Scientists trace autism 'pathway' from gene to brain

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Quinn, an autistic boy, and the line of toys he made before falling asleep. Repeatedly stacking or lining up objects is a behavior commonly associated with autism. Credit: Wikipedia.

There is much that scientists don't know about autism. They don't know, for example, why the complicated, vexing disorder has become more common. In 2000, the Centers for Disease Control and Prevention estimated that about 1 in 150 children in the U.S. were autistic; in 2010,

that number was 1 in 68.

And scientists still don't have a physical explanation for the symptoms of autism, which include a wide range of social impairments.

Most experts agree that a combination of genes and environmental factors are at play. Autism has been linked to air pollution, maternal nutrition, certain pesticides and endocrine-disrupting chemicals found in flame retardants and other products, said Linda Birnbaum, director of the National Institute of Environmental Health Sciences in Research Triangle Park.

But autism is also thought to be associated with genetic mutations, or errors in DNA. Last year, scientists sequenced the genomes of several thousand autistic children and found more than a thousand unique mutations on hundreds of genes.

Each of those mutations is a clue to solving the mystery of autism. But it's probably not the case that each mutation causes autism in its own unique way, said Mark Zylka, a professor at the University of North Carolina School of Medicine.

More likely, he said, these mutations actually represent a smaller number of autism "pathways."

Zylka and his team at UNC believe they have figured out the rough outlines of one such pathway, from the tiny genetic glitch on the gene to the physical changes that the glitch causes in the brain. Like many discoveries, it piggybacked on the work of others, involved a little luck and has raised more questions for researchers.

Zylka and the members of his lab, including postdoctoral fellow Jason Yi, study mutations in a gene that codes for an enzyme called UBE3A,

which helps clear bits of old proteins from cells. They knew that most patients with Angelman syndrome, a rare neurological disorder, have too little of this enzyme, and they knew that some people with autism have too much.

So last November, when a paper came out in the journal *Nature* that listed thousands of genetic mutations in autistic patients, Zylka asked Yi to comb through the data to see if any of those mutations was on the gene that codes for UBE3A.

"To be honest with you, I had gone through all of these mutations for UBE3A and I was kind of sick of making mutations at this point, so I didn't think much of it," Yi said.

Yi had recently identified the part of the gene, called a phosphorylation site, that codes for UBE3A's on/off switch. But, he said, the paper he wrote about his discovery was rejected for not having enough relevance to human health or disease.

It was "a very discouraging time for me," Yi said. "But (the Nature) study turned out to be a bolt of lightning."

What Yi's study described was a single mutation - a swap from an A nucleotide, or DNA molecule, to a G nucleotide - in the DNA of an autistic patient at the exact spot Yi had been researching.

Zylka recalls Yi coming back a few hours later with a big grin on his face.

"He said, 'You're not going to believe this, but that autism mutation is in the phosphorylation site,'" Zylka said.

That meant that the mutation disabled the enzyme's on/off switch,

leaving it permanently stuck in the 'on' position.

It made sense to Yi and Zylka that such a mutation was found in a patient with autism. Scientists already knew that too many copies of UBE3A is associated with a syndrome found relatively frequently in autistic patients. So too much active UBE3A could play a similar role in other autistic patients.

Following up on the Nature paper, Yi, Zylka, and their colleagues first confirmed the mutation made too much active enzyme. They studied cells from the same cell line the authors of that paper had studied. These cells came from an autistic child who had donated blood to the Simons Simplex Collection, a genetic warehouse for autism researchers.

Next, the team wanted to figure out what physical changes excess UBE3A causes that lead to autism.

Yi created a copy of mouse DNA that he mutated in the same way the autistic patient's DNA was mutated and injected it into fetal mice. Then he looked at what happened to the brains of the mice as young adults. He found that in these mice and in mouse neurons in petri dishes the brain cells created too many synapses - connections that help neurons communicate with one another.

That is a physical change in the brain that had already been found in children with autism, although no one understands why or how these extra synapses could lead to the array of symptoms that characterize the autism spectrum.

Yong-Hui Jiang, a professor at Duke Medical School who was not part of the UNC research team, called the study "very interesting" and "elegant" but added that more work needs to be done to truly understand the role of UBE3A in autism.

Yi and his colleagues were unable to show whether the mutation in the child's cell line came from the DNA of the mother or the father. That's important, Jiang said, because only UBE3A coded by the mother's DNA is expressed in brain development.

Understanding the genetic and physical basis for autism is "a complicated biological question," Jiang said, and one that is not easy or quick to study.

Both Zylka and Birnbaum of the National Institute of Environmental Health Sciences believe that in many cases genetic mutations and outside factors probably work together to trigger autism. As Birnbaum puts it, people whose DNA puts them at risk may be "kind of pushed over the edge" when exposed to one or more of these triggers.

With more and more people living with autism, it is becoming increasingly urgent to solve this biological question.

"There is a growing number of adults affected by autism and not a lot of people in the community who know how to support them," said Lauren Turner-Brown, assistant director at UNC's program TEACCH Autism.

Turner-Brown, a clinical psychologist, studies early childhood intervention in autistic children. But she sees a potential application for the genetic work that Zylka, Yi and other researchers are doing.

"With this research we may be able to, sooner than we thought, tailor interventions to particular pathways," she said. "Although I think it may be a while."

As frustrating as that wait might be, she said, this kind of research still inspires hope in families affected by autism.