NEWS

Single gene insufficient to account for dup15q, Angelman traits

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Active cells: *Neurons with genetic mutations in the 15q11-13 chromosomal region have increased excitability and atypical synaptic function.*

Multiple genes shape the traits of the autism-linked conditions dup15q syndrome and Angelman syndrome, according to two new unpublished studies. The work was presented Tuesday at **Neuroscience 2022** in San Diego, California.

Angelman syndrome is caused by deletions or mutations in the maternal copy of the 15q11-13 chromosomal region, whereas dup15q syndrome stems from duplications of it. Although traits differ for the two conditions — dup15q more frequently results in autism, for example — both syndromes are linked to an increased likelihood of seizures and developmental delay.

Researchers have long suspected that a single gene in the region, UBE3A, drives Angelman syndrome, and it has been considered an important target for dup15q syndrome as well. Over- or under-expression of the maternal, but not paternal, 15q11-13 region leads to one or the other of the two conditions — clueing researchers in to the idea that UBE3A, which is silenced on the paternal copy through imprinting, is at fault.

People with Angelman syndrome who lose expression of UBE3A and other genes within the 15q11-13 region have **more severe traits** than do those who lack only UBE3A. And animal models that overexpress UBE3A do not **fully capture** the dup15q syndrome phenotype — suggesting that other genes shape the traits associated with that condition as well.

But which traits stem from atypical expression of UBE3A, and which other genes might be involved, has been unclear, says **Marwa Elamin**, a postdoctoral fellow in **Eric Levine**'s lab at the University of Connecticut School of Medicine in Farmington, who presented one of the posters.

The new work confirms that changes to UBE3A expression contribute to many, but not all, of the atypical traits seen in neurons carrying dup15q and Angelman syndrome mutations.

The findings have important implications for the development of treatments, says **Ben Philpot**, professor of cell biology and physiology at the University of North Carolina at Chapel Hill, who was not involved in the studies. “Targeting some of the other genes might also provide therapeutic benefit.”

Neurons grown from stem cells of people with dup15q syndrome fire more spontaneous action potentials than do control neurons that have the same genetic background but no extra chromosomal region, the researchers **previously reported**. That sort of extra activity could lead to the seizures seen in people with the condition, the team hypothesizes.

Dup15q neurons also have decreased inhibitory postsynaptic currents and a more permeable cell membrane, the team found in the **study** Elamin presented, which is also available as an unpublished **preprint**. Lowering UBE3A expression using an antisense oligonucleotide (ASO), a short strand of RNA that can modify protein expression, normalizes the cells’ spontaneous activity and intrinsic excitability, but it does not alter their membrane permeability.

The most common form of dup15q syndrome stems from an ‘isodencentric duplication,’ which results in two extra copies of the maternal 15q11-13 chromosomal region. Because paternal UBE3A is silent, that results in three functional copies of the gene as opposed to the typical one.

To replicate that same excess of UBE3A without overexpressing other genes within the 15q11-13 region, Elamin and her colleagues used neurons derived from a person who has two copies of UBE3A on their paternal chromosome and used an ASO to unsilence those copies. Overexpression of UBE3A replicated the intrinsic hyperexcitability seen in dup15q cells but not the altered synaptic transmission or increased membrane permeability, the team found.

Neurons grown from stem cells from people with Angelman syndrome have different properties depending on how much of the 15q11-13 region is affected, the team found in work presented in their second **poster**, suggesting that UBE3A is not the whole story there either.

Cells that carry a full deletion of the region are more excitable and have more atypical synaptic activity than those that only have a loss-of-function mutation in UBE3A, the researchers showed.

“The other genes are clearly involved,” Levine says.

In addition to UBE3A, the 15q11-13 region contains genes that code for a receptor for the inhibitory **neurotransmitter** gamma-aminobutyric acid (GABA). Unlike UBE3A, those genes are expressed from both the maternal and paternal copies. And because many people with dup15q syndrome also have epilepsy, the team hypothesized that something may be going wrong with this receptor, which

is targeted by many anti-seizure medications.

Decreasing the expression of the receptor subunit GABRB3 using an ASO lessened the hyperexcitability of dup15q neurons. And doing the same in neurons from people with Angelman syndrome enhanced their problems with inhibitory transmission but did not affect other properties of the cell — leading the team to believe that decreased expression of GABRB3 is at least partially responsible for the synaptic changes seen in Angelman syndrome neurons.

Normalizing receptor levels during development may give the neurons “an opportunity to try and develop in a more typical way,” says **Deepa Anjan Kumar**, a graduate student in Levine’s lab who presented the work. But, she says, the results are preliminary and need to be confirmed.

The findings suggest that scientists will need to target genes other than UBE3A to address the full spectrum of traits seen in the conditions, Anjan Kumar says.

Doing so may have other benefits too. For one, normalizing UBE3A levels must happen early in development to have a strong effect, Levine says. But targeting other genes, such as those that encode the GABA-A subunits, he says, may be beneficial later in development.

The team plans to investigate how expression of other two GABA-A subunits — as well as other genes within the 15q11-13 region — contribute to neuronal function. If they can identify the genes other than UBE3A that contribute to the conditions’ phenotypes, researchers could develop better mouse models for translating treatments, Levine says.

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