Gene effects in autism: role of "epigenetics" explored

A new study suggests that autism involves a complex genetic malfunction involving both inherited gene anomalies and faulty gene "imprinting."

The proper functioning of a gene depends not only on its DNA structure but also on "epigenetic" effects—chemical alterations that cause genes to be expressed or silenced. Yong-hui Jiang and colleagues say their analysis of current research strongly suggests that autism involves dysregulation of two or more principal genes, leading to faulty imprinting which causes the overexpression, silencing, or misexpression of the proteins produced by these genes. This could occur, they say, in the absence of a structural genetic defect.

One gene the researchers have targeted in particular is theUBE3A gene on chromosome 15. Defects in the expression of this gene are already known to cause Angelman syndrome, and previous research has shown that maternal inheritance of extra material from chromosome 15 is linked to some cases of autism.

The researchers say that their theory of combined genetic and epigenetic effects does not rule out an effect of environmental insults. "The epigenetic component of [this] model can be considered in the context of possible environmental factors affecting the risk of *de novo* imprinting defects," they say. "Non-genetic factors could affect the risk for an epigenetic form of autism."

In related findings, a recent study reports that a considerable overlap exists between Angelman syndrome and autism. Sarika Peters and colleagues investigated the prevalence of autism in 19 children with Angelman syndrome. Peters and colleagues say that "42 percent of this population, eight of 19 children, met criteria for autism," with children in this group scoring lower on measures of language, adaptive behavior, cognition, and socialization and exhibiting a poorer outcome over the one-year course of the study. The researchers say their study provides more evidence that the UBE3A gene plays a role in autism.

Previous reports have also linked Angelman syndrome and autism. Symptoms of Angelman syndrome include early feeding and sleeping problems, short attention span, hyperactivity, severe learning disorders, lack of speech, epilepsy, below-average head size, unusual facial features, frequent laughing, and a characteristic "happy" disposition.

Editor's note: Many Angelman children are helped with the very safe supplement DMG (see ARRI 17/1, 15/4, 11/4).

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"A mixed epigenetic/genetic model for oligogenic inheritance of autism with a limited role for UBE3A," Y. H. Jiang, T. Sahoo, R. C. Michaelis, D. Bercovich, J. Bressler, C. D. Kashork, Q. Liu, L. G. Shaffer, R. J. Schroer, D. W. Stockton, R. S. Spielman, R. E. Stevenson, and A. L. Beaudet, *American Journal of Medical Genetics*, Vol. 15, November 2004, 1-10. Address: Yong-hui Jiang, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030.

—and—

"New genetic hypothesis for the cause of autism," news release, John Wiley & Sons, September 8, 2004.

—and—

"Autism in Angelman syndrome: implications for autism research," S. Peters, A. Beaudet, N. Madduri, and C. Bacino, *Clinical Genetics*, Vol. 66, No. 6, December 2004, 530-6. Address: Sarika Peters, Department of Pediatrics, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030.

Glutathione deficiency could be key to understanding link between thimerosal, autism

(continued from page 1)

the subjects. Additional studies are currently underway.

The EWP paper concludes that the findings of James et al. and others cast doubt on research showing no link between autism and the mercury in vaccines. "The epidemiologic studies used to dismiss a causal relationship between autism and thimerosal have assumed that all children have the same resistance to chemical exposure," the paper's authors note. "To properly investigate the potential harm from mercury-containing shots, researchers would have to compare autism rates in children with the same type of vulnerability."

Editor's note: See ARRI 18/1 for a related article describing the work of Richard Deth, who has found that even small amounts of thimerosal impair methylation.

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"Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism," S. J. James, P. Cutler, S. Melnyk, S. Jernigan, L. Janak, D. W. Gaylor, and J. A. Neubrander, *American Journal of Clinical Nutrition*, Vol. 80, No. 6, December 2004, 1611-17; and, "Thimerosal neurotoxicity is associated with glutathione depletion: protection with glutathione precursors," S. J. James, W. Slikker, S. Melnyk, E. New, M. Pogribna, and S. Jernigan, *Neurotoxicology*, Vol. 26, No. 1, January 2005, 1-8. Address for both: S. Jill. James, Department of Pediatrics, Arkansas Children's Hospital Research Institute, Little Rock, AR 72202.

—and—

"Overloaded: New science, new insights about mercury and autism in susceptible children," Environmental Working Group, December 13, 2004, http://www.ewg.org.

Autism, SLI both involve Broca's area anomaly

Autistic children with poor language skills exhibit a brain anomaly also seen in non-autistic children with specific language impairment (SLI), according to a new study. SLI is a term used to describe children who display delayed speech and language skills, but have no other disabilities.

Lies De Fossé and colleagues performed MRI scans on 42 children between the ages of 6 and 13, including 11 non-disabled control subjects, 9 children with a history of specific language impairment, and 22 children with autism (16 with impaired language, and 11 with normal language). To control for differences due to handedness or gender, all of the children were male and right-handed.

The researchers found that in both boys with autism and boys with SLI, Broca's area—a brain center involved in speech production and the understanding of complex grammatical rules—was larger on the right side than the left. Moreover, autistic or SLA subjects with the highest right-to-left ratio exhibited the most severe language impairment. In both non-disabled controls and autistic boys without language problems, Broca's area was larger on the left.

The researchers say their study "further strengthens the biological basis of the language problems seen in both autism and SLI," and is consistent with research showing that relatives of children with SLI have an increased risk of autism. Their data suggest, they say, that "Broca's area asymmetry reversal is related more to language impairment than specifically to autism diagnosis." However, they say additional studies are needed to see if abnormal Broca's asymmetry also occurs in females with autism, and in autistic adults as well as children.

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"Language-association cortex asymmetry in autism and specific language impairment," L. De Fossé, S. M. Hodge, N. Makris, D. N. Kennedy, V. S. Caviness, L. McGrath, S. Steele, D. A. Ziegler, M. R. Herbert, J. A. Frazier, H. Tager-Flusberg, and G. J. Harris, *Annals of Neurology*, October 11, 2004 (epub). Address: Gordon J. Harris, RAD CADx LAB, MGH, Zero Emerson Place #3A, Boston, MA 02114.

—and—

"Imaging studies clarify brain changes associated with language deficits in autism," news release, Massachusetts General Hospital, October 11, 2004.

—and—

"MRI shows brain changes underlying language deficits in autism, PsycPORT.com, October 28, 2004.

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