NEWS

Autism genes are surprisingly large, study finds

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Enzymes called topoisomerases are crucial for the expression of extremely long genes in neurons, according to a study published 5 September in *Nature*[1]. More than one-quarter of these genes are known autism candidates, the study found.

In the process of doing these analyses, the researchers stumbled on something surprising about autism genes in general: They're three to four times longer than the average gene expressed in neurons.

"It's pretty remarkable that, at least to my knowledge, no one had noticed this before," notes **Benjamin Philpot**, associate professor of cell biology and physiology at the University of North Carolina, Chapel Hill, and one of the study's leaders. "But the genes are definitely much longer. It's very striking."

The findings suggest that defects in topoisomerases — whether caused by genetic mutations or environmental influences — may contribute to some cases of autism and other developmental disorders, the researchers say.

If it's true that long genes are preferentially affected in autism, "the implications are really quite fascinating," notes **James Sutcliffe**, associate professor of molecular physiology and biophysics at Vanderbilt University in Nashville, Tennessee, who was not involved in the research.

In genetic sequencing studies, for example, mutations found in long genes tend to be discounted in statistical analyses. That’s because the longer a gene is, the more likely it is to harbor a mutation just by chance. But the new study suggests that mutations in long genes should be considered more carefully.

"This raises a really interesting question of whether we may be correcting away something that’s

inherent to disease risk," Sutcliffe says.

Transcription targets:

Topoisomerases are found in all cells and are known to play a role in unraveling knots in DNA.

"When a cell divides, the DNA gets tangled up, and these enzymes cut the DNA to unwind it," says **Mark Zylka**, associate professor of cell biology and physiology at the University of North Carolina, Chapel Hill, who led the new study along with Philpot.

Drugs that inhibit these enzymes gum up that process, preventing DNA replication and, as a result, cell division. Because of this, these drugs have been used to treat cancer for four decades.

In late 2011, Zylka and Philpot reported in *Nature* that in spinal cord neurons, a topoisomerase inhibitor called topotecan **activates the normally silent copy** of **UBE3A**, the gene that is damaged in **Angelman syndrome**, a developmental disorder related to autism. Duplications of UBE3A are also thought to **cause some cases of autism**.

It was a shock to find out that topotecan had this affect in neurons, Zylka says, because neurons don't divide. "So we wanted to figure out what the heck these enzymes were doing there."

Some studies had shown that, in addition to their role in untangling DNA, topoisomerases are involved in transcribing DNA into RNA sequences[2].

Following that lead, the researchers exposed cultured mouse and human neurons to topotecan and then measured changes in expression across the genome.

Topoisomerase inhibitors turn up the expression of 28 genes and dial down the expression of 155 genes, the study found. All of the dampened genes are large, at least 67 kilobases (kb).

"As you get bigger and bigger, the odds are greater that the gene’s expression goes down," Zylka says. "Around 200 kb or longer, the drugs inhibit like 90 percent of those genes."

The results suggest that topoisomerases are important for the expression of extremely long genes.

The paper showcases “some really, really beautiful cell biology," says **Brett Abrahams**, assistant professor of genetics at the Albert Einstein College of Medicine in New York, who was not involved in the study. "It's less clear to me what to make of the potential autism link."

Autism lists:

The researchers noticed that many of the genes regulated by topoisomerases are involved in the

function of **synapses**, the junctions between neurons, and also in autism. They cross-referenced their list with autism candidate genes catalogued by various sequencing studies and by **SFARI Gene**, a comprehensive database of genes linked to autism. (SFARI Gene is funded by the Simons Foundation, SFARI.org's parent organization.)

They found that 49 of the 183 genes affected by topoisomerases — 27 percent — had previously been linked to autism, a proportion much higher than would be seen by chance.

While this work was underway, two other studies appeared showing that a few individuals with autism carry **mutations in topisomerase genes**[3, 4]. This month, two studies in *Nature Neuroscience* linked TOP3B — a topoisomerase that influences RNA — with schizophrenia, cognitive impairment and **fragile X syndrome**[5, 6].

The researchers also found that the autism candidate genes on their list are 217 kb on average, compared with 59 kb for a typical gene expressed in neurons of the cortex.

Abrahams notes, however, that a lot of the genes on the list have been only weakly linked to autism. What's more, he says, it's unclear whether the long-gene effect is specific to autism.

"What about cancer genes? What about diabetes genes? What about genes involved in sleep regulation?" Abrahams asks. "If you were to take any of these other lists, would they also show enrichment for long genes?"

Nobody knows why autism genes might be so long. Zylka speculates that it might be because of mechanisms involved in replicating DNA. In dividing cells, he says, there is a selective pressure against long genes because the enzymes involved in making RNA and copying DNA can crash into each other.

Neurons don't divide, however. "We think that evolutionarily, neurons can express these really big genes because there aren't as many detrimental effects," he says.

In ongoing experiments, Zylka and Philpot are investigating drugs that, like topoisomerase inhibitors, have the ability to disrupt the enzymes and, in turn, upset a host of autism genes.

"That's something we're really, really interested in — environmental influences," Philpot says. So far, he and Zylka have found at least one compound that has effects on long genes similar to those of topoisomerase inhibitors. "We have some exciting data."

References:

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