NEWS

Web of genes may hold clues for autism treatments

BY **JESSICA WRIGHT**

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Five years ago, scientists saw an exciting pattern emerge from sequencing studies of people with autism: Many of the mutations they picked up affect the function of **synapse**s, the junctions between neurons.

There are trillions of synapses in the human brain, linking billions of neurons. Still, calling autism a '**disorder of the synapse**' gave it encouraging specificity. More data, they hoped, would narrow this spotlight to pinpoint a handful of pathways that could be targets for autism drugs.

Instead, the spotlight has become a floodlight.

In studies over the past few years, most of the genes that have emerged as the strongest autism candidates have turned out to be regulators — meaning that they regulate the expression of hundreds, if not thousands, of other genes. What's more, some of the target genes are themselves regulators, and may even loop back to influence the candidate gene.

"If autism has taught us anything, it's that however complex you think it might be, it's actually more complex," says **Stephan Sanders**, assistant professor of psychiatry at the University of California, San Francisco School of Medicine.

That autism involves so many regulators shouldn't come as a surprise. The defective gene in **fragile X syndrome**, which often leads to autism, controls **more than 800 other genes**, including about **90 autism candidates**[1]. And **MeCP2**, the gene mutated in Rett syndrome, another autism-related disorder, regulates **thousands** of genes.

Many researchers see this complexity as an opportunity: One way forward, they say, is to home in on a few specific pathways that repeatedly turn up among the candidates.

“Instead of saying we’re going to follow one gene that really matters and see what it does, we need to say that each gene is like a little star that points in many directions,” says Sanders. “We need to use these multiple different genes and look for the process, time and place where they all point the same way.”

Building webs:

The **closest thing to an ‘autism gene’** so far is **CHD8**, which emerged as candidate gene just two years ago[2]. CHD8 regulates gene expression by binding to DNA and changing its structure. In stem cells that give rise to neurons, CHD8 binds nearly 7,000 genes, according to a report earlier this month in the *Proceedings of the National Academy of* Sciences[3].

Many of CHD8’s targets **are themselves autism candidate genes**, including **FOXP1**, **DYRK1A** and **ADNP**. The lists of autism genes also frequently overlap with the targets of FMRP, the protein affected in fragile X syndrome[4]. Researchers say that the more candidate genes they uncover, the more they find that their targets may converge at key points.

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“There’s going to be far fewer pathways than there are genes that have been implicated,” says **Michael Talkowski**, assistant professor of neurology at Harvard Medical School and lead researcher on the new study. “I do think they will converge at a number of final points — not just one, but enough that we’ll have targets we can try to manipulate.”

Aiming to find these points of convergence, Talkowski and others are mapping the targets of other regulators implicated in autism, such as **AUTS2**, FOXP1 and **TBR1**. Each of these genes has been found to carry rare, harmful mutations in people with autism. But researchers will probably need to identify **common variants**, found throughout the population, to be able to find points of convergence. “We need to layer different types of data,” says Sanders. “Then you look for convergence, and that convergence leads you toward the true etiology of autism, which leads to a true therapy.”

Some statistical tools take the different types of mutations into account when ranking autism candidates. For example, an algorithm called TADA considers both **common and rare variants** in a gene when rating its significance for autism[5]. TADA’s next iteration, DAWN, will include information on whether a gene responds to an autism-linked regulator such as CHD8, says **Bernie Devlin**, professor of psychiatry at the University of Pittsburgh, who developed both statistical models.

DAWN also takes into account when and where a gene is expressed during development[6]. These

last factors acknowledge the fact that autism is a developmental disorder that **likely begins *in utero***.

“If you’re interested in a specific gene, there may be a way to begin to narrow in on where and when you might want to look, in order to understand how that mutation may be contributing to autism,” says **Matthew State**, professor and chair of psychiatry at the University of California, San Francisco.

Time and place:

Last year, State’s team used an **atlas of the developing brain** to find genes expressed **at the same time and in the same place** as nine autism candidate genes, including CHD8[7]. The networks they uncovered include many known autism candidates, and point to the prefrontal cortex during mid-fetal development as one birthplace for autism.

“All this heterogeneity is actually an advantage, because you can use different methods to understand the systems underlying it,” says **Jeremy Willsey**, a postdoctoral scholar in State’s laboratory. “But we should do it in such a way that tells us something about the particular point in development and the particular region of the brain that’s involved.”

In his new study, Talkowski’s team found that CHD8’s targets tend to fall into the same networks that State’s team found.

These efforts all center on finding one, or a few, converging pathways among autism genes. Another hypothesis holds that each autism symptom has a **separate genetic origin**. If that’s true, researchers may be able to pare down the number of pathways involved by focusing individual symptoms.

For example, Smith-Magenis syndrome is a monogenic disorder characterized by intellectual disability and sleep problems. Another disorder, called brachydactyly mental retardation syndrome (BDMR), is often confused with Smith-Magenis syndrome but stems from a different gene. **Sarah Elsea**’s team at Baylor College of Medicine in Houston, Texas, discovered in 2010 that the gene mutated in BDMR regulates the Smith Magenis syndrome gene[8].

Elsea is using the same approach to look at people who have autism, fragile X syndrome, Smith-Magenis syndrome or 2q23.1 deletion syndrome, all of which share problems with sleep and behavior[9].

“Our hope is that we can find common pathways that are dysregulated in multiple disorders, which could then lead us to a common therapeutic intervention that might be able to alleviate some of

their shared symptoms," says Elsea, associate professor of genetics at Baylor.

Far from being discouraged by autism's complexity, Elsea and others are thinking of creative ways to harness its diversity and find answers.

"There are two levels of complexity we see in autism: First, there are large numbers of genes. Second, each gene does many, many different things," says Sanders. "Each one of those on its own is a disaster moving forward, but actually the combination might make this easier [to solve] than other disorders."

Correction: This article was modified from the original. Matthew State is chair of psychiatry at the University of California, San Francisco, not professor of genetics at Yale University as the original version stated.

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