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Largest-ever search for autism genes reveals new clues

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The largest search for autism genes to date, funded in part by the National Institutes of Health (NIH), has implicated components of the brain's glutamate chemical messenger system and a previously overlooked site on chromosome 11. Based on 1,168 families with at least two affected members, the genome scan adds to evidence that tiny, rare variations in genes may heighten risk for autism spectrum disorders (ASD).

The study is the first to emerge from the Autism Genome Project (AGP) Consortium, a public-private collaboration involving more than 120 scientists and 50 institutions in l9 countries. Their report is published online in the February 18, 2007 issue of *Nature Genetics*.

With NIH support, the AGP is pursuing studies to identify specific genes and gene variants that contribute to vulnerability to autism. These include explorations of interactions of genes with other genes and with environmental factors, and laboratory research aimed at understanding how candidate susceptibility genes might work in the brain to produce the disorders.

"This is the most ambitious effort yet to find the locations of genes that may confer vulnerability to autism," said NIH Director Elias A. Zerhouni, M.D. "The AGP is revealing clues that will likely influence the direction of autism research for years to come."

"Although we know autism is highly heritable, complex gene interactions

and submicroscopic anomalies create a din of statistical noise that drowns out detection of signals from linked sites in the genome," explained Dr. Bernie Devlin, University of Pittsburgh, who served as a corresponding author on the project along with the University of Toronto's Dr. Stephen Scherer. "To amplify these signals, we brought to bear gene chip technology with a huge sample, and also screened for these fine-level anomalies, factoring them into the analysis."

Clues emerged adding to evidence that implicates components of the brain's glutamate neurotransmitter system in autism. Glutamate increases neuronal activity and plays an important role in wiring up the brain during early development. Since autism likely stems from faulty wiring, a genetic blueprint gone awry in this pivotal neurotransmitter system is a prime suspect. Some key genes associated with the glutamate system are located in chromosome regions previously associated with autism, note the researchers.

Previous studies have also linked abnormal glutamate functioning to disorders such as Fragile X syndrome and tuberous sclerosis, which share some symptoms with autism. It's not unusual for individuals with either syndrome to be diagnosed with autism.

Among the new clues is stronger evidence for an association between autism and sites of genes for neurexins, molecules that build glutamate synapses – the connection machinery by which brain cells communicate.

A site on chromosome 11 most strongly linked to autism in this study harbors genes for proteins that shuttle glutamate across the synapse. Although detected previously, the linkage signal at this site was regarded as less important until now.

Submicroscopic anomalies – tiny deletions, or the doubling, tripling or even multiplying of stretches of genetic material – are relatively

common in the human genome and aren't necessarily harmful. However, recent evidence suggests that these anomalies may contribute to risk for – or rarely even cause – autism if they affect certain sites associated with the disorder. The AGP researchers found a number of these variations in such suspect chromosomal locations in affected individuals, including deletion of a neurexin gene.

These anomalies can also make it more difficult to detect the genes that more commonly account for autism risk, say the researchers. Since each major autism candidate gene likely contributes to risk for a relatively small percentage of families, its linkage signal can easily be lost in the statistical noise generated by those of the anomalies – just as a high level of static can drown out a weak radio signal.

To amplify the power of possible linkages detected, the researchers analyzed many subsets of data, variously excluding from the sample factors like the submicroscopic anomalies, female sex, and ethnicity. These analyses unmasked several suggestive linkages that would otherwise have eluded detection.

Researchers last Fall reported discovery of a gene version linked to autism and how it likely works at the molecular level to increase risk. The AGP researchers propose that multiple such gene variants, perhaps interacting with each other and with the tiny anomalies, contribute to risk. As more such genes are identified, studies of how they work in the brain – in mice and other model systems – will help to sort out the genetic and proposed environmental influences on autism spectrum disorders, say researchers.

A second phase of AGP studies will follow up on leads suggested in this first phase.

Source: NIH/National Institute of Mental Health