NEWS

Mutations in both gene copies more common in autism

BY **EMILY SINGER**

30 OCTOBER 2012

Double hit: Researchers have identified a number of new autism candidate genes by looking for those in which both copies are mutated.

Double hit: Researchers have identified a number of new autism candidate genes by looking for those in which both copies are mutated.

People with autism are twice as likely as controls to have mutations that disable both copies of a

gene, according to preliminary research presented Wednesday at the **Autism Consortium Research Symposium** in Boston.

Researchers say this complete loss of function in a gene may account for as much as five percent of autism cases.

Lead investigator **Mark Daly**, associate professor of medicine at Massachusetts General Hospital, says that like autism studies of **copy number variations** — deletions or duplications of DNA — and **point mutations**, or single-letter changes, these findings also implicate a greater burden of mutations in people with autism.

“There is a clear excess of complete knockouts in autism, but the mutations are scattered throughout the genome,” Daly says. “As we look at more sequence data, we are finding certain genes being hit multiple times, but we need larger numbers to have confidence.”

Daly and his collaborators sequenced the **exomes** — the protein-coding portions of the genome — of 933 people with autism and 869 controls.

They identified five fully disabled genes, each in a single individual with autism, that are linked to Mendelian diseases and five fully disabled genes in more than one person with autism.

Most of these genes have not previously been linked to autism. They include FAAH2, SLC25A43, VSIG4, LUZP4, DGAT2L6, all of which were identified in at least two cases; USH2A, which has been linked to blindness and deafness; and SRPX2, which has been linked to **epilepsy**.

The list also includes **MeCP2**, mutations in which cause Rett syndrome, and KIAA2020 and **AFF2**, both of which have been linked to intellectual disability.

Looking at data collected from 8,000 people for other projects, the researchers found that the two-fold increase of disabled genes in people with autism is specific to rare mutations — those found in less than five percent of the population.

Some non-essential genes, such as those involved in smell, are mutated fairly frequently in the human genome. Disabling mutations in these genes are equally common in people with autism and controls, suggesting that the rare mutations do contribute to autism risk, says Elaine Lim, a graduate student in Daly’s lab who presented the poster at the meeting.

The researchers also looked at the X chromosome of trios — unaffected parents and a child with autism. Because boys have only one copy of the X chromosome, loss of just one copy of its genes constitutes a complete knockout.

Boys with autism are more likely to have a mutation that disables the function of an X chromosome

gene than their unaffected fathers are, the researchers found.

Other researchers are trying to confirm the findings in sequences from many more people with autism.

Klaus Schmitz Abe, a postdoctoral fellow in **Christopher Walsh**'s lab at Boston Children's Hospital, identified a similar pattern in consanguineous families — those in which the parents are close relatives. Looking for genes in which both copies are mutated in children with autism in these families, Abe and his collaborators have identified23 strong candidate genes.

One example Abe gave at the conference is PSD3, a gene important for maintaining the connections between neurons. Autism-affected families in multiple databases appear to have disabling mutations in this gene.