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Whole-exome sequencing identifies inherited mutations in autism

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While autism clearly runs in some families, few inherited genetic causes have been found. A major reason is that these causes are so varied that it's hard to find enough people with a given mutation to establish a clear pattern. Researchers at Boston Children's Hospital have pinpointed several inherited mutations—among the first to be identified—through an unusual approach: using whole-exome sequencing to study large Middle Eastern families with autism.

The study, published in the January 23 issue of the journal *Neuron*, also found evidence for some of the same mutations in U.S. families. It shows that a number of genes implicated in severe genetic syndromes can have milder mutations that primarily cause autism, and could broaden the number of genetic tests available to families.

Researchers Tim Yu, MD, PhD, Maria Chahrour, PhD, and senior investigator Christopher Walsh, MD, PhD, of Boston Children's Hospital, began with three large Middle Eastern families that had two or more children with autism spectrum disorders (ASDs), looking for recessive mutations—those requiring a "double hit" for the child to have an ASD.

"Families from the U.S. are not ideal for finding inherited genetic mutations, since family sizes are often small," says Walsh, chief of Genetics at Boston Children's and an investigator of the Howard Hughes Medical Institute.

In all three families, the parents were first cousins, a common tradition in the Middle East and one that greatly facilitates the identification of inherited mutations. The researchers first used genetic mapping techniques to narrow their search to specific chromosomal locations, then sequenced the protein-coding genes in those areas (known as whole-exome sequencing).

That turned up recessive mutations in three genes not previously known to be involved in autism, but rather in severe genetic syndromes:

- Mutations in AMT, a gene classically associated with a severe metabolic syndrome known as nonketotic hyperglycinemia, marked by severe seizures and death during infancy.
- Mutations in PEX7. Typical PEX7 mutations cause rhizomelic chondrodysplasia punctata, a severe syndrome causing metabolic and bone abnormalities, cataracts, severe epilepsy and early death.
- Mutations in SYNE1, a gene associated with brain malformation, severe motor and muscle problems, and possibly bipolar psychiatric disease.

The severe syndromes linked to these genes often include autistic behavior or intellectual disability, but not as the primary symptom. Interestingly, the milder mutations discovered in these families seemed to cause disease that is more brain-specific.

"This is the first time these genes have been associated with autism," says Chahrour, who shares first authorship of the study with Yu. "The AMT and PEX7 mutations weren't picked up by standard tests for metabolic disorders, but when you're able to sequence the entire exome, you can find them."

These findings inspired the team to look for other metabolic and other genetic syndromes affecting cognition and behavior with milder forms showing up simply as autism. They screened 163 Middle Eastern families with autism for mutations in 70 genes associated with these syndromes, using a whole-exome approach but analyzing only the 70 genes of interest.

This approach turned up several additional families with ASD mutations, including:

- An additional family with a recessive mutation in AMT
- Two families with recessive mutations in VPS13B (known to cause Cohen syndrome, which includes intellectual disability, obesity, vision and joint problems, and small head size)
- A family with a recessive mutation in POMGNT1 (known to cause muscle-eye-brain disease, marked by brain malformation, intellectual disability, muscle and vision problems)
- A family with an X-linked mutation in MECP2 in two boys (MECP2 mutations are known to cause Rett syndrome in girls, but are typically lethal in boys)

"We have textbook descriptions of all these diseases, but in real life, there can be atypical, milder presentations of the same disease," says Yu. "The kids we were studying with autism were alive at age 13. They had double hits for these mutations, but they were much milder mutations. The proteins retained a bit of their function."

The team also examined a cohort of U.S. patients, looking for recessive mutations in six of the genes they identified. They analyzed whole-exome sequence data from 612 families with ASDs, part of a registry known as the Simons Simplex Collection. The analysis suggested that some of the affected children had causative recessive mutations in at

least two of the genes identified in the Middle Eastern families, and that larger-scale efforts to examine all 70 genes more fully for recessive mutations may prove fruitful.

"It's not clear yet how many U.S. families have these recessive mutations," says Yu. "Further studies could begin to estimate what fraction of autism cases might fall under this model."

The Boston Children's study complements another study published in the same issue of *Neuron*, led by Dr. Mark Daly of Massachusetts General Hospital and the Broad Institute. That study looked for recessive mutations across the entire genome in 933 cases and 869 controls—but specifically sought those that completely abolished a gene's function.

"Together, these two studies firmly establish that recessive mutations contribute importantly to autism, not just in specialized populations but in the population at large," says Yu. "Genome sequencing is going to be a huge advance in identifying more of these mutations, since there are a lot of rare syndromes that are otherwise very difficult to detect."

More information: *Neuron*, Yu et al.: "Using whole exome sequencing to identify inherited causes of autism."
dx.doi.org/10.1016/j.neuron.2012.11.002 .
Neuron, Lim et al.: "Rare complete knockouts in humans: population distribution and significant role in autism spectrum disorders."
dx.doi.org/10.1016/j.neuron.2012.12.029 .

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https://medicalxpress.com/news/2013-01-whole-exome-sequencing-inherited-mutations-autism.html