NEWS

Gene screen reveals altered chemical tags in autism brains

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One of the largest genome-wide screens of chemical tags in postmortem brains has found that people with autism have three unique regions of methylation, reports a study published 3 September in *Molecular Psychiatry*[1].

Methyl groups are chemical tags on DNA that switch genes on or off without changing the DNA sequence. Environmental factors such as stress or diet can alter methyl tags and other DNA modifications, collectively called **epigenetic** tags.

Known genetic variants in DNA account for **less than half of autism cases**, according to researchers, underscoring the importance of other rare genetic or environmental influences that may contribute to the disorder.

"What I think our study shows is that maybe you need to combine the genetic and the epigenetic analyses to find out what's really happening," says senior researcher **Andrew Feinberg**, director of the Center for Epigenetics at Johns Hopkins University School of Medicine in Baltimore, Maryland.

Studies have previously linked epigenetics to autism: A 2011 postmortem brain analysis of the prefrontal cortex, an area of the brain associated with decision-making, found **different chemical changes** on the histones, proteins entwined with DNA, in people with autism versus controls.

In the new study, Feinberg and his colleagues looked at postmortem brains from 19 people with autism and 21 controls. They inspected the DNA of these individuals, looking for methyl groups attached to the DNA base cytosine.

Their test found three regions with unusual patterns of methylation in autism brains — specifically in

the temporal cortex, a part of the brain associated with memory, hearing, and language and speech production. They did not find significant differences between the two groups in the prefrontal cortex and the cerebellum, the other two areas they screened.

The researchers replicated their findings with two independent tests, one of which involved a different methylation assay.

"What I liked is the fact that it held up in the replication study," says **Janine LaSalle**, professor of medical microbiology and immunology at University of California, Davis, who was not involved in the study. "There's a lot of interest about whether there are epigenetic marks that can be found in autism, but I think this is one of the larger genomic looks at autism in postmortem brains."

Methylation measures:

For their study, Feinberg and his colleagues used postmortem brains from three brain banks: the **Autism Tissue Program**, the **Harvard Brain Tissue Resource Center** and the National Institute of Child Health and Human Development's **Brain and Tissue Bank for Developmental Disorders** .

The three brain regions the researchers focused on have all been implicated in autism. In the autism group, they had six tissue samples of the temporal cortex, six of the prefrontal cortex and seven of the cerebellum.

In the temporal cortex of autism brains, they found three sections in the genome, each a few hundred base pairs long, that have significantly more or fewer methyl tags than controls do.

The first section includes part of a gene called PRRT1. The second resides within the promoters — sequences that control gene expression — of two genes, TSPAN32 and C11ORF21, and extends into part of C11ORF21.

Little is known about these regions, but PRRT1 has been found to be active in the hippocampus of marmoset monkeys, often used to model the human brain[2]. Interestingly, some people with autism have been shown to have a larger hippocampus than controls do[3].

The third genomic region is located between genes, but is closest to a gene called ZFP57. This gene maintains proper imprinting during development, in which the gene from one parent is turned off — an event that goes awry in several disorders associated with autism, including Rett syndrome[4].

These findings are intriguing, but represent a preliminary step toward understanding the epigenetics of autism, experts say.

"It's fine for a first pass, but it's really limited in terms of where it's looking," LaSalle says, adding that little methylation occurs at promoters, where the screen tends to concentrate.

For example, it's surprising that the researchers found only three regions of difference between the autism and control groups, says **Valerie Hu**, professor of biochemistry and molecular medicine at George Washington University in Washington, D.C., who was not involved in the study. "I expected more," she says.

Looking at a larger number of postmortem brain tissues may reveal more regions that are methylated, she adds. Also, two of the threeregions identified in the temporal cortex are about 8 percent less methylated than controls, and the third is 9 percent more so — not a big difference, says Hu.

Still, experts say, the study provides proof of principle that epigenetic differences exist between people with autism and controls, and paves the way for more rigorous — and more expensive — screening for methylation patterns.

References:

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