Middle Eastern families yield intriguing clues to autism

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Research involving large Middle Eastern families, sophisticated genetic analysis and groundbreaking neuroscience has implicated a half-dozen new genes in autism. More importantly, it strongly supports the emerging idea that autism stems from disruptions in the brain's ability to form new connections in response to experience – consistent with autism's onset during the first year of life, when many of these connections are normally made.

Interestingly, not all the affected genes were actually deleted, but only prevented from turning on – offering hope that therapies could be developed to reactivate the genes. The study, led by researchers at Children's Hospital Boston and members of the Boston-based Autism Consortium, is the cover article in the July 11 issue of *Science*.

Autism genes have been difficult to identify because the disorder is complex, with a variety of causes stemming from many possible genes or combinations of genes. In addition, since people with autism tend not to have children, most of the genes identified thus far aren't inherited from a parent, but instead are mutated during embryonic development, making them hard to track through traditional linkage studies in families.

Christopher Walsh, MD, PhD, chief of genetics at Children's Hospital Boston, approached the problem by studying Middle Eastern families. In traditional Arab societies, it is common for cousins to marry, increasing the likelihood that offspring will inherit rare mutations. Middle Eastern families also tend to have many children, making them ideal for

mapping genes.

"To map a gene for autism in American families, averaging two to three kids per family, you would need to pool many families," says Walsh, who is also a Howard Hughes Medical Institute investigator at Beth Israel Deaconess Medical Center (BIDMC). "In larger families, one family alone may be enough to definitively localize a gene."

The Homozygosity Mapping Collaborative for Autism (HMCA) recruited 104 families with a high incidence of autism from the Arabic Middle East, Turkey and Pakistan; 88 of these families have cousin marriages. Local clinicians were rigorously trained in administering standardized autism research assessments. Walsh's team later flew to sites in Turkey, Dubai, Kuwait and Saudi Arabia to confirm the diagnoses.

Using a technique called homozygosity mapping Walsh and colleagues compared the DNA of family members with and without autism, searching for recessive mutations—those that cause disease only when a child inherits two copies.

"We check each set of chromosomes from beginning to end, looking for one place where the child has two identical pieces of DNA on both chromosomes," Walsh explains. "Eventually we find a spot where all affected children have two identical chunks of DNA, and where unaffected children have something different."

Just over 6 percent of the 88 families showed rare, inherited deletions within DNA regions linked to autism. These affected DNA regions varied among families, further indication of autism's large variety of genetic causes. In all, the technique identified five chromosome deletions affecting at least six identifiable genes (C3orf58, NHE9, PCDH10, contactin-3 [CNTN3], RNF8, and genes encoding a cluster of

cellular sodium channels).

One of the genes, NHE9, was also found to be mutated in European and American children with autism (particularly those with both autism and seizures).

Experience-dependent learning: A common thread

The genes discovered are diverse in function, but all seem to be part of a fundamental molecular network that orchestrates the refinement and maturation of brain connections, or synapses, in response to input from the outside world. It is the refinement of these synaptic connections that is the basis of learning and memory, suggesting that autism at its heart may represent molecular defects of learning.

"This network can be disrupted in a myriad of ways, and may be one mechanism that people with a variety of autism-linked mutations share," says Michael Greenberg, PhD, a coauthor on the paper and director of the Neurobiology Program at Children's Hospital Boston.

Normally, as a neuron (brain cell) receives an incoming message at the synapse, a network of reactions is sparked that extends all the way to its nucleus. Greenberg and his colleagues had long been mapping this network, and had previously found that it activates at least 300 genes. These genes then communicate back to the neuron's surface, telling the cell to make a new synapse, strengthen the synapse that's already there, eliminate a synapse, or make a different kind of synapse. This give-and-take system is how the brain builds its circuitry; neuroscientists call it "experience-dependent learning."

Working independently of Walsh, Greenberg and his colleagues had already identified three of the same genes found in the Middle Eastern patients (c3orf58, NHE9, and PCDH10) while looking for genes that

turn on or off in neurons as part of this network – either in response to synaptic activity or through so-called transcription factors that are activated by synaptic activity.

The work bolsters a growing body of evidence that autism may represent a disruption of the brain's ability to modify its synaptic connections in response to experience.

"Taken together, our findings suggest that experience-dependent learning could be relevant to autism, and that autism might result from the deregulation of any one of a number of genes that are part of the same signaling pathway," Greenberg says.

Can normal function be revived?

Interestingly, only one chromosome deletion found in the Middle Eastern families actually removed a gene – in most cases, what was lost was a region adjacent to the gene that contains its "on/off" switches. This has important implications for therapy, because it suggests that autism mutations don't always remove a gene altogether, but only inhibit its activity in certain contexts, says Eric Morrow, MD, PhD, of Massachusetts General Hospital, who is co-first author of the paper with Seung-Yun Yoo, PhD. "This means that we would not need to replace the gene, if we could only figure out how to reactivate it, perhaps with medications," says Morrow, who also holds appointments at BIDMC and Children's.

The findings also support the use of behavioral therapies in autism, which expose children to a rich environment and highly repetitive activities that may help turn on the genes and strengthen synaptic connections, Morrow adds.

"This publication a big event in the world of autism research," says

Clarence Schutt, PhD, Scientific Advisor to the Nancy Lurie Marks Family Foundation, which funded work by both the Walsh and Greenberg labs. "To have discovered a connection between autism and activity-related gene expression at the synapse will put this field at the center of neuroscience."

Source: Children's Hospital Boston