

Gene Predicts Better Outcome as Cortex Normalizes in Teens with ADHD

August 6, 2007 -- Brain areas that control attention were thinnest in children with attention deficit hyperactivity disorder (ADHD) who carried a particular version of a gene in a study by the National Institutes of Health's (NIH) National Institute of Mental Health (NIMH). However, the areas, on the right side of the brain's outer mantle, or cortex, normalized in thickness during the teen years in these children, coinciding with clinical improvement. Although this particular gene version increased risk for ADHD, it also predicted better clinical outcomes and higher IQ than two other common versions of the same gene in youth with ADHD.

"Since this gene version had similar structural effects in healthy children as in children with the disorder, our findings suggest that ADHD is at the far end of a continuum of normal traits," said Philip Shaw, M.D., NIMH Child Psychiatry Branch, who led the research. "ADHD likely stems from interactions between several such genes and non-genetic factors."

Shaw, Judith Rapoport M.D., and colleagues report on their magnetic resonance imaging (MRI) study in the August 2007 Archives of General Psychiatry.

"This study provides us with a first glimpse of how variation in a specific gene influences both brain development and clinical prognosis in ADHD," said NIMH Director Thomas R. Insel, M.D.

When the NIMH researchers first reported last year that normalization of right cortex thickening was associated with better clinical outcomes in ADHD, there were few hints of a genetic connection. Yet evidence from several previous studies led them to suspect involvement of an ADHD-implicated version of a gene that codes for a receptor protein that binds to the brain chemical messenger dopamine.

This version of the dopamine D4 receptor gene, called the 7-repeat variant, accounts for about 30 percent of the genetic risk for ADHD, making it by far the strongest candidate gene implicated in the disorder. It's called the 7-repeat because it contains the same repeating sequence in its genetic code seven times. Everyone inherits two copies of the D4 receptor gene, one from each parent, so some people have two copies of the same version while others may carry two different versions.

For the current study, the researchers scanned and determined the D4 gene types of 105 children with ADHD and 103 healthy controls and re-scanned them through their teen years.

They found that nearly one-fourth of youth with ADHD and in about one-sixth of the healthy controls had at least one copy of the 7-repeat version. Nearly two thirds of the ADHD youth and three-fourths of the healthy controls had the most common 4-repeat version; fewer than one-tenth in each group had a 2-repeat version.

While the 7-repeat version was linked to thinner attention-controlling cortex in both ADHD and healthy subjects, it appeared to confer advantage only among youth with ADHD. For example, participants with ADHD who lacked at least one copy of this 7-repeat variant had significantly lower IQs, and more than half of them still had pronounced ADHD symptoms when followed-up about six years later, compared to only 21 percent of those with at least one copy of the 7-repeat variant. There was also a trend toward better overall functioning among those with at least one copy of the 7-repeat variant at follow-up.

The MRI scans revealed that 7-repeat carriers with ADHD started out with the thinnest cortex areas important for controlling attention (right orbitofrontal and posterior parieto-occipital). The next thinnest were children with ADHD who did not have the 7-repeat version, followed by healthy children with the 7-repeat. Healthy children lacking the 7-repeat had the thickest cortex, but this did not appear to affect their IQ. However, the researchers note that other studies have found correlations between cortex thickness and certain measures of memory and intelligence.

In 7-repeat carriers with ADHD, the attention-controlling areas thickened to normal by age 16 (see time-lapse image below). Gene variants of two other dopamine system components showed few such anatomic correlates, confirming that the findings were specific to the D4 receptor gene.

"Some genes have a good side, even though they're linked to disorder," said Shaw, who noted that other traits linked to the 7-repeat version, such as novelty seeking and impulsiveness, might confer advantage in some settings. "Evidence suggests that the 7-repeat may be a relatively new variant that may have been favored through evolution because such traits proved adaptive for survival."

The researchers are following up with studies on the relationship between cortex thickness and cognitive features of ADHD, such as working memory and the ability to inhibit responses.

Also participating in the research were: Jay Giedd, Michele Gornick, Jason Lerch, Anjene Addington, Jeffrey Seal, Deanna Greenstein, Wendy Sharp, NIMH; Alan Evans, McGill University; F.Xavier Castellanos, New York University.

Source: National Institutes of Health