NEWS

Diverse causes of autism converge on common gene signature

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The brains of people with autism show a distinct molecular signature, according to the largest-yet postmortem study of people with the condition[1]. The signature reflects alterations in how genes are pieced together and expressed.

The findings confirm and extend those from two smaller **studies of autism brains** — one from 2011 by the same research team and another **from 2014** by a different group.

“We can be now fairly certain that this pattern really means something,” says lead researcher **Daniel Geschwind**, distinguished professor of neurology, psychiatry and human genetics at the University of California, Los Angeles. “However, it goes beyond the convergence,” he adds. “There’s a lot of new biology we’ve learned.”

The study, which appeared 14 December in *Nature*, suggests that the diverse molecular underpinnings of autism converge on a key set of biological pathways.

“Even with very different genetic and presumably also environmental risk factors that place these people with an autism diagnosis, they all seem to share certain features of their gene expression,” says **Evan Macosko**, assistant professor of psychiatry at Harvard University, who was not involved in the study. The findings “could give us some deep insight not only potentially into the cause of autism, but also how we might be able to [treat] it.”

Pattern recognition:

Geschwind’s team sequenced RNA in postmortem brain tissue from 48 people with autism and 49 controls. The samples come from either the cerebellum, which coordinates movement, or the frontal and temporal regions of the cerebral cortex, which play key roles in attention, planning and thought.

The researchers identified 584 genes that are expressed at higher levels in the cortical tissue from people with autism than in controls, and 558 expressed at lower levels. This pattern appears in more than two-thirds of the autism samples.

Geschwind's team found that many of the same genes show altered expression in the cerebellum of people who have autism compared with controls, but the differences are not statistically significant.

Of the RNAs expressed at different levels in the autism brains, 60 are '**long noncoding RNAs**.' These are RNAs that are not translated into protein but can regulate the expression of other genes. Levels of two of the RNAs — LINC00693 and LINC00689 — normally decrease during development, but are unusually high in autism brains, Geschwind and his team found.

The researchers then looked at gene expression patterns in the frontal and temporal regions of the cortex. They found that the expression of 523 genes differs between the two regions in control brains, but not in the autism brains. This finding could reflect problems in the specialization of these two regions of the cortex in people with autism, Macosko says.

Cut and paste:

RNA copies of genes can be cut and pieced together in various ways via a process called alternative splicing. Compared with controls, the autism brains show a distinct pattern of splicing in the cortex, but not in the cerebellum, the researchers found.

Many of the 833 genes that show atypical splicing in autism brains are important in neurons. Geschwind's team found unusually high or low expression of genes necessary for splicing in neurons.

The splicing seen in the brains of people with autism is known to occur in response to increased neuronal activity. Some people with autism are thought to have an **excess of excitatory brain signals**.

Splicing alterations may either underlie this imbalance in brain signals or occur in response to it, says **Chaolin Zhang**, assistant professor of systems biology at Columbia University, who was not involved in the study.

In a companion paper published in December in *Molecular Cell*, Geschwind and his colleagues explored the behavioral effects of altered splicing by deleting one copy of a splicing factor gene called nSR100/SRRM4 in mice. These mice show hypersensitivity to sounds and a decrease in social behavior, both of which are associated with autism[2].

The findings help to firmly establish altered splicing patterns as an important component of autism,

Zhang says. “This gives a more complete picture of the landscape of autism mechanisms,” he says.

Aligned expression:

Geschwind and his team looked in detail at a subset of people in their study who had an extra copy of the **15q11-13 chromosomal region** — a genetic change **tied to autism**. These nine individuals have gene expression and splicing patterns similar to the rest of the autism group, the researchers found.

“I find that result interesting and remarkable,” says **Lilia Iakoucheva**, associate professor of psychiatry at University of California, San Diego, who was not involved in the work. “It points to convergence between different subtypes of autism.”

To evaluate how altered gene expression affects brain function, the researchers used a statistical analysis that grouped genes into 24 ‘modules’ based on their expression patterns in brain tissue. They then compared the functions of the genes in each module.

Three of the modules show increased activity in the autism brains and contain genes involved in **immune processes**. These genes function primarily in star-shaped brain cells called **astrocytes** and immune cells called **microglia**, both of which are implicated in autism.

Another three modules show dampened activity in autism brains. These include genes that operate in neurons and coordinate their communication.

The researchers then explored how the activity in each module varies by age of the donor. (The donors ranged from 2 to 67 years.) They found that the differences between people with autism and controls tend to be most apparent in teenagers and young adults.

“This pattern isn’t necessarily there in everybody at birth — there’s a window of time over which these patterns appear,” Geschwind says. “Maybe there’s a treatment window there, where you could prevent that from occurring.”

Preliminary data suggest that part of the gene expression signature the researchers found is **specific to autism**, but the team has not yet fully explored possible overlap with related conditions. The next step is to figure out how mutations linked to autism alter gene expression.

REFERENCES:

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2. Quesnel-Vallières M. *et al. Mol. Cell* **64**, 1023-1034 (2016) **PubMed**