Research groups tentatively link multiple genes to increased vulnerability to autism

Mounting evidence indicates that while a number of genetic variations increase vulnerability to autism, the gene-gene and gene-environment interactions in autism are likely to be complex. Among recent studies:

—James Sutcliffe, Randy Blakely and colleagues report an association between autism and a number of different mutations in the 5-HT transporter gene (SERT), which plays a key role in regulating brain levels of the neurotransmitter serotonin. This is consistent, they say, with studies showing abnormal platelet serotonin levels in up to 25 percent of autistic individuals. Studying families with more than one autistic member, the researchers found 19 different SERT variants with a significant linkage to autism and obsessive-compulsive behavior; four of the variants were in coding regions (areas of the gene that are translated into proteins), and15 were in noncoding regions which may regulate expression of the gene. The researchers say their research shows that "there are specific [serotonin] signaling pathways that cannot talk to SERTS with these mutations."

—D. Q. Ma et al. report that variants of two GABA genes may interact to increase the risk of autism. GABA, in addition to playing an important role in early neurological development, is an inhibitory neurotransmitter, and abnormalities in the GABA system could help explain why autistic children are easily overwhelmed by sensory input.

Study co-author Margaret Pericak-Vance says the findings show that the idea of a single "autism gene" is simplistic. "We know autism is complex," she says, and when I think of a complex trait I think of gene-gene and gene-environment interactions. And I am sure that's what's going on in autism if I had to bet—a combination of both."

—According to Merlin Butler and colleagues, a gene known as PTEN, which is altered in many forms of cancer, shows similar alterations in some autistic children with larger-than-normal heads (macrocephaly). The researchers detected PTEN mutations in three subjects, all male, in a group of 18 macrocephalic autistic patients.

—Rita Cantor and colleagues report isolating a gene linked to autism on chromosome 17, and then duplicating this finding in a separate group of subjects. The gene appears to contribute to autism only in males.

—Anne Philippi and colleagues report evidence that variations in a gene on chromosome 16, encoding for protein kinase c-beta, are associated with autism.

—Cynthia Molloy et al. report that genes in specific regions on the long arms of chromosomes 7 and 21 "are likely to confer susceptibility to autism or modify the disease presentation in a subgroup of children characterized by a history of developmental regression."

Editor's note: Reports of the discovery of a new "autism gene" make the news almost every week, because nearly all funding currently allocated to autism research is going to efforts to define the "genetics of autism," with almost nothing being spent (except by our Institute) on discovering and refining safe biomedical treatments. Morover, almost no funding is going to researchers investigating environmental smoking guns such as thimerosal.

I was the first to document, in 1964, a genetic role in autism. However, the current attempt to define autism solely as a "genetic disease" is tragically misguided. While a variety of genes appear to make some children more vulnerable to autism than others, genes do not cause an epidemic—and that is what we are currently experiencing. By focusing almost exclusively on genes (which one gene researcher was honest enough to admit will explain only about 10 percent of cases of autism),researchers are wasting desperately needed funds that could be used to find and eliminate the environmental culprits that are the primary cause of this epidemic, and to provide real help for its victims.

—

"Allelic heterogeneity at the serotonin transporter locus (SLC6A4) confers susceptibility to autism and rigid-compulsive behaviors," J. S. Sutcliffe, R. J. Delahanty, H. C. Prasad, J. L. McCauley, Q. Han, L. Jiang, C. Li, S. E. Folstein, and R. D. Blakely, *American Journal of Human Genetics*, Vol. 77, No. 2, August 2005, 265-79. Address: J. S. Sutcliffe, Center for Molecular Neuroscience, Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, TN 37232-0615, james.s.sutcliffe@vanderbilt.edu

—and—

"Identification of significant association and gene-gene interaction of GABA receptor subunit genes in autism," D. Q. Ma, P. L. Whitehead, M. M. Menold, F. R. Martin, A. E. Ashley-Koch, H. Mei, M. D. Ritchie, G. R. Delong, R. K. Abramson, H. H. Wright, M. L. Cuccaro, J. P. Hussman, J. R. Gilbert, and M. A. Pericak-Vance, *American Journal of Human Genetics*, Vol. 77, No. 3, September 2005, 377-88. Address: D. Q. Ma, Center for Human Genetics, Duke University Medical Center, Durham, NC 27710.

—and—

"The age of autism: gene suspects located," Dan Olmsted, *Washington Times*, August 3, 2005.

—and—

"Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations," M. G. Butler, M. J. Dasouki, X. P. Zhou, Z. Talebizadeh, M. Brown, T. N. Takahashi, J. H. Miles, C. H. Wang, R. Stratton, R. Pilarski, and C. Eng, *Journal of Medical Genetics*, Vol. 42, No. 4, April 2005, 318-21. Address: M. G. Butler, Section of Medical Genetics and Molecular Medicine, Children's Mercy Hospitals and Clinics, University of Missouri-Kansas City School of Medicine, Kansas City, MO, mgbutler@cmh.edu.

—and—

"Replication of autism linkage: fine-mapping peak at 17q21," R. M. Cantor, N. Kono, J. A. Duvall, A. Alvarez-Retuerto, J. L. Stone, M. Alarcon, S. F. Nelson, and D. H. Geschwind, *American Journal of Human Genetics*, Vol. 76, No. 6, June 2005, 1050-6. Address: Rita Cantor, Department of Human Genetics, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA 90095-7088, rcantor@mednet.ucla.edu.

—and—

"Haplotypes in the gene encoding protein kinase c-beta (PRKCB1) on chromosome 16 are associated with autism," A. Philippi, E. Roschmann, F. Tores, P. Lindenbaum, A. Benajou, L. Germain-Leclerc, C. Marcaillou, K. Fontaine, M. Vanpeene, S. Roy, S. Maillard, V. Decaulne, J. P. Saraiva, P. Brooks, F. Rousseau, and J. Hager, *Molecular Psychiatry*, Vol. 10, No. 10, October 2005, 950-60.Address: Anne Philippi, IntegraGen SA, 4 rue Pierre Fontaine, 91058 Every Cedex, France..

—and—

"Evidence for linkage on 21q and 7q in a subset of autism characterized by developmental regression," C. A. Molloy, M. Keddache, and L. J. Martin, *Molecular Psychiatry*, Vol. 10, No. 8, August 2005, 741-6. Address: C. A. Molloy, Center for Epidemiology and Biostatistics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Department of Pediatrics, Cincinnati, OH 45229-3039, cynthia.molloy@cchmc.org.

Lovaas findings replicated

(continued from page 1)

be implemented in a clinical setting outside a university with a similar sample and that the earlier findings by the UCLA group regarding favorable outcome could in large part be replicated without aversives." One surprising finding, they say, was that children in the parent-directed program fared as well as those in the clinic-directed program.

While some replications of UCLA's intervention have reported a lower percentage of children achieving normal IQ and ability levels, Sallows and Graupner note, "Hours of treatment in this study came closer than any previous replication to the intensity of hours provided in the UCLA study, averaging 38 hours per week for two years in the clinic-directed group, and the results were also the most comparable."

—

"Intensive behavioral treatment for children with autism: four-year outcome and predictors," Glen O. Sallows and Tamlynn D. Graupner, *American Journal on Mental Retardation*, Vol. 110, No. 6, November 2005, 417-38. Address: Glen O. Sallows or Tamlynn D. Graupner, Wisconsin Early Autism Project, 6402 Odana Road, Madison, WI 53719, weap@wiautism.com.