Scientists discover tiny gene fragments linked to brain development and autism

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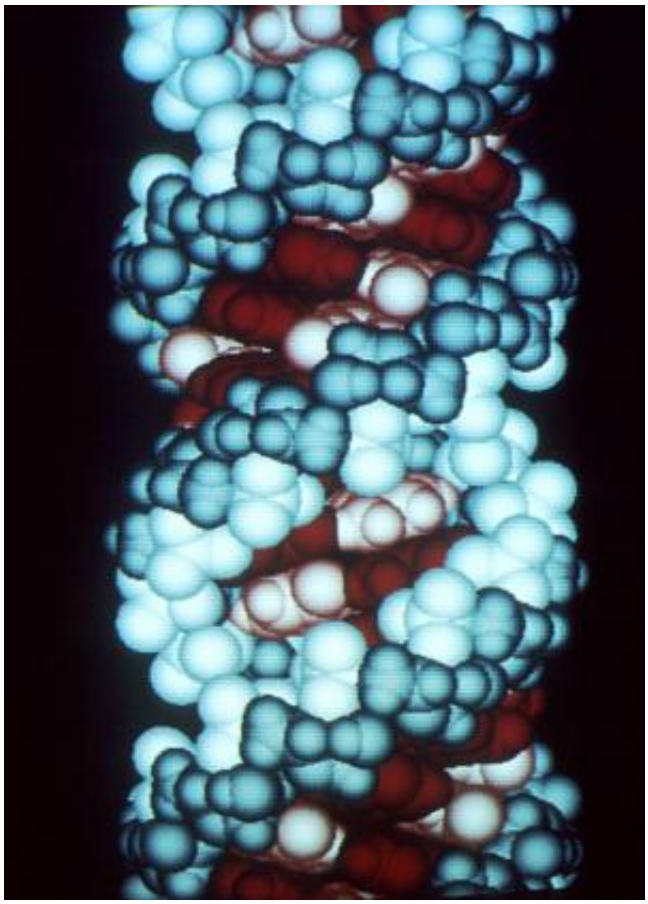

This is a computer graphic of an RNA molecule. Credit: Richard Feldmann/Wikipedia

Very small segments of genes called "microexons" influence how proteins interact with each other in the nervous system, scientists at the University of Toronto have found, opening up a new line of research into the cause of autism.

The researchers found that microexons are used in neurons by alternative splicing, a process in which a single gene can produce many different proteins. Microexons are pasted—or spliced—into gene messengers (mRNAs) to generate forms of proteins that the nervous system needs to function properly. Misregulation of this process, the researchers found, can have major effects on how proteins function.

"We're seeing a new landscape of splicing regulation that is highly specific to the nervous system, and which is very important for controlling how proteins interact with each other," said Benjamin Blencowe, a Professor in the University of Toronto's Donnelly Centre for Cellular and Biomolecular Research and Department of Molecular Genetics. "In addition, a large number of the microexons we detected show misregulation in people with autism."

Scientists—including Blencowe and his colleagues at U of T—previously created algorithms to predict which exons are spliced in mRNAs to produce proteins. But these algorithms failed to capture microexons.

In their new study, Blencowe and his colleagues, led by postdoctoral fellow Manuel Irimia, created a new computational tool that detects many more splicing combinations within a cell, including those that involve microexons. They used their tool to discover splicing of microexons in neurons.

The leading biomedical research journal *Cell* published the findings.

"We were really surprised to find that some microexons encode just 1 or 2 amino acids—the basic building blocks of proteins," said Irimia, who recently took a position as a junior group leader at the Centre for Genomic Regulation in Barcelona, Spain, where he is setting up his own lab. "And they modify proteins—changing their surface structures—in ways that longer exons cannot. Microexons perform a type of microsurgery on proteins to alter their function."

The researchers also found that neuronal microexons are highly conserved during evolution,

which strongly suggests they play conserved functional roles. They discovered the existence of similar microexons in many vertebrate species, including mice and humans.

Perhaps most importantly, the researchers also found that even though microexons make very small changes to proteins, the effects of those changes can be dramatic. For example, when they deleted microexons they found that in some cases proteins completely lost their ability to interact with partner proteins.

As well, the group found that many neuronal microexons are weakly spliced in the brains of some individuals with autism, and that this reduced splicing activity is linked to the under-expression of a splicing regulatory protein called nSR100. Blencowe is cautiously optimistic about the potential therapeutic value of this discovery. "While a lot more work has to be done to understand the functions of microexons in the nervous system, we were amazed by the extent to which microexons are misregulated in people with autism, which suggests they are an important component of this neurological disorder."

Blencowe and his colleagues are pursuing the role of nSR100 in autism as they map the function of microexons in more detail. By following this line of research, they hope to learn how the misregulation of microexons contributes to autism as well as other disorders of the nervous system.

"Microexons are an underappreciated class of splicing event that is highly conserved. They change the way proteins interact and clearly play an important role in development, so understanding their role in human neurological disorders represents a major avenue of future research," said Blencowe.

More information: Irimia M et al. "A highly conserved program of neuronal microexons is misregulated in autistic brains" *Cell* 18 Dec 2014.

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