Gene studies begin to unravel autism puzzle

Julie Steenhuysen, Reuters

(Reuters) - A sweeping study of hundreds of families with autism has found that spontaneous mutations can occur in a parent's sperm or egg cells that increase a child's risk for autism, and fathers are four times more likely than mothers to pass these mutations on to their children, researchers said on Wednesday.

The results of three new studies, published in the journal Nature, suggest mutations in parts of genes that code for proteins - called the exome - play a significant role in autism.

And while these genetic mistakes can occur across the genetic code, and many are harmless, they can cause big problems when they occur in parts of the genome needed for brain development. One of the three teams found these glitches may result in a five to 20 times higher risk of developing autism.

"These results confirm that it's not the size of the genetic anomaly that confers risk, but its location," said Dr. Thomas Insel, director of the National Institute of Mental Health, one of the National Institutes of Health, which funded one of the studies.

Among the other findings, the teams - led by Mark Daly of the Broad Institute at Harvard and Massachusetts Institute of Technology, Dr. Matthew State of Yale University and Evan Eichler of the University of Washington in Seattle - identified several hundred new suspect genes that could eventually lead to new targets for autism treatments.

Many of the researchers were part of the Autism Sequencing Collaborative, the largest effort of its kind to use advanced gene sequencing technology to identify the genetic underpinnings of autism.

Autism encompasses a wide spectrum of disorders, ranging from profound inability to communicate and mental retardation to relatively mild symptoms, as in Asperger's syndrome.

In the United States, an estimated 1 in 88 children have autism, according to the latest figures from the U.S. Centers for Disease Control and Prevention, and while scientists believe genetics account for 80 to 90 percent of the risk for developing autism, most cases of autism cannot be traced to a known inherited cause.

Scientists previously have found dozens of genes that may raise the risk of autism. But genetic causes only explain about 10 percent of cases, and recent studies have pointed to environmental factors, possibly arising at conception, as a potential trigger.

SEQUENCED DATA

For this study, researchers sequenced data from 549 families that included both parents and a single child with autism. In most of these families, only one child had autism.

They identified at least three genes using this approach, and a fourth using a different approach.

Joseph Buxbaum, director of the Seaver Autism Center at Mount Sinai School of Medicine in New York and a co-author of one of the studies, said the combined results from the three studies suggest some 600 to 1,200 genes may contribute the risk of developing autism.

The trick will be identifying specific networks in the brain in which these genes interact, so that researchers can begin to develop new treatments.

"We now have a good sense of the large number of genes involved in autism," Buxbaum said.

One of the studies by Dr. Evan Eichler and colleagues at the University of Washington in Seattle suggested how environmental factors might influence genetics.

They looked specifically to see where these spontaneously occurring genetic mistakes were coming from: the father's sperm or the mother's egg cells.

They found that new mutations occurred four times more frequently in sperm cells than in egg cells, and the older the father, the more likely he was to have sperm with these spontaneous mutations.

One possible reason for this, Buxbaum said, is that men make sperm every day, and this high turnover rate increases the chance for errors to occur in the genetic code that could be passed on to their offspring.

"It tells us that sperm production is an imperfect process," Buxbaum said in a telephone interview.

"It's primarily driven by a dad's age. That makes sense. As you get older, there are more and more chances for problems."

He said these findings support other studies that show older fathers have a slightly increased risk of having a child with an autism spectrum disorder.

Buxbaum stressed that everyone has these slight mistakes in their genetic code, but when they occur in areas critical to brain development, they can cause different types of autism.

Kevin Mitchell, a geneticist at Trinity College Dublin, who was not involved in the research, said in a statement the studies help explain how autism can be an

inherited disorder but not always run in families.

"The explanation is that many cases are caused by new mutations - ones that arise in the germline (eggs and sperm). The studies reported in Nature are trying to find those mutations and see which genes are affected," he said.

The researchers say the studies just scratch the surface of what will be needed to fully understand the genetic causes of autism. But the new approach, sequencing genetic changes in the region where genes code for proteins, appears to be the best place to look.

"Prior to the advent of new DNA sequencing technology, we were largely wandering in the dark searching for autism genes," said Matthew State, co-director of the Yale Program on Neurogenetics and a senior author of one the three papers.

"Now we are getting a clear view of the genetic landscape and finally have the tools in hand to find a large proportion of the many genes contributing to autism."

(Reporting By Julie Steenhuysen; Editing by Vicki Allen [1])

Links:
[1] http://blogs.reuters.com/search/journalist.php?edition=us&n=vicki.allen&