NEWS

Middle Eastern families yield new genetic clues to autism

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Autism may interfere with the brain?s ability to adapt to experience early in development, according to a study published today in *Science* that uncovers several new risk genes for the disorder[1].

Because the brain relies on experiences, such as seeing or hearing, to fine-tune its connections early in life, any loss of plasticity would derail brain development.

Based on a study of 104 families in the Arabic Middle East, Turkey and Pakistan, a team of researchers led by Harvard University?s **Christopher Walsh** identified several genes, which may all be involved in turning nerve cell responses triggered by experience into substantial changes in the levels of certain proteins in the brain. In essence, this process allows experiences to sculpt the brain.

When these genes are mutated, as they are in some people with autism, the brain loses this adaptability.

“There are elaborate mechanisms to ensure that the production of proteins used to make and break synaptic connections keeps up with demand,” says **Mark Bear**, professor of neuroscience at the Massachusetts Institute of Technology. This new study, he says, supports the idea that “out-of-control protein synthesis at synapses ? either too much or too little ? is a cause of autism.”

Walsh and his colleagues initially set out to discover whether autism is a recessive disorder.

Recessive disorders result when a child inherits one disabled copy of a gene from each parent. The parents are only ‘carriers? of the disease, and have one working copy and one disabled copy. Because this double hit of disease genes in the child is rare, the researchers upped their odds of finding them by studying people with a history of autism in their families in regions where marriage between first or second cousins is common.

“All of us carry about a half a dozen silent mutations,” notes Walsh, chief of genetics at Children?s Hospital Boston. “But parents who have shared ancestry tend to carry the same silent mutations as each other.”

Using a technique called ‘homozygosity mapping,? the team found double deletions in individuals with autism in 5 of the families.

The deletions are large and rare, and absent in thousands of controls. “They're like a smoking gun there,” Walsh says. “They just present themselves as soon as you take your first look at the data.”

As expected for a recessive disorder, each parent carries one copy of the deletion, and unaffected siblings either have no deletions or carry one copy.

“Their evidence strongly suggests that homozygosity of these deletions is sufficient to cause autism,” says **John Rubenstein**, professor of psychiatry at the University of California, San Francisco.

Diverse disorder:

The deletions are diverse, located in different regions of the genome in each family. This diversity is a recurring finding in autism genetics, which has so far implicated individually rare mutations.

Walsh has noted a similar phenomenon in other developmental brain disorders, such as mental retardation. “It?s very rare to find two kids who have the same gene involved,” he says. “And so I expected autism to behave exactly the same way.”

One deletion eliminates a gene called C3orf58, which encodes a protein involved in localizing other proteins within cells. Other deletions affect enhancers, which control the genes? on-off switches.

These enhancers target PCDH10, a gene involved in the growth of axons, and NHE9, which encodes a sodium-hydrogen exchanger important for maintaining ion concentrations within cells.

Protein trafficking, axon outgrowth, and ion exchange are diverse and seemingly unrelated cellular functions. But the researchers found that the expression of all of these genes increases in response to nerve cell activity.

This discovery was “completely serendipitous,” says Walsh, and arose from a chance conversation with his Harvard colleague **Michael Greenberg**.

Greenberg?s work traces the molecular pathway that translates brain activity into changes in gene expression, which, through protein synthesis, can then lead to real effects downstream, such as synapse maturation.

“It?s an intricate process involving many genes,” says Greenberg. “It may be subtle abnormalities in that process which will be found to be a root of autism.”

Greenberg says fewer than five percent of all genes are regulated by neuronal activity, but after hearing Walsh?s talk at an Autism Speaks symposium in January he realized that several of the genes in Walsh?s study belong to this select group.

“[Greenberg] said, ‘Your genes, they're all on our list,” recalls Walsh. “Then the sparks started flying.”

Different mutations in autism might interfere in this molecular pathway at different points, says Walsh.

There is some evidence supporting this hypothesis: one component of the pathway is MECP2, the gene mutated in Rett syndrome[2].

“[This] might be a way of unifying, maybe not all, but many different autism mutations into a common mechanism that might still represent a therapeutic avenue,” Walsh says.

Restoring gene expression and protein production to normal levels might be one way to treat autism. Bear and his colleagues have used this approach to **reverse symptoms in a mouse model** of fragile X syndrome[3], a disorder characterized by autism. Another group has done the same in a mouse model of Rett syndrome[4].

References:

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