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The genetics of autism: four large-scale studies find no answers

Without question, genes play a role in autism. Twin studies prove this conclusively: when autism affects one identical twin, it affects the other twin 75 percent of the time, while fraternal twins (who only share half their genetic material) are concordant for autism only about 3 percent of the time. Moreover, the risk of having a second autistic child, while small, is significant.

Spiker concludes, "Based on the findings of all of the autism linkage scans published to date, including the four described above, it is now apparent that no single region contains a gene with a large effect on the risk of autism in most families."

But are we, as some researchers suggest, close to breakthroughs in identifying "autism genes?" Current large-scale studies from around the world indicate, on the contrary, that no specific genes play a significant role in causing autism.

In particular, four research groups have conducted "genome scan by linkage analysis" studies, in which researchers examine random DNA markers in an attempt to identify areas where an autism susceptibility gene or genes may lie. Autism is a disorder likely to be influenced by multiple genes interacting with each other, and linkage analysis can reveal how large an effect any one gene may have.

The largest of these studies, recently conducted by Neil Risch et al. at Stanford, involved the screening of 360 gene markers in 90 families containing 97 sibling pairs with autism. In a second stage of the study, the researchers examined an additional 49 families with 50 independent sibling pairs, and tested an additional 157 markers. In addition, they enlisted non-autistic siblings as controls.

Risch et al. report that autistic sibling pairs did show more "sharing" of genetic markers than sibling pairs in which one child was autistic and the other was not. However, this difference could not be attributed to a small number of genes. "In fact," study co-author Spiker told ARRI, "the increased sharing observed in pairs concordant for autism was most consistent with a large number (at least 20) of susceptibility genes, none of which has a large effect." While the most significant results were seen for a region on chromosome 1, followed by a region on chromosome 17, neither of these findings was statistically significant.

In a follow-up to this study, Risch et al. analyzed additional markers in both sets of families, choosing gene markers in areas identified by other studies as good candidate sites for autism-related genes. "Our evidence for linkage on chromosome 1 increased slightly," Spiker told ARRI, "but was still short of formal statistical significance. Nonetheless, it was still the strongest result we obtained. The evidence we originally observed on chromosome 17 was diminished but still positive." They were unable to replicate smaller studies suggesting autism may be linked to a gene or genes in chromosome regions 15q, 7q, and 13q.

Similarly, three other large-scale genomic screening and linkage analysis studies have failed to isolate any genes that might play a significant role in the development of autism. The studies are:

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Serotonin gene link: another negative finding

Few studies of genetic influences on autism have generated as much interest as the report by Edwin Cook and colleagues in 1997 (see ARRI 11/2) of an association between the disorder and a shortened form of the serotonin transporter (5-HTT) gene. The finding appeared consistent with reports of altered serotonin levels in autistic individuals, as well as studies showing that drugs that affect serotonin levels sometimes reduce autistic symptoms.

Cook et al's study, however, was followed shortly by a report by S. M. Klauck and colleagues, who found that the long form of the gene (not the short form, as reported by Cook et al.) tended to be inherited by autistic children. And a new study, by Antonio Persico and colleagues, casts doubt on both sets of findings.

In their study, Persico et al. studied two ethnically different samples: 54 Italian families with one autistic child each, and 37 American families, each with either one or two autistic children. Using two different techniques, the researchers determined that each group "displayed no evidence of linkage/association between 5-HTT gene promoter alleles and autistic disorder." Previous studies showing an association between autism and either the long or the short form of the gene, Persico et al. say, "appear most likely false-positives due to their relatively small sample size given the complexity of the disease under scrutiny."

The researchers suggest that 5-HTT gene variants may be associated with specific subgroups of autism, and recommend that future studies target subjects with elevated serotonin levels, or those with obsessive-compulsive behaviors that may be linked to serotonin abnormalities.

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"Lack of association between serotonin transporter gene promoter variants and autistic disorder in two ethnically distinct samples," Antonio M. Persico, Roberto Militerni, Carmela Bravaccio, Cindy Schneider. Raun Melmed, Monica Conciatori, Valerio Damiani, Alfonso Baldi, and Flavio Keller, *American Journal of Medical Genetics*, Vol. 96, 2000, pp. 123-127. Address: Flavio Keller, Lab. Of Neuroscience, L.U.C.B.M., Via Longoni 83, I-00155 Rome, Italy.