Gene on chromosome 15 linked to autism subgroup

Several research groups have tentatively identified a defect on chromosome 15 as a culprit in autism. A study by Duke University researchers now suggests a link between a one gene on this chromosome and cases of autism in which symptoms include extreme resistance to change.

Evaluating data from families with more than one autistic child, Margaret Pericak-Vance and colleagues used a technique called "ordered subset analysis" to analyze subgroups of autistic children grouped according to specific traits. This allowed the researchers to determine if certain subsets of children shared particular genetic risk factors. The process, they say, revealed that one gene linked only weakly to autism in general was significantly more common in families of autistic children whose symptoms include repetitive compulsions and extreme difficulty in changing daily routines.

The gene plays a role in encoding a neurotransmitter receptor called the gamma-aminobutyric acid receptor beta3-subunit (GABRB3). Pericak-Vance et al. note that this gene is in the same area of chromosome 15 that is linked to Angelman syndrome and Prader-Willi syndrome, both of which involve repetitive behaviors. 'These results," they say, "narrow our region of interest on chromosome 15 [as it relates to autistic disorder] to an area surrounding the gamma-aminobutyric acid-receptor subunit genes."

Study co-author Michael Cuccaro says that ordered subset analysis will facilitate research into genetic influences on autism. "In the short term," he says, "...I think what this will allow us to do is encourage clinicians and researchers working with autistic children to think about autism as consisting of different types or subgroups and not a one-dimensional disorder. I think that subgrouping, over time, will allow us to develop a better understanding of how to treat each individual with autism."

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"Fine mapping of autistic disorder to chromosome 15q11-q13 by use of phenotypic subtypes," Y. Shao, M. L. Cuccaro, E. R. Hauser, K. L. Raiford, M. M. Menold, C. M. Wolpert, S. A. Ravan, L. Elston, K. Decena, S. L. Donnelly, R. K. Abramson, H. H. Wright, G. R. DeLong, J. R. Gilbert, and M. A. Pericak-Vance, *American Journal of Human Genetics*, Vol. 72, No. 3, March 2003, 539-48. Address: Margaret Pericak-Vance, Duke University Medical Ctr., Durham, NC 27710.

—and—

"New genetic 'fishing net' harvests elusive autism gene," press release, Duke University, February 6, 2003.

Risperdal: new warnings

ARRI 16/4 summarized a number of reports on side effects of the drug risperidone (Risperdal), including findings that the drug may increase the risk of strokes and other cardiovascular problems. The drug's manufacturer, Janssen, is now issuing a warning to doctors, noting that the drug may increase the risk of stroke in elderly. A representative for the consumer group Public Citizen is calling on regulators to determine if the drug also increases the risk of strokes among young patients.

Constipation is another adverse effect of risperidone, and a new report suggests that the drug can cause a far more serious side effect known as "megacolon" in which the colon becomes grossly distended and obstructed, causing pain, fever, shock, and in some cases death. Singapore physicians D. K. Lim and R. Mahendran have reported a case of megacolon occurring in a 44-year-old schizophrenic man being treated with risperidone. He recovered after surgical treatment and a reduction in drug dosage. "While direct attribution might be debatable, " Lim and Mahendran say, "risperidone appeared to be the most likely contributing factor in the development of megacolon in this patient, given that there was no underlying GI problem such as idiopathic chronic constipation."

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"Risperidone and megacolon," D. K. Lim and R. Mahendran, *Singapore Medical Journal*, Vol. 43, No. 10, October 2002, 530-2. Address: D. K. Lim, Department of General Psychiatry, Institute of Mental Health, Woodbridge Hospital, Singapore 539747, dominic.lim@chmeds.ac.nz.

—and—

"Company to warn of possible Risperdal stroke risk," Reuters, April 11, 2003.

Maternal antibodies associated with autism, language disorder

Maternal antibodies that attack neurons in unborn infants' brains may contribute to autism, according to a new study.

Paola Dalton et al. detected serum antibodies against Purkinje cells and other neurons in a mother of three children, one of whom was autistic and another of whom had severe language disorder. When serum from the mother was injected into pregnant mice, their offspring showed altered exploration and motor coordination and changes in the cerebellum, in comparison to mice injected with sera from mothers of non-autistic children.

"This evidence," the researchers say, "supports a role for maternal antibodies in some forms of neurodevelopmental disorder."

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"Maternal neuronal antibodies associated with autism and a language disorder," P. Dalton, R. Deacon, A. Blamire, M. Pike, I. McKinlay, J. Stein, P. Styles, and A. Vincent, *Annals of Neurology*, Vol. 53, No. 4, 2003, 533-7. Address: Angela Vincent, Neurosciences Group, Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DS, UK.

The Autism Research Institute maintains a list of schools and services for autistic individuals. If your facility should be included on our list, and you believe it may not be, please send a self-addressed, stamped envelope to receive our referral list questionnaire.

Gene may be link between pesticides, neurological ills

Variations in a single gene may explain why some people develop attention deficit hyperactivity disorder, Gulf War syndrome, or other neurological problems following exposure to organophosphates, researchers at the Salk Institute report.

Carrolee Barlow, Christopher Winrow and colleagues found that in mice, exposure to organophosphates—chemicals used in nerve gas and certain pesticides—inhibits the activity of a gene called neuropathy target esterase, or NTE. Mice specially bred to lack the NTE gene died before birth, but those with only one copy of the gene developed behaviors resembling ADHD when exposed to organophosphates. Mice with two functional copies of the NTE genes also showed some signs of ADHD-like behavior after exposure to organophosphate pesticides, but their symptoms were far more mild.

The researchers note that mice with only one copy of the NTE gene had a 40 percent decrease in the enzyme produced by the NTE gene. This enzyme is found in brain and nervous system regions controlling movement, including the spinal cord, hippocampus, and cerebellum.

Barlow says, "NTE is a large gene. It's possible that we all have slightly different forms of the NTE enzyme, which may explain why some may get ADHD when they're exposed at young ages, and why some may get Gulf War syndrome at a later age, or why some of us have no symptoms at all. It appears to be a case of delayed toxicity, inhibiting the function of NTE."

Many anecdotal reports link childhood hyperactivity to exposure to pesticides. Veterans of the 1991 Gulf War were potentially exposed to organophosphate chemicals while destroying Iraqui munitions containing nerve gas, and one study found that veterans who participated in or witnessed the destruction of these chemicals were more likely to report Gulf War symptoms than were other veterans.

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"Loss of neuropathy target esterase in mice links organophosphate exposure to hyperactivity," Christopher J. Winrow, Matthew L. Hemming, Duane M. Allen, Gary B. Quistad, John E. Casida, and Carrolee Barlow, *Nature Genetics*, online advance publication, March 17, 2003. Address: Carrolee Barlow, carrolee_barlow@merck.com.