NEWS

Researchers home in on dosage effects of 15q11-13 region

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Image 15q quotas: People with a third copy of a part of chromosome 15 fare worse than those who have a duplication of that region.

To the uninitiated, the developmental disorders linked to the 15q11-13 region of the genome can be tough to keep straight. The region may, in fact, be “the most complicated in the genome in terms of how it’s regulated,” **Scott Dindot**, assistant professor of veterinary medicine at Texas A&M University, said Thursday at a conference in Boston **organized by the Dup15q Alliance**.

People can wind up with too little or too much of the products of genes within the region in a multitude of ways: The region is susceptible to copy number variations — deletions or duplications of DNA — and subject to imprinting, a process in which either the maternal or paternal copy of a gene is silenced.

Deletion of the maternal copy leads to **Angelman syndrome**, an autism-related disorder, and **duplication of the maternal copy** is linked to autism. Deletion of the paternal copy of the region leads to Prader-Willi syndrome, which is characterized by intellectual disability and extreme hunger.

To further complicate the situation, duplications of the region come in two main flavors: an ‘interstitial’ duplication within the chromosome that leads to an extra copy and an ‘isodicentric’

form, in which people have extra genetic material from chromosome 15, generating two extra copies of the region.

Taken together, the different cases represent a range of doses of genes within the region and an opportunity to explore the role that gene dosage plays in these disorders.

Clear culprit:

A gene called **UBE3A** within this region is thought to be the primary cause of neurodevelopmental disorders. The paternal copy of the gene is silenced in neurons, and mutations in it are sufficient to cause Angelman syndrome.

One major question that researchers are trying to answer is whether changes in the number of copies of UBE3A are responsible for the autism symptoms seen in people with Angelman or 15q duplication syndrome.

The answer is not yet clear, but researchers are beginning to better grasp the differences in autism symptoms between children with 15q duplications and those with idiopathic autism — meaning of unknown cause — as well as the differences between the interstitial and the isodicentric duplications.

The majority of research into 15q duplications has focused on the isodicentric form, probably because individuals with this form have more severe symptoms and are more likely to seek medical care or be referred to research studies. These children also have higher rates of seizures than those with other types of autism.

What's more, says **Carolyn Schanen**, head of Human Genetics Research at A.I. duPont Hospital for Children in Wilmington, Delaware, their social behavior appears different from that of other children with autism.

"They are not aloof and can be very social," Schanen said at the conference. "But they don't have a sense of their own space or yours."

According to unpublished data she presented at the conference, children with the interstitial duplication appear to have milder symptoms.

"They have higher [intelligence quotients], higher-functioning autism and fewer seizures," said Schanen, who is studying a group of these children in collaboration with **Larry Reiter**, associate professor of neurology at the University of Tennessee in Memphis. "You really get a sense of dose effect."

Reiter has found that some children with a paternally inherited duplication show symptoms as

well. Two of four children the researchers have studied have an autism spectrum disorder. (Two of the children are siblings; one is affected and the other is not.) All of the children with a maternally inherited duplication have an autism diagnosis.

Reiter's team also found electroencephalography recordings in patterns reminiscent of those from people taking benzodiazepines, even though none of these children took these drugs, he says.

Cellular effects:

Researchers are also tackling the question of gene dosage on a cellular level.

Stormy Chamberlain, assistant professor of genetics and developmental biology at the University of Connecticut in Farmington, is developing induced pluripotent (iPS) stem cells— adult cells that have been reprogrammed into a stem-cell state — from people with either 15q duplications or deletions.

One notable sample came from a woman who is a 'mosaic' for the duplication, meaning that the extra DNA is present in only some of her cells. Researchers can make **iPS cell lines** with and without the duplication from this one woman, allowing them to compare the effect of the duplication in two otherwise genetically identical lines of cells.

According to research Chamberlain presented at the conference, imprinting of these cells is stable throughout the reprogramming process, an issue that has been of concern in some iPS cell models.

The researchers plan to differentiate these stem cells into neurons and compare neuronal shape in people who have 15q duplications with those with Angelman or Prader-Willi syndromes. Comparing these three types of neurons may help researchers understand more precisely the cellular effect of different levels of UBE3A.

"This could be a powerful comparison to determine if these disorders are really [UBE3A] dose-dependent," said Chamberlain.

Examining gene-expression changes in neurons from people with either 15q duplication or Angelman syndrome reveals some surprising similarities. "We see far more similarities than differences," said Chamberlain.

One of the potential benefits of iPS cell models of different disorders is the ability to screen drug candidates in human cells. Chamberlain says her team has identified a compound that decreases UBE3A expression, which could be useful in treating people with 15q duplications.

*For more reports from the 2012 Dup15q Scientific Meeting, please **click here**.*