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Middle Eastern Families Help Scientists Pinpoint Autism Genes

The hunt for gene mutations that contribute to autism has proceeded slowly, largely because autism encompasses a spectrum of diseases. Just as its symptoms vary widely among individuals, so do the genetic mutations that cause them.

Now, Howard Hughes Medical Institute investigator Christopher Walsh, in collaboration with scientists and physicians in the United States, Turkey, Saudi Arabia, Pakistan, and Kuwait, has used a new strategy to identify six genes that, when mutated, contribute to autism. By focusing on large families in which both parents share a recent ancestor, Walsh and his colleagues were able to hone in on rare mutations that had remained elusive in previous studies.

"By being able to characterize more about the genetic mutations at work in various forms of autism, we may be able to predict which kids need gene therapy, and which just need some form of training."

- Christopher A. Walsh

Walsh, who is at Beth Israel Deaconess Medical Center and at Children's Hospital Boston, geneticist Eric Morrow of Massachusetts General Hospital, Seung-Yun Yoo, and their colleagues report their findings on July 11, 2008, in the journal *Science*.

Walsh likens autism to Leo Tolstoy's novel *Anna Karenina*, "where all happy families are the same, but every unhappy family is unhappy in their own way." Autistic children share three key traits: they're slow to develop

language, they are poor at social interactions, and they repeat stereotyped behavior over and over. But that's where the similarities end; some forms of autism are subtle, whereas others devastate every aspect of functioning.

This variation is evidence of the wide variety of genes that can contribute to the disorder, Walsh says, and makes finding those genes difficult. It's not possible to look for a single gene that is mutated in all individuals with the disorder, as has been done with diseases such as cystic fibrosis or Huntington's disease. So while scientists agree that the causes of autism are largely genetic, they are far from understanding those factors. "At the moment, we understand the genetic causes of 15 to 20 percent of autism," Walsh said. "The remaining 80 percent remain unexplained."

Walsh and his colleagues have been attempting to identify autism genes by comparing the genomes of autistic and non-autistic siblings. In the United States, the task is particularly difficult due to the typically small size of most families, Walsh said.

So Walsh collaborated with researchers from the Middle East, where families are typically larger. The average of six children per family—versus two or three in the United States and Europe—makes it much easier to compare genes within a family.

Walsh and his colleagues took another step to make finding autism genes easier: they specifically targeted families in which the mother and father shared a recent ancestor. "This shared ancestry roughly doubles the chance of offspring being affected," he explained. "This increase in risk is modest—about the same as having a child at age 40 versus at age 20—but more importantly, the shared ancestry provides a trace that makes it easier to track inherited mutations."

Walsh and his colleagues studied 88 such families, from eight countries: Jordan, Saudi Arabia, Kuwait, Oman, Pakistan, Qatar, Turkey, and the United Arab Emirates. In five of those families, they found that large segments of individuals' genomes were missing. While family members who retained one functional copy of these segments did not have autism, those with both copies missing had the disorder.

Many of these deletions inactivated genes involved in learning, Walsh said. Specifically, they help nerve cells carry out the physical changes to their synapses that underlie learning and the formation of new memories. Walsh

said that in a developmental disorder like autism, that was an important find. “There's lots of evidence to suggest that this process of synaptic learning is key to autism,” he said.

But he and his colleagues are also excited because of the way in which the deletions they found alter gene activity. “Only one of these deletions completely removed a gene,” he said. The others removed areas close to the genes that contain the genes' “on/off switches.”

Walsh said that raises new possibilities about how to treat some forms of autism. When autism is caused by a missing gene, the only option may be to replace it using gene therapy, he said. But when the cause is a broken on/off switch, “there are other ways in which some of these genes can be activated,” he said. For instance, studies have shown that placing many autistic children in enriched learning environments helps them move past the disease. These environments can activate pathways in the brain that bypass the broken on/off switches, Walsh said. “By being able to characterize more about the genetic mutations at work in various forms of autism, we may be able to predict which kids need gene therapy, and which just need some form of training,” he said.

Walsh says the team will continue to sift through data from the study to identify more autism-related genes, but he stressed that there is also a larger message. “One of the most exciting areas of investigation is trying to understand what these autism mutations are telling us about how genes are regulated in the context of learning,” he said. “The more we can understand about the control of these genes, the more we can help a lot of different kids.”