

CNV Analysis Reveals Genetic Basis for ADHD

BY SHARON WORCESTER

FROM THE LANCET

Attention-deficit hyperactivity disorder is a neurodevelopmental disorder, rather than a purely social construct, according to British researchers who have found that a type of

[doi:10.1016/S0140-6736(10)61109-9].

The CNVs identified in this study are similar to those found in patients with schizophrenia and autism, and are significantly enriched for loci that have previously been implicated in those disorders, with particular overlap at a region on chromosome 16 that spans a number of genes, including one that affects brain development.

Furthermore, although the rate of CNVs was significantly higher in children with ADHD with and without intellectual disability, compared with the general population, the rate was particularly high in those with intellectual disability, defined as those with an IQ of less than 70 (rates of 0.424 and 0.075, respectively).

The findings are noteworthy because despite evidence that ADHD might be a genetic condition – for example, it has an estimated heritability of 76% – there has been a great deal of debate over whether it is a result of bad parenting or other external factors, coauthor Dr. Anita Thapar said during a press conference on the findings.

“ADHD can be stigmatizing ... and finding this direct genetic link to ADHD should help clear this misunderstanding and address this issue of stigma,” said Dr. Thapar, professor of child and adolescent psychiatry at Cardiff University.

In addition to providing a window into the biology of the brain, the findings will also influence the way in which ADHD is classified and will improve communication between scientists and clinicians about “what we mean by ADHD,” she said.

“This will be the start of a much more

scientific venture because our findings are going to help us unravel the biological basis of ADHD, and that’s going to be really important in turn in the further future to help us develop new and much more effective treatments for affected individuals.”

The subjects were recruited from community clinics and had met diagnostic criteria for ADHD or hyperkinetic disorder. They were aged 5-17 years (mean, 10.5 years), were of white U.K. origin, and had a mean IQ of 86. Controls were unrelated, ethnically matched children from the 1958 British Birth Cohort.

The findings have important clinical

and research implications. “First, our results emphasize that further investigation of CNVs in ADHD is a priority for research into this disorder,” the investigators wrote.

Also, the finding that more than a third of ADHD children with intellectual disability carried a large, rare CNV – and the fact that none of these children had been assessed for this type of mutation by clinical services – suggest that routine referral to clinical geneticists and screening for such mutations could be helpful for children with ADHD who also have intellectual disability, they said. ■

VITALS

Major Finding: The genome-wide burden of CNVs was significantly greater in the ADHD patients, compared with the controls (rates of 0.156 vs. 0.075, respectively).

Data Source: A genome-wide analysis of CNVs in 366 children with ADHD and 1,047 controls.

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genetic variation associated with brain disorders such as schizophrenia and autism also occurs in excess in ADHD patients.

The findings, published online in *The Lancet*, provide the first direct evidence of a genetic basis for ADHD, Dr. Nigel Williams of Cardiff University, Wales, and his colleagues reported.

The investigators performed a genome-wide analysis of large, rare chromosomal deletions and duplications known as copy number variants (CNVs) in 366 children with ADHD and 1,047 controls.

The genome-wide burden of CNVs was significantly greater in the ADHD patients, compared with that in the controls – rates of 0.156 and 0.075, respectively, they found (*Lancet* 2010 Sept. 30

New Insights on Brain Development

The findings of this study provide “a new chapter to the genetics of neurodevelopmental disorders,” Dr. J. Peter H. Burbach said.

Not only do they give insight into the neurological basis of ADHD, they also show that ADHD shares specific genes with autism, schizophrenia, and mental retardation. In particular, they highlight the importance of the chromosome 16p13.11 region previously implicated in these and other brain disorders, he said.

However, although the findings are exciting, it remains unclear how they will be clinically translated, he said, noting that to help clinician’s better understand and interpret the diversity of neuropsychiatric phenotypes in light of these findings about overlapping genotypes, future studies should explore in more detail how the genotypes

and phenotypes are linked.

“The first gains beyond today’s study might be initial insight into the pathogenesis and neurobiology of brain development as influenced by these genetic variants,” he wrote, adding, “This knowledge will eventually enter the clinic and might affect the way people think about and treat neurodevelopmental disorders by accounting for the biological consequence of the specific patient’s genotype.”

DR. BURBACH is with the department of neuroscience and pharmacology, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, the Netherlands. He wrote a commentary accompanying the report (*Lancet* 2010 Sept. 30 [doi: 10.1016/S0140-6736(10)61192-0]). He reported having no conflicts of interest.

VIEW ON THE NEWS

Rate of Young Athletes With Concussion Increases in the ED

BY HEIDI SPLETE

FROM PEDIATRICS

Approximately 40% of emergency department visits for sports-related concussions in young athletes occurred in children aged 8-13 years, based on data from concussion-related ED visits in the United States between 2001 and 2005.

There are two main concerns about sports-related concussion in younger children, compared with college athletes and adults, lead author Dr. Lisa L. Bakhos said in an interview. She had conducted the study while she was a teaching fellow at Brown University in Providence, R.I. (*Pediatrics* 2010 Aug. 30 [doi:10.1542/peds.2009-3101]).

First, many adults feel that because these athletes are so young, they could not possibly get seriously hurt. “This is, of course, not the case,” said Dr. Bakhos, an emergency physician at the Jersey Shore University Medical Center in Neptune, N.J.

“Also, a few good studies have shown that head injury in younger children can have more long-term effects, as you are essentially damaging a developing brain,” she explained. More data have surfaced about cognitive deficits in older children after concussion, she said, “which leads to conjecture that younger children would suffer the same – if not more – deficits long term.” However, this

link needs further study. The American Academy of Pediatrics has just released “Sport-Related Concussion in Children and Adolescents” (*Pediatrics* 2010 Aug. 30 [doi:10.1542/peds.2010-2005]).

Dr. Bakhos and her colleagues reviewed 1997-2007 data from the NEISS (National Electronic Injury Surveillance System), and 2001-2005 data from the NEISS-AIP (All-Injury Program). The NEISS system allows researchers to investigate injury- and product-related ED visits.

In 2001-2005, about half of all ED visits for concussion across older and younger age groups were related to sports, including 58% of visits in children aged 8-13 years and 46% of visits in those aged 14-19 years. About 4 in 1,000 children aged 8-13 years and 6 in 1,000 of those aged 14-19 years went to the ED for a sports-related concussion.

During the 1997-2007 period, ED visits for the most popular organized team sports (football, ice hockey, soccer, basketball, and baseball) doubled in 8- to 13-year-olds and increased by more than 200% in 14- to 19-year-olds.

“The take-home message for pediatricians is, take concussion seriously even in the very young athlete,” said Dr. Bakhos. “Children with concussion should be followed just as closely as a child with a sprained ankle or a broken bone. Return-to-play guidelines should be followed closely and stressed to parents.”

“We as pediatricians should also stress to parents the importance of concussion prevention in sport as well, mostly [by] the use of helmets at all times,” she noted.

The study was limited by the exclusion of sports-related concussions that were treated in non-ED settings, and by underreporting of sports-related concussions, the researchers noted. The AAP has published a new clinical report that “outlines the current state of knowledge on pediatric and adolescent sport-related concussions,” wrote lead authors Dr. Mark E. Halstead and Dr. Kevin D. Walter, on behalf of the AAP’s Council on Sports Medicine and Fitness. It includes the SCAT 2 (Sport Concussion Assessment Tool 2), a standardized method of evaluating concussion in athletes aged 10 and older.

The report includes the following recommendations:

► **Stay off the field.** Even if symptoms subside, young athletes should never return to play on the same day they have a concussion. They need more recovery time than do older athletes.

► **See a doctor.** Any children or adolescents who suffer concussions during sports should be medically cleared by a physician before they return to activity.

► **Rest mind and body.** All young athletes should refrain from physical and mental activity until they are

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