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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 vs. 0.075, respectively.

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 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 lack of evidence 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 the 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 biologic 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 that 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.
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 implant- ed with a neurologically–related medical de- vice for up to 1 year. Despite the slow progress, the agency signaled at the workshop that the trial re- mains 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 imple- ment 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 stimulator, cerebral spinal fluid shunt, vagus nerve stimulator, and cochlear implant. The children will be required to par- ticipate in two 1–hour in-person or tele- phone 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 Cleve- land Clinic. Patients also will be required to answer questionnaires about general quality of life. Regulators hope to obtain information on human factors, safety, usability, ad- verse events, and possible marketplace is- sues immediately following implementa- tion 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 neurorehabili- tation 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 rel- evant data on quality of life if it were to include patients who have had device im- plants beyond 12 months, rather than limit- ing the time frame to within 12 months. Dr. Philip Pearl, chief of the division of child neurology at Children’s Nation- al 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 chil- dren’s devices that are smarter, smaller, and, ideally, self–contained, without ex- posed wires that children could play with and damage. Lauri Rush, who spoke about her daughter’s experience with the device, emphasized the need to fac- tor 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 popula- tion because they do not always see profit potential. The 2007 Amendments Act included a provision allowing device firms to profit from pediatric–targeted in- ducations of humanitarian use devices, though industry says it needs more incen- tives.

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 exer- tion — including doing homework, watching TV, and playing video games — can exacerbate symptoms post con- cussion. In the last few years, several states have passed laws requiring educational mate- rials about sports–related concussion for school–age athletes, coaches, and par- ents. The AAP began working on the re- port before the first law was passed, said Dr. Halstead, director of the sports con- cussion program at Washington Uni- versity in St. Louis. “We felt there was a need to address specifically the [pedi- atric] 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 particularly published in sports med- icine 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,” he said. The high–lighted some of the new research on neuroimaging, balance assessments, long–term complications, education, and neuropsychological testing,” Dr. Hal- stead said.

Dr. Walter added, “I think it is also im- portant to recognize that because we have learned more about concussion di- agnosis, treatment, and complications, the treatment that coaches and parents received when they had a concussion

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**View on the News**

**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 bet- ter 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 conscious- ness. But what we have learned in the past decade is that the subtleties of this injury are absolutely criti- cal 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 manage- ment, 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 con- cussion, 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 in- jury, as well as its many assess- ment tools, into pedi- atric offices. Clinics are available around the Unit- ed States to help pediatri- cians who want to incor- porate neurocognitive testing into their practices.

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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 Youth Practices” tool kit for physicians. He disclosed that he is a cofounder of IMPACT, a computerized neurocognitive testing tool.