Gene on Chromosome 7 Associated With Autism

Three studies show that the integrity of neuroligin-neurexin axis is critical for normal development.

BY MARY ANN MOON
Contributing Writer

Three independent studies implicate the CNTNAP2 gene on chromosome 7 as an autism-susceptibility gene, researchers reported.

The three studies used different strategies to examine the possible genetic basis for autism, and all independently arrived at the same conclusion: Variations—some common and some rare—in the CNTNAP2 gene predispose carriers to autism.

"It will be important to begin to characterize the genotype-phenotype correlations across this gene so that we may begin to use CNTNAP2 as a diagnostic and prognostic tool," Dr. Dietrich A. Stephan said in an editorial comment accompanying the three reports (Am. J. Hum. Genet. 2008;82:7-9).

"These preliminary findings lead one to speculate whether early detection of CNTNAP2 mutation carriers, coupled with early intervention, could coax children through a critical period in development (12-24 months of age) and allow them to emerge undamaged and continue to develop normally thereafter," said Dr. Stephan of the Translational Genomics Research Institute, Phoenix.

In the first study, Maricela Alarcón, Ph.D., of the University of California, Los Angeles, Center for Autism Research and Treatment and her associates built on their previous finding linking a region of chromosome 7q35 that contains approximately 200 known genes with language deficits and autism spectrum disorders. They first genotyped the region in 172 parent-child trios from the Autism Genetics Research Exchange database on 2,758 single nucleotide polymorphisms. This narrowed the search to four likely candidate genes, including CNTNAP2.

This gene was already suspected of being involved in autism since it is a member of the neurexin superfamily; in case studies, mutations in these genes have been linked to severe autism, temporal lobe seizures, language regression, and repetitive behaviors.

'Early detection of CNTNAP2 mutation carriers, coupled with early intervention, could coax children through a critical period in development.'

The researchers then tested a different set of 304 parent-child trios and confirmed that only the CNTNAP2 gene significantly correlated with a delay in language acquisition—specifically, the age at which carriers used their first word. The investigators then identified a rare microdeletion within CNTNAP2 that was present in an autistic child and his father but not in 1,000 control chromosomes.

Dr. Alarcón and her associates also examined regional gene expression in human fetal brains, and found that CNTNAP2 was highly restricted to areas "known to contribute to complex human behaviors including speech and language, reward, frontal executive function, as well as joint attention, a core deficit in autism spectrum disorders."

"Our demonstration of the developmental expression of CNTNAP2 being confined to brain circuitry known to be disrupted in autism spectrum disorders provides, to our knowledge for the first time, a link between genetic risk for language dysfunction in autism and specific brain regions known to underlie core processes impaired in this disorder," the investigators noted (Am. J. Hum. Genet. 2008;82:150-9).

In the second study, Dan E. Arking, Ph.D., of Johns Hopkins University, Baltimore, and his associates genotyped 72 families with multiple affected children in the National Institute of Mental Health Autism Genetics Initiative database.

They confined their analysis to the most strict phenotypic inclusion criteria ever used in a sample of that size, "which allowed [the] subtle association to be detected without genomewide background noise," Dr. Stephan said.

Dr. Arking and his associates identified one common single nucleotide polymorphism, rs7794745, in the CNTNAP2 gene that was significantly associated with autism. They then confirmed the finding by genotyping a separate sample of 1,295 parent-child trios from the database. The researchers also found that transmission frequency was significantly greater from mothers than from fathers.

"It is likely that additional genetic variants in this gene that contribute to autism susceptibility remain to be discovered," Dr. Arking and his associates said (Am. J. Hum. Genet. 2008;82:160-4).

In the third study, Dr. Betul Bakkaloglu of Yale University, New Haven, Conn., and associates mapped balanced rearrangements in children who had social and cognitive delays "as a means of identifying candidate genes that may harbor rare disease alleles." They found an inversion of chromosome 7 in a mentally retarded child with autistic features, and further analysis showed disruption in the CNTNAP2 gene at 7q35.

Dr. Bakkaloglu and associates then resequenced all 24 exons of CNTNAP2 in a sample of 635 subjects with autism spectrum disorders and 942 controls. They found eight rare variants predicted to have an adverse effect on the gene's function. These variants occurred twice as often in affected subjects as in controls.

One particular deleterious variant, I869T, was found in four autistic children from three different families, but was not present in more than 4,000 chromosomes assessed in controls, Dr. Bakkaloglu and associates said (Am. J. Hum. Genet. 2008;82:165-73).

"Now that we have definitive evidence from several perspectives that integrity of the neuroligin-neurexin axis is critical for normal development, we must launch into a candidate gene-resequencing effort to fully describe mutations in the other members of these gene families in autism spectrum disorders," Dr. Stephan noted. ■

Two Mutations on Chromosome 16 May Cause 1% of Autism

BY MARY ANN MOON
Contributing Writer

A novel, recurrent microdeletion, as well as a reciprocal microduplication, on a specific region of chromosome 16 appears to confer substantial susceptibility to autism, researchers have reported in the New England Journal of Medicine.

The two mutations might account for approximately 1% of cases of autism, a frequency that is the same as that for the most common known cause of autism (duplication of the Prader-Willi/Angelman region), according to Lauren A. Weiss, Ph.D., of Massachusetts General Hospital's Center for Human Genetic Research, Boston, and her associates.

The investigators conducted a genomewide analysis of a sample of families in the Autism Genetic Resource Exchange to identify any recurrent deletions or duplications that conferred risk of autism in multiple families. One region on chromosome 16p11.2 carried deletions in four independent families with five autistic children. The same region showed duplication rather than deletion in another three independent families with seven autistic children.

The researchers then attempted to confirm their findings by searching for the same microdeletion in a genetic database of 512 children with autism, developmental delay, or mental retardation from Children's Hospital Boston. They found identical deletions with exactly the same boundaries in five autistic boys.

In contrast, they found no such deletions in a sample of 434 Children's Hospital patients who had undergone genetic testing because of dysmorphic features, multiple congenital anomalies, congenital heart disease, seizures, or other disorders unrelated to autism. Similarly, there were identical duplications at 16p11.2 in four children in the sample with autism, developmental delay, or mental retardation, but none in the sample of children with disorders unrelated to autism.

Dr. Weiss and her associates then tried to replicate their findings in a genetic database of more than 19,000 members of the general population in Iceland. They found three cases of the 16p11.2 deletion in the subgroup of 299 subjects who had autism or developmental disorders, "a finding that was consistent with the 1% frequency observed" in the Children's Hospital cohort with autism or developmental disorders.

In contrast, only two cases of the deletion were found in the 18,834 Icelandic control subjects, a rate that was 1/100th of that in the autistic Icelanders.

The microduplication mutation was not seen in any Icelandic subjects who had autism but was found in two people with bipolar disorder and in five unscreened control subjects.

Interestingly, a separate study of the Icelandic cohort showed that the deletion occurred "at a markedly increased rate" in people who had various language or psychiatric disorders. It was found in one subject each with schizophrenia; bipolar disorder; attention-deficit hyperactivity disorder; panic disorder, anxiety, depression, or addiction; and dyslexia.

"In total, we have observed the identical deletion of nearly 600 kb [kilobase] in 13 subjects with autism or developmental or language delay (10 confirmed de novo mutations, 2 confirmed inherited mutations from parents with ADHD or mental retardation, and 1 mutation of unknown inheritance), with the reciprocal duplication of the same region documented in 11 additional subjects," said Dr. Weiss, also with the Autism Consortium, and her associates (N. Engl. J. Med. 2008 Jan. 9 [doi:10.1056/NEJMoa075974]).

"The fact that [the deletion mutation] is seen extremely rarely in the general population not only establishes a significant difference between rates in autism and control populations, but also unambiguously establishes that strong natural selection is acting against transmission of this deletion (as might be expected from an allele that increases the risk of autism by as much as a factor of 100), given how often it arises de novo in a single generation," added the researchers, whose study was funded by several organizations, including the Autism Consortium. The researchers reported no conflicts of interest.

In an accompanying editorial, Evan E. Eichler, Ph.D., and Dr. Andrew W. Zimmerman said that after larger case-control groups have undergone genotyping, it is possible that some of the 50 other large de novo events observed by Dr. Weiss and her colleagues and other events described in recent studies might be specifically associated with autism. Dr. Eichler is affiliated with the University of Washington, Seattle; Dr. Zimmerman is with the Kennedy Krieger Institute and Johns Hopkins University, Baltimore.

"The discovery of significant associations for the rarer loci may require the screening of tens of thousands of DNA samples from patients rather than a few thousand," they wrote [doi:10.1056/NEJMe0708756]).

"Deeper sample collection and new cost-effective genomic techniques may be needed to peel away the remaining layers of the onion," they added. ■

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