

# 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

*Continued on following page*

# FDA Neuro Device Trial Slowly Gets Underway

BY MARK HOLLMER

FROM A FOOD AND DRUG  
ADMINISTRATION WORKSHOP

SILVER SPRING, MD. – The ASK Children study, a Food and Drug Administration–led clinical trial designed to gather data about the use of neurologic devices in children, has enrolled 18 patients since launching in March 2009.

Through 2011, the FDA wants to enroll 100 pediatric and adolescent patients aged 7-15 years who have been implanted with a neurologic-related medical device for up to 1 year.

Despite the slow progress, the agency signaled at the workshop that the trial remains an important priority. The gathering was called to collect information on how to improve regulators' approach to evaluating pediatric neuroprostheses.

The ASK Children (Assess Specific Kinds of Children, askchildrenstudy.org) initiative is an important part of that strategy, said Carlos Peña, Ph.D., senior science policy adviser for the FDA's Office of the Commissioner, and one of the study's two principal investigators. "We have taken the study very seriously," he said.

Through interviews with the children and adolescents, the agency will gather data about scientific and medical de-

vice–related issues. Regulators hope the data will lead to more efficient approaches in evaluating the devices and the patients' experiences with them, as well as the development of similar, new technologies.

## Requirements Are an Ongoing Issue

Including pediatric needs in the device evaluation process is an ongoing issue for the FDA, and one that has gotten more attention as the agency strives to implement pediatric-focused provisions of the FDA Amendments Act of 2007.

This is an "emerging science area as we continue to learn about the nervous system," said Dr. Peña, who is leading the trial with Kristen Bowsher, Ph.D., an engineer in the FDA's Office of Device Evaluation.

Study organizers hope to enroll 20 children and adolescents each who have been implanted within the last year with five kinds of neurologic devices: deep brain stimulator, spinal cord simulator, cerebral spinal fluid shunt, vagus nerve stimulator, and cochlear implant.

The children will be required to participate in two 1-hour in-person or telephone interviews about 6 months apart. Three sites have been chosen for the study: the FDA Parklawn Building in

Rockville, Md.; the Arkansas Children's Hospital in Little Rock; and the Cleveland Clinic. Patients also will be required to answer questionnaires about general quality of life.

Regulators hope to obtain information on human factors, safety, usability, adverse events, and possible postmarket issues immediately following implementation of high-risk devices. The initial study will be expanded in the future into other pediatric-related device areas.

## Unique Considerations Are Needed

Dr. Warren Marks, medical director of the movement disorder and neurorehabilitation program at Cook Children's Medical Center in Fort Worth, Tex., said the FDA should consider quality of life factors in evaluating neurologic device use, as well as safety and efficacy, because "there is no really good quality of life measure out there right now."

He argued the trial would gain more relevant data on quality of life if it were to include patients who have had device implants beyond 12 months, rather than limiting the time frame to within 12 months.

Dr. Philip Pearl, chief of the division of child neurology at Children's National Medical Center in Washington, said the upper-age cut-off for classifying child

neurology device implant patients as "adolescent" should be extended from 18 to 21 years because the unique emotional needs in dealing with the implants and their related health conditions are still prevalent at that older age.

Workshop attendees pushed for children's devices that are smarter, smaller, and, ideally, self-contained, without exposed wires that children could play with and damage. Lauri Rush, who spoke about her daughter's experience with the device, emphasized the need to factor in a child's active lifestyle with devices such as cochlear implants. "How do you keep on a device while [a child] is in gymnastics?" she asked.

The workshop participants agreed that it is difficult to encourage companies to develop devices for the pediatric population because they do not always see profit potential. The 2007 Amendments Act included a provision allowing device firms to profit from pediatric-targeted indications of humanitarian use devices, though industry says it needs more incentives.

Dr. Marks and Dr. Pearl said they had no conflicts of interest. ■

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*Continued from previous page*

asymptomatic at rest and when active. Evidence suggests that cognitive exertion – including doing homework, watching TV, and playing video games – can exacerbate symptoms post concussion.

In the last few years, several states have passed laws requiring educational materials about sports-related concussion for school-aged athletes, coaches, and parents. The AAP began working on the report before the first law was passed, said Dr. Halstead, director of the sports concussion program at Washington University in St. Louis. "We felt there was a need to address specifically the [pediatric] athlete and address all the recent research that has been published on this topic," he said in an interview.

"The recommendations presented aren't significantly different from other recent documents published, but these were primarily published in sports medicine journals, which many pediatricians do not review. We wanted to bring these recommendations to the forefront to the pediatric community, and expand upon the details provided in previous documents published. We have highlighted some of the new research on neuroimaging, balance assessments, long-term complications, education, and neuropsychological testing," Dr. Halstead said.

Dr. Walter added, "I think it is also important to recognize that because we have learned more about concussion diagnosis, treatment, and complications, the treatment that coaches and parents received when they had a concussion

themselves at a young age is likely different [from treatment] today." Many parents and coaches don't think concussion is a big deal because they had one when they were younger and they "toughed it out" and "are fine now," said Dr. Walter, program director of pediatric and adolescent sports medicine at Children's Hospital of Wisconsin in Milwaukee.

The authors acknowledged the lack of published baseline neuropsychological data on children younger than 12 years, and noted that assessment by a neuropsychologist might be helpful for children who have had more than one concussion, or whose postconcussive symptoms persist for several months.

Dr. Halstead emphasized the following take-home tips for clinicians:

- ▶ Never should young athletes return to play on the day of their concussion, nor should they return to play until they are symptom free both at rest and at exertion.
- ▶ A concussion is an injury to the brain, and rest is paramount. "If an athlete injures an ankle or knee and cannot run on it, we wouldn't think twice about resting that injury until it healed. Why should we treat the brain any differently?"
- ▶ Doctors are interested in getting an athlete back to play and activity as soon as possible. "But we need to be smart about it and make sure it is safe for that young athlete first."
- ▶ Continue to educate everyone involved – coaches, parents, teachers, and athletes – in preventing and managing sports-related concussions.

None of the researchers mentioned in this story had any financial conflicts to disclose. ■

## Awareness Drives Rise in Reports

I'm not surprised by the increase in reports of concussions in young athletes. And because not every kid with a concussion goes to the ED, there are even more injuries occurring that are not being reported.

I think greater awareness and better diagnosis are the main reasons why the number of sports-related concussions is rising. Until 10 years ago, the medical literature focused only on concussions that involved loss of consciousness. But what we have learned in the past decade is that the subtleties of this injury are absolutely critical for diagnosis. (My 2003 paper shows that amnesia or memory loss around the time of the concussion is 10 times more predictive than a loss of consciousness.) Changes in the way we define the injury are driving the rise in reported concussions in young athletes.

As we continue to peel the onion on concussion, we realize that it is an extremely complex injury. We now have animal models that help show what happens in the brain after a concussion. This knowledge base has accumulated at warp speed over the last 10 years, and with that has come better recognition, better management, and better understanding of the injury, as well as more concern.

Most importantly, neurocognitive

testing is becoming more widely used as a way to assess sports-related concussion, and it is the key to why there is so much attention now being paid to the injury: We now have a way to measure it by collecting baseline data. The sensitivity and specificity of such tests are impressive.

One of the keys to improving the management of pediatric concussion is to get knowledge related to this injury, as well as its many assessment tools, into pediatric offices. Clinics are available around the United States to help pediatricians who want to incorporate neurocognitive testing into their practices. The American Academy of Pediatrics' report by Dr. Halstead and Dr. Walter lists several assessment tools, and it includes other valuable, relevant information about managing sports-related concussions in young athletes.



MICHAEL COLLINS, PH.D., is the assistant director of the sports medicine concussion program at the University of Pittsburgh Medical Center. He coauthored the Centers for Disease Control and Prevention's "Heads Up: Brain Injury in Your Practice" tool kit for physicians. He disclosed that he is a cofounder of ImPACT, a computerized neurocognitive testing tool.