region we've identified on chromosome 11," Constantino says. "That receptor is important in many brain functions. But there are many genes in the regions we've identified, and our focus is on refining the signal so that we can reduce the number of candidate genes and then look more closely at how those genes might be contributing to this devastating disorder."

Constantino believes ultimately the search will lead to the discovery of many genes that contribute to autism and that scientists may need to find several of them before they begin to understand how genetic variations actually lead to the disorder.

"The genetic factors tend to interact with one another," he says. "One gene might increase risk by 10 percent, but two genes, in the proper combination, might increase the risk 10-fold. We expect that as we find additional susceptibility factors the amount of their causal influence will increase exponentially, and we'll get a clearer picture of how genes contribute to autism and may even find ways to intervene."

Source: Washington University School of Medicine

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