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Autism mutations, scattered across genes, merge into network of interactions

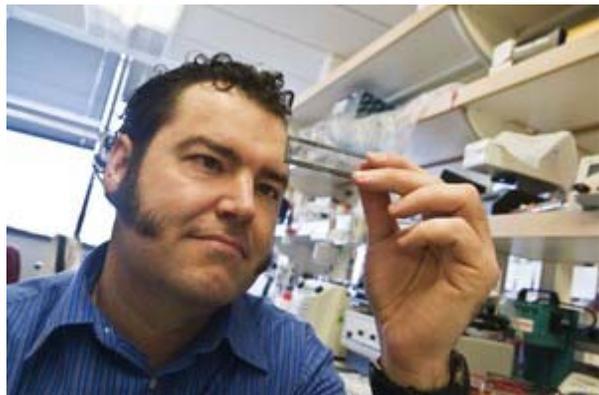
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Read the Nature [paper](#)

Today University of Washington researchers announced their findings from a major study looking into the genetic basis of autism spectrum disorders with an approach piloted at the UW. Their results are reported in the journal *Nature*.

The researchers have been studying ASD in children who have no family history of this or related impairments - so called "sporadic autism" - and also why autism varies in its symptoms and severity. By focusing on "sporadic autism", the researchers sought to evaluate a specific genetic model for ASD risk, namely the appearance of new mutations (termed *de novo*) in children with ASD that were not found in either parent.



Clare McLean

Dr. Brian O'Roak, a postdoctoral fellow in genome sciences, led the study of autism mutations in children from families with no previous history of autism.

By uncovering new gene mutations that disrupt the function of proteins, the researchers have discovered a pathway related to modifying chromatin – the tightly coiled spools of DNA in the cell -- and to regulating genes in the brain and nervous system. Various changes in this pathway contribute to children developing autism in different ways. Mutations in this pathway also may contribute to a variety of childhood intellectual, social, and psychiatric disabilities, with implications beyond autism.

To identify these new mutations, the researchers used the latest sequencing technologies and analytical methods to determine the sequence of the protein-coding portion of the human genome, called the "exome", in family trios (father, mother, and child). This approach was piloted this past year at the University of Washington with an initial set of 20 autism families. The pilot demonstrated the technical feasibility and potential impact of this approach. (see <http://www.washington.edu/news/articles/sporadic-mutations-identified-in-children-with-autism-spectrum-disorders>).

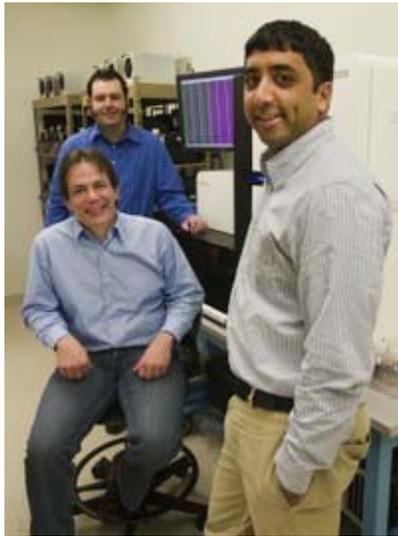
For the current study, the researchers expanded the research to include 677 individuals from 209 families with a single child with autism. They also sequenced the exomes of 50 unaffected brothers and sisters. In the newly reported results, 248 *de novo* mutations were validated, and 120 of these were classified as severe. These were predicted to produce, for example, proteins that were truncated or malfunctioning. The researchers then narrowed in on 60 top candidates most likely to contribute to autism risk, based on the nature of the mutation, functional evidence, or previous studies.

“It is important to point out that in each generation there is on average one new coding mutation per child and not all of these will cause developmental problems. However, in the case of children with autism, what we are finding is disruptions in many genes that are known to directly interact and also look similar to genes previously associated with autism,” said Brian J. O’Roak, a senior fellow in the Department of Genome Sciences working with senior authors Dr. Jay Shendure and Evan Eichler. In fact, researchers found that 49 of the genes mutated had products known to directly interact by forming a highly interconnected network. Interestingly, many of the proteins in this pathway are important in terms of remodeling chromatin—changing the way DNA is packaged in the cell-- and controlling the expression and function of other genes and proteins. These protein pathways are thought to be critical in brain cell formation, brain cell connections, and nerve-cell signaling.

Having this large data set also allowed the researchers to evaluate the parental source of these new mutations - that is, whether they came from the sperm of the father or egg of the mother. Their analysis revealed that the new mutations were overwhelming paternal in origin (in a ratio of 4:1) Their results confirmed a prediction population geneticist J.B.S. Haldane made in 1935. Moreover, the new mutations occurred at a rate that correlated with the age of the father. These findings, they said, support other studies that show older fathers have a slightly increased risk of having a child with an autism spectrum disorder.

What is also very clear from this study and two additional studies appearing concurrently in the same issue of *Nature* is that autism risk mutations are scattered across many genes. One of the other studies was led by Mount Sinai Medical Center in New York, the second by Yale University in New Haven.

In the UW study, recurrent protein-altering mutations were discovered in only two genes, NTNG1, and CHD8. The data suggest that, at the molecular level, there are many different forms of autism and that the term “autism spectrum disorder” is better thought of as an umbrella disorder with many root causes. The authors predict that although no single gene will account for more than 1 percent of autism, collectively all of these rare mutations will account for much of the genetic basis of the disease.



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Brian O’Roak, Evan Eichler (seated) and Jay Shendure (right) in one of the UW labs where researchers search for sporadic mutations associated with autism.

While this level of complexity is a major challenge for the field, the authors are already working on a solution using next-generation sequencing approaches. To tackle this challenge, the researchers implemented a new cost-effective screening technology that allowed them to screen more than 2,500 individuals for mutations in six genes in only a month. In so doing they found strong evidence for the involvement of a glutamate receptor gene GRIN2B for a subset of cases with autism. This same approach will allow the authors to screen all of the newly discovered genes to rapidly test which ones are truly disease-causing.

Among the other genes they discovered with de novo mutations in children with autism, several have been previously implicated in intellectual disability and developmental delay. This indicates, the authors said, that the divisions clinicians made between these various types of diseases in children may not readily translate into differences at the molecular level. The researchers added that it is still uncertain whether there are subsets of people with autism who share a common or strongly related causative mechanism in their underlying molecular biology, or how large those groups might be.

In addition to O’Roak, Shendure, and Eichler, other researchers on the study were Laura Vives, Santhosh Girirajan, Emre Karakoc, Nik Krumm, Bradly P.Coe, Roie Levy, Arthur Ko, Choli Lee, Joshua D. Smith, Emily H. Turner, Ian B. Stanaway, Benjamin Vernot, Maika Malig, Carl Baker, Beau Reilly, Joshua M. Akey, Elhanan Borenstein, Mark J. Rieder, and Deborah A. Nickerson, all from the UW Department of Genome Sciences, and Rapheal Bernier, of the UW Department of Psychiatry and Behavioral Sciences. Eichler is also an investigator with the Howard Hughes Medical Institute, and Borenstein also holds appointments in the UW Department of Computer Science and Engineering and at the Santa Fe Institute.

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