Tiny, spontaneous gene mutations may boost autism risk

15 March 2007

Tiny gene mutations, each individually rare, pose more risk for autism than had been previously thought, suggests a study funded in part by the National Institute of Mental Health, a component of the National Institutes of Health.

These spontaneous deletions and duplications of genetic material were found to be ten times more prevalent in sporadic cases of autism spectrum disorders than in healthy control subjects – but only twice as prevalent in autism cases from families with more than one affected member. The results implicate the anomalies as primary, rather than just contributory, causes of the disorder in most cases when they are present, according to the researchers. Although they might share similar symptoms, different cases of autism could thus be traceable to any of 100 or more genes, alone or in combination.

Drs. Jonathan Sebat, Michael Wigler, Cold Spring Harbor Laboratory (CSHL), and 30 colleagues from several institutions, report on their discovery online, March 16, 2007 in *Science Express*.

"These structural variations are emerging as a different kind of genetic risk for autism than the more common sequence changes in letters of the genetic code that we've been looking for," explained NIMH director Thomas Insel, M.D. "The best evidence yet that such deletions and duplications are linked to the disorder, these findings certainly complicate the search for genes contributing to autism. These are rare changes, dispersed across the genome, and they tell us that autism may be the final common path for many different genetic abnormalities."

"Our results show conclusively that these tiny glitches are frequent in autism, occurring in at least ten percent of cases, and primarily in the sporadic form of the disease, which accounts for 90 percent of affected individuals," added Sebat. "Understanding such sporadic autism will require different genetic approaches and stepped-up recruitment of families in which only one individual has the disease."

Sebat and colleagues used new high resolution array technology to detect mutations that were present in a child but not in either parent. They screened genetic material from 264 families drawn, in part, from the Autism Genetic Resource Exchange (AGRE) and the NIMH Center for Collaborative Genetic Studies of Mental Disorders.

They found the spontaneous mutations in 14 of 195 people with autism spectrum disorders compared to two of 196 unaffected individuals. Among the 14 autism patients with mutations, 12 were the only affected members of their family, while two were in families with other affected individuals.

Since the rate of mutations was much lower in families with more than one affected member, the researchers propose that "two different genetic mechanisms contribute to risk: spontaneous mutation and inheritance, with the latter being more frequent in families that have multiple affected children."

The two mutations detected in 196 healthy controls were duplications, while 12 of those in people with autism were deletions of genetic material. Relatively more females had the mutations, suggesting that the anomalies may contribute to disease more equally across the sexes than other causes of autism. Boys with autism outnumber girls 4 to 1.

Since each mutation is individually rare – few were seen more than once – the results suggest that many different sites in the genome likely contribute to autism.

"Failure to develop social skills and repetitive and obsessive behavior may in fact be the consequence of a reaction to many different

cognitive impairments," note the researchers.

Source: NIH/National Institute of Mental Health