NEWS

Changes in chromosome 16 firmly linked to autism

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Roughly ten percent of autism cases that occur as part of other clearly defined disorders, such as Rett or fragile X syndromes, have an obvious genetic cause.

What of the other 90 percent?

Mark Daly and his colleagues have hunted down a 593 kilobase 'hot spot' of genetic sequence that, when duplicated or deleted, substantially boosts the risks of autism seen independent of other syndromes.

In a paper published today in *The New England Journal of Medicine*[1], the researchers have identified a segment containing 25 genes on chromosome 16 that was deleted or duplicated in

roughly one percent of children with autism. The results are based on samples drawn from three different populations in three independently conducted studies.

"It's a beautiful paper that demonstrates a clear association between a genetic locus and autism," says **Arnold Levine**, a molecular biologist who heads the Simons Center for Systems Biology at the Institute for Advanced Study at Princeton University.

Unlike his predecessors, Daly and his team didn't simply identify a suspect region, but found it in numerous affected individuals, Levine notes. "This paper has been held to a higher standard," Levine says. "It asked for reproducibility of observations and it got it. That's the power of this paper."

The finding provides unequivocal evidence that these genetic variations are a risk factor for autism, says Daly, assistant professor of medicine at Massachusetts General Hospital and Harvard Medical School and an associate member of the **Broad Institute** in Cambridge, Massachusetts.

Using sophisticated gene-scanning technology from **Affymetrix**, Daly hunted for instances in which an individual carries fewer or more than the standard two copies of any given gene. This so-called 'copy number variation' ? which boils down to the duplication or deletion of a genetic sequence ? became a hot area in autism research following the publication last year of a paper in *Science*[2]. That paper, written by **Mike Wigler** and **Jonathan Sebat** at Cold Spring Harbor Laboratory and their colleagues, reported a laundry list of *de novo* ? meaning new or non-inherited ? copy number variations in individual children with autism.

Using DNA samples from 1,441 subjects with autism from the **Autism Genetic Resource Exchange**, Daly found five *de novo* deletions and seven duplications in that specific region of chromosome 16, a rate of nearly one percent.

"The fact that it's been identified as a *de novo* event, and that it's recurrent ? that is, that they found it in one percent of patients with autism ? is the exciting part," says **Evan Eichler**, a Howard Hughes Medical Institute investigator at the University of Washington in Seattle who wrote an accompanying commentary on the Daly paper. "So it's not a transmitted mutation from grandparents to parents to offspring. This is something that is happening in the germ line."

Repeat occurrence:

Daly's team also examined the DNA from two more sets of cases and controls, one from **Boston Children's Hospital** and the other from **deCODE genetics** in Iceland. The same chunk of chromosome 16 was duplicated or deleted in substantially greater numbers in subjects with autism from these groups than in controls. Among all three groups, deletions and duplications in the region occurred in roughly one percent of subjects with autism; among controls it was close to zero.

"Because we see this specific event many, many times in many, many patients and hardly at all in the general population, we know specifically that this event has great importance to autism," Daly says.

Sebat says Daly's findings further legitimize the notion that although autism is heritable, spontaneous mutations have an important role in causing the disorder. "The kids with the [chromosome] 16p deletions, most of their risk comes from that single, primary insult," Sebat says. "The six-word message is: 'heritable' does not always mean inherited."

The finding is likely to have immediate, practical implications for diagnosis of autism and for genetic counseling, Sebat says. "If you know a first child is carrying a *de novo* deletion in this region of chromosome 16, the chance of a second child having the same deletion is low."

The role of the newly flagged region in autism remains mysterious. Of the 25 genes, ranging from some expressed in the brain to others that are important for the immune system, "there's nothing obvious," to autism's causation, says Daly. Still, they provide a tantalizing way forward. The MAPK3 gene in the region, for instance, codes for a regulatory protein involved in cell growth and brain wiring.

As important as the new results are, however, they are unlikely to yield a one-size-fits-all answer for autism. For instance, five children in four of the families had *de novo* deletions of the relevant region of chromosome 16. But three other autistic children in the same families did not have the deletion.

"There are going to be other genes and maybe even environmental factors that modify the phenotype," Levine says. "It isn't going to be so simple as to say, 'this gene causes this disease.'"

References:

1. Weiss L.A. *et al. N. Engl. J. Med.* Epub ahead of print (2008) **PubMed ?**

2. Sebat J. *et al. Science* **316**, 445-449 (2007) **PubMed ?**