

Genes provide landmarks on the roadmap of autism

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Many roads can lead to the same place, often crossing over one another and sometimes passing the same landmarks.

The interactome or protein interaction network for [autism spectrum disorders](#) developed by researchers at Baylor College of Medicine and the Jan and Dan Duncan [Neurological Research Institute](#) at Texas Children's Hospital in collaboration with scientists at the Center for Cancer Systems Biology (CCSB) at Dana-Farber Cancer Institute demonstrates how protein pathways converge, diverge and interact to arrive at the same devastating condition.

In a report in the current issue of the journal [Science Translational Medicine](#), Dr. Huda Zoghbi, director of the Neurological Research Institute and professor of neurology, neuroscience, molecular and human genetics and pediatrics at BCM, and her colleagues describe the network that identifies hundreds of new interactions among proteins encoded by [genes](#) associated with [autism](#) spectrum disorder.

It also relays new information about idiopathic autism, which has no known cause. It does this by building on what is known about syndromic autism that often occurs as a symptom of a broader genetic disorder such as fragile X, tuberous sclerosis and Phelan-McDermid syndrome. The three core features of autism present in both idiopathic and syndromic cases include impaired social skills, delayed language and [repetitive behaviors](#).

"The interactome is a more functional approach," said Zoghbi. "It can help us understand how mutations in different genes can cause similar clinical symptoms."

When the study started, she and her colleagues began with 26 genes known to be associated with syndromic autism. Studying each of those singly

and devising a therapy would take a lifetime, said Zoghbi. Together, they account for no more than 30 percent of autism cases. (There are now more than 60 genes associated with autism spectrum disorder, a sign of advances in the field).

"We had these 26 genes that seemed to have little to do with each other but still resulted in autism-like symptoms," said Zoghbi. "We thought that perhaps they cause autism by interacting with some shared partners that function in pathways that lead to similar phenotypes (similar characteristics)."

They took each protein associated with autism and determined the proteins with which they interacted. The complicated network that resulted encompasses 539 proteins that interact with the 26 proteins associated with syndromic autism spectrum disorders. These protein interactions include a variety of genes including transcription factors, RNA-binding proteins, cell adhesion molecules and enzymes involved in modifying and degrading proteins.

Compiling the interactome was a massive undertaking, said [Dr. Chad A. Shaw](#), assistant professor of molecular and [human genetics](#) at BCM and a computational scientist who was a co-corresponding author of the study.

"One of the most important contributions of this interactome is that it provides a deep, experimentally driven foundation that can be used to understand complicated genetic variation," he said.

He credits the paper's first author, Dr. Yasunari Sakai, with important work in constructing the interactome itself which Shaw and his laboratory then analyzed; Sakai also validated random selections of interactions in the laboratory, an exacting, time-consuming task. Sakai was a postdoctoral fellow in Zoghbi's laboratory.

The network confirmed many previously known or hypothesized connections and revealed previously unsuspected connectivity between two syndromic autism spectrum disorder proteins - SHANK3 (SH3 and multiple ankyrin repeat domains 3) and TSC (tuberous sclerosis protein 1).

Shaw compared the information in the network to information from published studies on chromosomal differences known as copy number variations (duplications or deletions of genetic information from chromosomes) that had been observed both in normal subjects and in patients with non-syndromic or idiopathic autism spectrum disorder. He looked for genes that were present both in their network and in the copy number variations in the individuals within the normal and autism groups.

The autism patients had a greater rate of copy number variations that included the genes in the interactome than did the control group.

The team also performed microarray or gene chip analysis for all of the genes in the network on tissue from 288 subjects with idiopathic autism collected by the Simons Foundation Simplex Collection. None of these subjects had any of the symptoms associated with syndromic autism and their intellectual capacities were fairly high.

They identified three previously unrecognized copy number variations that involve three genes found in the network, further confirming the [protein interaction](#) network as a framework for identifying as-yet unknown causes of autism and understanding the molecular pathways that involve both syndromic and idiopathic autism.

"We are at a point in time of being able to measure people's complete genotype," said Shaw. "We can measure more variation than we can interpret. The interactome lets us tag variations to a disease-relevant network. That's why resources like the interactome are important. They help tie the complexity together. If you are trying to diagnose a person, you don't have to have a research study around each gene."

Provided by Baylor College of Medicine

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