NEWS

Close look at autism-linked region reveals complex biology

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Word reversal: Children who lack one copy of the 16p11.2 chromosomal region (top) tend to use the right hemisphere of the brain to process language, whereas controls use the left hemisphere (bottom).

Having too many or too few copies of a gene, or a chromosomal region, would presumably have opposite effects on the body. But that's not always the case, new research suggests.

Deletions or duplications of large stretches of DNA, called **copy number variations**, are increasingly thought to **play a major role in autism**. About 1 percent of people with autism have deletion or duplication of **16p11.2**, one of the best-known risk regions for the disorder. The region, which spans 29 genes, has also been linked to **intellectual disability**, **epilepsy** and schizophrenia.

Deletion and duplication of 16p11.2 do have opposite effects on brain size — an intuitive result — researchers reported earlier this month at the **2013 Society for Neuroscience annual meeting** in San Diego. But these alterations produce similar abnormalities in the brain's processing of sound.

There's also evidence that deletions and duplications are **not harmful to the same degree**. Deletion of the 16p11.2 region tends to have more serious neurodevelopmental effects than does duplication, although it is unclear why this is so.

Roughly 20 percent of individuals who carry the deletion and 10 percent of those with the duplication have autism. In six posters presenting unpublished data, researchers painted a complicated picture of the biology underlying these alterations.

Early studies simply pegged 16p11.2 as an autism 'hotspot,' notes **Shafali Spurling Jeste**, assistant professor of psychiatry and neurology at the University of California, Los Angeles, who is not involved in any of the work.

"What's emerging in the field of neurogenetics of autism is that the location of a mutation is only one part of it," Jeste says. "The kids with the deletion look very different from the individuals with the duplication."

Foggy findings:

The posters presented at the conference are part of the **Simons Variation in Individuals Project** (Simons VIP), an effort to comprehensively study people with deletion or duplication of 16p11.2. (The project is funded by the Simons Foundation, SFARI.org's parent organization.)

"The hope when we first started was that a genetics-first approach would give us a very clear finding," says **Srikantan Nagarajan**, director of the Biomagnetic Imaging Laboratory at the University of California, San Francisco, who is involved in collecting and analyzing brain imaging data for the project.

Enlarge image >>Emily Elert

Emily Elert

If anything, the data so far, which include measures of brain structure as well as function, seem to

suggest the opposite.

Four posters included data from up to 32 children with deletions and up to 20 adults with duplications. The other two included data from children with deletions alone.

The researchers are also studying children with duplications, although none of these data have yet been reported. The project includes only a handful of adults with deletions because most people with a deletion have significant impairments, making them difficult to recruit for a study as adults.

For example, many individuals with 16p11.2 deletion have intellectual disability. More than one-third have larger-than-normal head size, or **macrocephaly**, and one-quarter have epilepsy. They also have a tendency **to become obese**.

Individuals with the duplication are more likely to have smaller-than-normal head size. They also have elevated rates of epilepsy and intellectual disability compared with controls. Overall, however, people with 16p11.2 duplication often have relatively mild symptoms compared with those who carry a deletion.

Adding to this impression, many of the adults with duplications in the Simons VIP study are parents or other relatives of the children with duplications, and were only identified as having the duplication after the children enrolled.

Brain scans of the Simons VIP participants show that children with 16p11.2 deletion have more gray matter and total brain volume, and a larger thalamus and cerebellum, than controls do. As one might expect, adults with duplications show the opposite pattern.

Results from this analysis also suggest that the abnormalities in brain growth happen early in development, consistent with **studies of the region in zebrafish**.

Another poster probed the structure of white matter, the long bundles of cellular fibers that connect neurons. The analysis found that in children with 16p11.2 deletion, nerve fibers fan out less than those of controls as they travel from one area of the brain to another. This suggests that the nerve fibers are more organized than in controls, says **Pratik Mukherjee**, professor of radiology at the University of California, San Francisco, who presented these results.

That’s surprising, because studies of neuropsychiatric disorders have often shown that people with autism have white matter with less integrity — meaning it is more disorganized — than in controls. However, some studies have found more organized white matter in **infant siblings of children with autism** who go on to develop the disorder themselves, as well as **in people with Williams syndrome**.

It’s not yet clear how this pattern of organization relates to the symptoms seen in people with

16p11.2 deletion. “It’s an observation at this point,” says Mukherjee.

Language links:

Some of the work presented at the conference focused on the structure and function of language areas of the brain in people with 16p11.2 alterations.

Individuals with either deletions or duplications commonly have language impairments. They have low verbal intelligence quotients and tend to do poorly on tests of non-word repetition, which measure how fast and accurately a person can repeat meaningless syllables.

Emily Elert

Source: Luo R. *et al. Am. J. Hum. Genet.* (2012) **PubMed**

“They just have a hard time speaking in general,” says **Leighton Hinkley**, a postdoctoral scholar in the Biomagnetic Imaging Laboratory at the University of California, San Francisco.

Magnetoencephalography, which uses powerful magnets to measure the electrical currents generated when nerve cells fire in the brain, shows that children with 16p11.2 deletion have auditory processing delays **similar to those seen in autism**, but of about half the magnitude.

That pattern is seen even in those who have the deletion but are not diagnosed with autism. “It’s not specific to the autism phenotype,” says **Tim Roberts**, vice chair of pediatric radiology at the Children’s Hospital of Philadelphia.

More broadly, Roberts and others have shown some overlap in patterns of brain activity between deletion and duplication carriers, as well as patterns distinctive to each group.

For example, brain activity triggered by hearing simple tones, a measure called the M100, occurs a few milliseconds later in children with 16p11.2 deletion than in controls, Roberts’ team found. The same delay occurs in adults with the duplication.

“There is a sort of prevailing notion that deletions are worse than duplications, but I’m not sure

that's true in all domains," Roberts says.

On the other hand, the brain's response to hearing a change in speech sounds — a 'u' after a series of 'a' sounds or *vice versa* — is delayed in children with 16p11.2 deletion but faster among adults with the duplication.

"The fact that they find differences between the deletion and the duplication is important, because that might inform how we design language-based interventions," says Jeste.

When it comes to spoken language, too, deletion and duplication carriers differ. Asked to name objects in a picture, such as a hammer or a cat, controls tend to show more activity in the left hemisphere of the brain, and so do adults with 16p11.2 duplication. But children with the deletion are more likely to show right-hemisphere dominance.

"The more they use the right hemisphere, the more severely they are impaired in non-word repetition," says Hinkley, who presented this work.

These studies give a more complex — and thus more accurate — view of the effects of 16p11.2 deletion and duplication, but they don't answer a key question: why only some individuals with these genetic alterations also have autism.

"The problem with 16p is that we don't diagnose 16p until the kid has autism, because that's why they get the genetic testing," Jeste says. Studying children with autism-linked genetic conditions that are typically diagnosed earlier in life — such as tuberous sclerosis or duplication of the 15q11-13 chromosomal region — might better enable researchers to follow children as autism emerges, she says.

"The bottom line is that we need to do some really rich brain-based phenotyping across syndromes," Jeste says — for example, comparing individuals with the five or six most common genetic alterations linked to autism. "I think it's time to take it to the next step, and look deeper."

For more reports from the 2013 Society for Neuroscience annual meeting, please ***click here****.*

Correction*: The graphic on the genetic underpinnings of 16p mutations has been changed to indicate that most deletions of the region occur spontaneously and most duplications are inherited. A previous version of the graphic suggested the opposite.*