New Joubert Syndrome Gene Discovered

In a study published in the journal Nature Genetics, a team of research affiliates at the Center on Human Development and Disability (CHDD) identified a fifth gene, RPGRIP1L, responsible for Joubert syndrome (JS). Research into the genetic causes of JS has resulted in diagnostic and carrier testing and has the potential to improve treatment of this rare developmental disorder. JS research is also illuminating the process of brain development, as well as the function of a previously obscure cellular structure, the cilium, that is being implicated in diseases of the brain, kidney, liver, and retina.

JS is characterized by a variety of conditions that can include cognitive impairments, ataxia (lack of coordination), hypotonia (decreased muscle tone), irregular breathing, visual impairment, abnormal eye movements, kidney or liver failure, and extra fingers or toes. JS is an autosomal recessive disorder. Recessive disorders are caused defects in both copies of a gene; the term autosomal means that the gene does not reside on the X or Y chromosome. Often one defective copy of the gene is inherited from each parent. The syndrome is estimated to affect at least one in 100,000 children in the U.S., or about 40 each year.

JS was defined by clinical features until 1997, when researchers identified a characteristic brain malformation on axial magnetic resonance imaging (MRI) that looks like a molar tooth, “the molar tooth sign.” This appearance results from abnormal development of the brainstem and cerebellar vermis, the structure between the two cerebellar hemispheres. The brainstem and cerebellum are involved in control of breathing, eye movements, limb movements, muscle tone, and possibly cognition.

Prior to recent genetic research, individuals with JS could only be identified by these clinical and imaging features. “Now, we have specific genetic tests to identify the disorder,” said Daniel A. Doherty, M.D., Ph.D., assistant professor of pediatrics, NIH Roadmap KL2 clinical research scholar, CHDD research affiliate, and an author of the recent study, published in Nature Genetics (see sidebar, page 2). To find mutations in RPGRIP1L, investigators analyzed samples from nearly 200 families affected by JS. The research team included CHDD research affiliates Melissa Parisi, M.D., Ph.D., assistant professor of pediatrics; Ian Glass, M.D., professor of pediatrics; and Phillip Chance, M.D., professor of pediatrics and medicine; and Phillip Chance, M.D., professor of pediatrics and medicine, and Phillip Chance, M.D., professor of pediatrics and medicine.
Joubert Genes Discovered by CHDD Research Affiliates

NPHP1: The first gene of Joubert syndrome (JS) identified in 2004 by Parisi, Chance, Glass, and collaborators. Mutations in this gene have been found in 1-2 percent of individuals studied who have JS. The prevalence in persons with JS who have juvenile kidney disease may be higher. Proteins coded by this gene are found in basal bodies and cilia.

AH1: Mutations in this gene are responsible for 10-15 percent of cases of JS; many of these individuals also have retinal or kidney disease. The protein encoded by this gene appears to play an important role in brain development. In 2006, Parisi, Doherty, Chance, Glass, and collaborators described a large cohort of patients with AH1 mutations, including the first patient with renal disease.

RPGRIP1L: Mutations in this gene cause about 3 percent of cases of JS. The protein encoded by this gene is found in basal bodies and cilia, and interacts with the protein encoded by NPHP4, which is involved in kidney and retinal function. The mutations were identified in 2007 by Doherty, Parisi, Glass, and Farin, in collaboration with a research group in the Netherlands. [Arts, H.H., Doherty, D., van Beersum, S.E.C., et. al. (2007) Mutations in the gene encoding the basal body protein RPGRIP1L, a nephrocystin-4 interactor, cause Joubert syndrome. Nature Genetics, 39(7), 882-888.]

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and director of the University of Washington Joubert Center. Essential collaborators included researchers at Radboud University in Nijmegen, Netherlands and Federico Farin, M.D., Ph.D. director of the Microarray Component of the CHDD Genetics Core.

Identifying the genes responsible for JS is the first step in figuring out why some children with the syndrome develop progressive retinal, renal, and/or liver disease, while others do not. Very preliminary evidence from animal models indicates that pharmacologic and gene therapies may slow or even reverse progressive retinal and renal disease. Better understanding of the different types of JS allows health care professionals to give more accurate prognostic information and provides opportunities to slow or stop associated progressive diseases, said Doherty. For example, if a health care team knows an individual is susceptible to kidney disease, they can proactively monitor kidney function and provide supportive treatment.

In addition, this work by CHDD research affiliates and the work of many others links JS to a disparate group of disorders known as ciliopathies that are associated with disruptions in the function of fundamental cellular structures known as cilia and basal bodies. There are two types of cilia: motile cilia (capable of independent movement) and nonmotile cilia, also known as primary cilia. Motile cilia are best known as the whip-like structures that propel mobile cells such as paramecia and sperm. Primary, non-motile cilia are found throughout the body, for example, in the epithelial cells that line kidney tubules and in the photoreceptor cells of the retina. Basal bodies anchor cilia in the cell and are formed from centrioles. Centrioles are best known for their involvement in the separa-
Preparing for school was a struggle for one nine-year-old who, like many children with fetal alcohol spectrum disorders (FASDs), had problems with memory and organization. Every morning, the child’s mother had to ask the same set of questions: Do you have your lunch? Your homework? Your coat?

With the help of a specialist from the Families Moving Forward (FMF) Program, the mother developed a strategy of “accommodations” to make school preparation less stressful. “She took photos of everything she wanted her daughter to take with her when she left the house and pasted them to the door frame of the front door. Then her daughter could remember what she needed to take with her,” said Allison Brooks, Ph.D., licensed psychologist, a current FMF trainer, and a former FMF specialist.

FASDs can be especially hard for families because they are “invisible” disorders that show up primarily as behavior and learning problems.

- Heather Carmichael Olson

It can be extremely difficult for parents to create these kinds of environmental changes when they’re raising “a child who every minute is hard to parent,” said Heather Carmichael Olson, Ph.D., licensed psychologist, FMF director, and developer of the FMF intervention. FMF specialists can provide a new perspective that helps families to look at their children with FASDs differently. This new perspective can then help them change the home environment to reinforce desirable behaviors while also minimizing triggers for challenging behaviors, said Carmichael Olson, who is also senior lecturer of psychiatry and behavioral sciences, and a research affiliate with the Center on Human Development and Disability (CHDD).

“Invisible” Disorders

The term FASDs refers to a spectrum of neurodevelopmental disabilities caused by exposure to alcohol before birth. Individuals with FASDs may have difficulties with learning, attention, social communication, memory, problem solving, and/or regulating their behavior. “Alcohol can affect the developing brain in so many ways,” said Brooks. FASDs may affect up to as many as one in a hundred children born in the U.S. The prevalence of this spectrum disorder is still under careful study.

FASDs can be especially hard for families because they are “invisible” disorders that show up primarily as behavior and learning problems, said Carmichael Olson. While some children with FASDs can have global delays or impairments, the majority of children with FASDs appear to have fairly typical physical development (though some have growth problems and characteristic facial features). Aspects of the cognitive development of children with FASDs may be typical for their age, yet their overall learning profiles can vary greatly. For example, a nine-year-old child might test at age level for the kinds of problem-solving skills evaluated on an IQ test, but function at the level of a five-year-old in the ability to understand and regulate emotions and actions, and at a three-year-old level when it comes to paying attention.

As a result, behavior actually linked to the disability may be misinterpreted as poor attitude and motivation. Parents of children with FASDs first have to grapple to understand these issues themselves, said Brooks. Then they have to explain them to “every teacher, every coach, every Sunday school teacher because their child’s behavior is compromised but the child doesn’t look like he or she has a developmental disability.”
Evidence-Based Program for Families

Funded by the Centers for Disease Control and Prevention (CDC), FMF is filling the need for a new evidence-based intervention for caregivers raising preschool and school-aged children with FASDs and clinically concerning behavior problems. An initial efficacy study begun in 2001 showed the effectiveness of the flexible, personalized counseling and support provided by the FMF intervention, which took place in families’ homes. Of 52 families in this randomized control trial, half received the FMF intervention and half received standard community support. The FMF intervention included a minimum of 16 home visits of about 90 minutes each over a 9- to 11-month period. Participating families were from a wide range of ethnic and demographic groups and included birth, adoptive, and foster parents.

Among other findings, immediately after treatment parents in the FMF intervention group reported a greater reduction in their children’s disruptive behaviors and a greater increase in their feelings of parenting effectiveness than parents who did not receive the FMF intervention. A striking 96 percent of parents completed the entire intervention. The initial efficacy study was co-directed by Carmichael Olson and directed by Susan Astley, Ph.D., professor of epidemiology, CHDD research affiliate, and director of the University of Washington Fetal Alcohol Syndrome Diagnostic and Prevention Network (FAS DPN).

FMF is being implemented and evaluated in the community in a new efficacy study, also funded by the CDC. Carmichael Olson is the primary investigator of the current study and Astley is a co-investigator. About 30 families are receiving the FMF intervention. Their outcomes will be compared with those from families in the original study. Research project partners are Children’s Hospital, which is administering the project, and the University of Washington through the Fetal Alcohol Syndrome Diagnostic and Prevention Network, which is the recruitment source for families involved in the studies.

In the current study, training for the FMF specialists has been streamlined and the home-based counseling program is managed by The Institute for Family Development (IFD), a community-based non-profit that has extensive experience in providing in-home, evidence-based services to families. Shelley Leavitt, Ph.D., IFD associate director, is an FMF co-investigator.

Another community partner, the National Organization on Fetal Alcohol Syndrome (NOFAS) Washington, provides FMF specialists with information on community services, and sponsors community programs such as social skills groups and family camps. FMF specialists pass this resource information to the families, who may also be linked directly with the NOFAS parent support groups or community programs. Julie Gelo, NOFAS Washington Executive Director and legal mother to eight children with FASDs, is a study consultant.

The synergies created by the FMF project partnerships are improving the continuum of service for families raising children with FASDs. “We’ve always known that some of the kids we work with [in other programs] might have FASDs,” said Leavitt, Ph.D. “Our involvement with Families Moving Forward not only helped us to be more aware of FASDs, for example to provide referrals to the FAS DPN clinics, but also to look at our interventions in our other programs a little differently.”

The Intervention: Reframing, Accommodations, and Brainstorming

The FMF intervention centers around three primary treatment processes. The first is to help caregivers of children with FASDs reframe their thinking, and to understand challenging behaviors as a result of “brain-based learning deficits, not willful disobedience,” said Carmichael Olson. Once caregivers understand the brain-based causes of their children’s behaviors, they can begin to adjust their own expectations and responses.

After reframing, the intervention helps parents learn to create accommodations for their child’s neurodevelopmental disability. The goals are to help the caregiver reorganize the home environment to eliminate factors that can cause frustration or confusion, and so trigger challenging behaviors such as tantrums. Another goal of the re-organization is to provide support for positive behaviors, such as a child using words to say what he or she needs or asking adults for help. Accommodation strategies might include providing visual cues, such as those described at the beginning of this article. Other strategies are to take tasks that seem overwhelming to a child, such as cleaning a room, and breaking these tasks into more manageable steps, such as putting certain types of toys into a specific box.
In addition to working intensively with families to help them develop interventions specific to their home and child, FMF specialists also train the caregivers in brainstorming to help them develop systematic, practical behavior plans to support positive behaviors and decrease undesirable, problem behaviors. In addition, FMF specialists may help caregivers in communications with schools, consult with other community providers, link families with support services with the help of NOFAS Washington, and encourage caregivers to engage in self-care.

**Long-Term Benefits: Stability and Hope**

In addition to providing support and relief for families, the FMF intervention may also help to prevent adverse life outcomes for their children with FASDs. Persons with FASDs are susceptible to mental health problems and to school disruption (including suspension and sometimes even expulsion), as well as trouble with the law, according to research by Ann Streissguth, Ph.D., emeritus professor of psychiatry and behavioral sciences, and emeritus CHDD research affiliate. Study participants who avoided these and other problems were more likely to have had a nurturing, structured, and stable home environment in childhood, the very kind of environment that FMF can help families provide.

Families may need to provide a nurturing environment for many years because some persons with FASDs can need lifelong support. The length of care can seem overwhelming, and is one of the greatest challenges for caregivers. That’s why the FMF logo shows a door opening to a sunlit path, said Carmichael Olson. “The logo says there’s hope, that it’s a long road, and we’ll walk it with you as long as we can.” The families, in turn, give Carmichael Olson the motivation to keep herself on the road of FASDs research. “The families are amazing. They’re heroic. They’re taking on wonderful children who have life-long problems and sticking to it.” Their dedication, said Carmichael Olson, makes FASD intervention “something you want to work on night and day.”

More information is available at:

**Families Moving Forward:**
http://depts.washington.edu/fmffasd
**NOFAS Washington:**
www.nofaswa.org
**Institute for Family Development:**
www.institutefamily.org
**Fetal Alcohol Syndrome Diagnostic and Prevention Network**
http://depts.washington.edu/fasdpn/

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**Joubert . . . from pg. 2**

Joubert syndrome is relatively rare, but shares features with other neurological disorders, including autism spectrum disorders. Mutations in RPGRIP1L disrupt network interactions with the NPHP4 protein, a known component of basal bodies and primary cilia required for kidney and retinal function. The network also includes the protein encoded by NPHP1, the first gene linked to JS in an effort led by Parisi.

Although the effects of the mutations that disrupt this network of proteins can be severe, resulting in JS and other disorders, researchers don’t understand exactly how these disruptions impair cilia function. Information on primary cilia is especially scarce. Until recently, these organelles were thought to be evolutionary remnants with little function. However, a growing body of research indicates that primary cilia can serve as sensory organelles, detecting chemicals, signaling proteins, and movement in the environment outside of cells. Basal bodies and primary cilia also help orient cells in their environment.

“In just a few years the cilium has gone from being perceived as a vestigial organelle to being recognized as a huge player in cell biology and human disease,” said Doherty. “It has become apparent that the cilium is vitally important for the development and function of a variety of body parts, including the brain, kidney, retina, liver, hands, and feet.”

In addition to JS, serious genetic disorders recently categorized as ciliopathies include Bardet-Biedl syndrome, which causes cognitive impairment, obesity, and kidney disease; nephronophthisis, the most common genetic cause of kidney failure in children; Leber congenital amaurosis, which causes severe vision loss, sometimes combined with other neurological disorders; Senior-Løken syndrome, which leads to kidney failure and blindness; and Meckel-Gruber syndrome, which causes serious brain, kidney, liver, and limb abnormalities.

In addition to helping individuals with JS and their families, study of JS genetics will contribute to a better understanding of brain development. “Joubert syndrome is relatively rare, but shares features with other neurological disorders,” said Doherty. Several studies have linked one JS gene, AH11, to schizophrenia. In addition, a variety of evidence has linked autism to abnormalities in the cerebellum, and behavioral characteristics associated with JS overlap with those of autism spectrum disorders.” The possibility that understanding JS might shed light on autism is intriguing,” said Doherty.

More information is available at the UW Joubert Center web site:
I\text{t} s it ever ethical or legal to restrict the growth of a child with a developmental disability? Who benefits if growth restriction makes such a child easier to lift and transport as he or she ages? Can families provide consent for such procedures or should the courts? What about prevention of possible future health issues through procedures that result in sterilization? What are the reproductive rights of persons with developmental disabilities, especially given the history of forced sterilizations in the U.S.? Faculty, staff, and trainees at the Center on Human Development and Disability (CHDD) are working to address these and other significant ethical and legal issues that were most recently raised when growth limitation in children with developmental disabilities. Sharan Brown (above left), UCEDD associate director, moderated a panel considering the roles of ethics committees and judicial review in providing safeguards for individuals with developmental disabilities. Panelists were (left to right), David Carlson, Disability Rights Washington; David Loeben, Midwestern University; and Ed Holen, Washington State Developmental Disability Council.

**Ashley’s Treatments**

The young girl at the center of this controversy is the first child with a developmental disability known to have received growth attenuation treatments. The girl’s name, Ashley, and her nickname, “Pillow Angel,” were released to the public by her parents. Ashley’s development is profoundly affected. In early 2007, at age nine, she was unable to walk, talk, or hold up her head. Ashley began receiving growth attenuation treatments involving high doses of estrogen when she went into early puberty in 2004 at the age of six.

Ashley’s parents have stated that maintaining Ashley’s small size will make it easier for her to be bathed, carried, and to travel with family members in a car, thus improving her future quality of life. In their online blog, Ashley’s parents have also written “given Ashley’s mental age, a nine and a half year old body is more appropriate and provides her more dignity and integrity than a fully grown female body.”

Ashley also underwent two surgical procedures: a hysterectomy and removal of her breast buds. Ashley’s parents stated that they requested the two surgical procedures to prevent possible future discomfort and health problems. The hysterectomy was performed to prevent possible discomfort from future menstruation and from uterine bleeding expected to occur as a result of the growth attenuation treatments. Ashley’s breast buds were removed to prevent possible discomfort she might experience from the chest straps required to keep her seated, and to prevent the possibility of breast disease. These were concerns because the women in Ashley’s family have a history of large breasts, painful fibrocystic breast disease, and breast cancer. Ashley’s parents also stated that they wished to minimize the potential for future sexual abuse by caretakers.

The treatments were performed at Children’s Hospital and Regional Medical Center (CHRMC) and were reviewed and approved by the CHRMC Ethics Committee. Private insurance paid for the procedures.

The publication of a 2006 scientific article in the *Archives of Pediatric and Adolescent Medicine* provided the first public knowledge of the growth attenuation treatment and surgical procedures Ashley received, and sparked intense debate.

In January 2007, Ashley’s parents initiated their blog where they stated that the three procedures Ashley received could be beneficial for other children and their families. They referred to the treatments collectively as “The Ashley Treatment.” CHRMC physicians have stated that they did not consider the procedures as a package and evaluated the need for each separately.

After Ashley’s parents posted their blog, The Washington Protection and Advocacy System (WPAS), now called Disability Rights Washington (DRW), initiated an investigation of Ashley’s treatments. DRW is a private non-profit organization charged with protecting the rights of people with disabilities.

In a report released May 8, 2007, DRW stated that the CHRMC physicians violated a ruling by the Washington State Supreme Court when they performed Ashley’s hysterectomy without a court order. On May 8, the administration of CHRMC agreed that the ruling had been violated due to “an internal miscommunication” and stated that in the future a court order would be required for “growth attenuation through hormone treatment, and for breast bud removal and/or hysterectomy when it involves a child with a developmental disability.”
Collaborating for Education and Advocacy

The CHDD is working with advocacy and other groups to educate the public and health care providers about the issues raised by Ashley’s case, and to advocate for the rights of children with developmental disabilities and their families regarding consent for medical procedures. Many efforts involve trainees with the Leadership Education in Neurodevelopmental and Related Disabilities (LEND) Interdisciplinary Training Program, part of the CHDD Clinical Training Unit (CTU). The goal is to help LEND trainees better examine and understand the complexity of these and other issues related to medical care for persons with developmental disabilities. CHDD collaborators include DRW and the Washington State Developmental Disabilities Council (DDC), a 33-member council appointed by the governor of Washington State to plan comprehensive services for citizens with developmental disabilities. The DDC and DRW, like the CHDD, receive funding from the United States Department of Health and Human Services Administration on Developmental Disabilities.

These collaborations have generated education and advocacy efforts for persons with developmental disabilities and their advocates, health care professionals, and the general public. Education for health care providers has included a LEND seminar, Developmental Disabilities: The Ashley Case, Judicial, Legislative, and Advocacy Updates, held April 23, 2007. Seminar speakers were Ed Holen, DDC executive director, and Sharan Brown, J.D., Ed.D., associate director, CHDD University Center for Excellence in Developmental Disabilities (UCEDD), and research associate professor of educational leadership and policy studies.

Collaborations between the CHDD, DRW, and the DDC have included participating in the planning and execution of a daylong symposium for health care professionals, academics, and the public. The symposium, The Ethical and Policy Implications of Limiting Growth in Children with Severe Disabilities, was held May 16, 2007 at the University of Washington (UW). It was sponsored by the UW Disability Studies Program and the Trueman Katz Center for Pediatric Bioethics, Children’s Hospital and Regional Medical Center (CHRMC); co-sponsors were the CHDD, the UW Department of Medical History and Ethics, and the UW Program on Values in Society. Webcasts of the symposium are available online (see sidebar). More than 150 people attended.

Discussions at the May 16 symposium took place in the context of the May 8 agreement between CHRMC and DRW. During the symposium, DDC Executive Director Ed Holen said that advocates for persons with disabilities are “going to watch and monitor [CHRMC] responses to the May 8 report.”

Intense Debate at Symposium

Debates at the May 16 symposium covered a wide range of issues related to the ethics of performing medical procedures on persons whose disabilities prevent them from giving consent. Although the conference was intended to focus on growth attenuation, participants initiated multiple discussions of the hysterectomy performed on Ashley, especially in the context of the history of forced sterilizations of persons with developmental disabilities in the U.S. during the 19th and 20th centuries. Some participants spoke about their

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Online Resources

Archived webcasts of the May 16 symposium, The Ethical and Policy Implications of Limiting Growth in Children with Severe Disabilities


Blog by Ashley’s parents, discussing her treatment: http://ashleytreatment.spaces.live.com/blog


CHDD faculty moderated two of the panels at the conference. Kathleen Watson, R.N., Ph.D., research assistant professor of nursing, and an associate director of the CHDD University Center for Excellence in Developmental Disabilities (UCEDD), moderated a panel entitled Balancing Interests: Parental Decision-making, Doctors, and the Community. Panelists were Joanne O’Neill, coordinator of parent training, King County Parent Coalition, The Arc of King County; Ted Carter, M.D., CHRMC; and Alice Domurat Dreger, Ph.D., Northwest University Feinberg School of Medicine, Chicago. Brown moderated the panel Institutional, Legal, and Policy Responses and the Impact on Families and Communities, where DRW was represented by David Carlson, J.D., and the DDC by Holen. Greg Loeben, Ph.D., Midwestern University, Phoenix, was also a panelist.

After the conference, Holen said the medical, legal, and advocacy communities need to develop an ethical consensus to guide physicians and hospitals faced with requests like those made by Ashley’s parents. Advancements in technology and medicine could provide health care providers and the courts with “any number of similar situations,” said Holen. “And what do we base our decision making on? My bottom line is that this procedure or any procedure like it would never happen again. People with developmental disabilities are people first, and they have all the rights of any other person, including the right to grow up.”

Continuing Efforts

Continuing efforts by the CHDD include advocacy and education by John McLaughlin, M.D., professor of pediatrics, CTU director, and CHDD research affiliate; Samuel Zinner, M.D., assistant professor of pediatrics; and Ross Hays M.D., associate professor of rehabilitation medicine, a certified ethicist, and a CTU discipline leader for ethics and rehabilitation medicine. Advocacy efforts by McLaughlin include membership on a CHRMC committee to review any requests for treatments and procedures such as those performed on Ashley. He has also been consulted by members of the CHRMC Ethics Committee.

Brown continues to address legal and ethical issues related to Ashley’s case through disabilities studies courses she teaches for the UW Disabilities Studies Program, which serves students in law, social work, and other disciplines, and is part of the CHDD Community Disability Policy Initiative.

Brown and Watson are also planning a paper to address conflicts between the ideals of equality and human rights for individuals with developmental disabilities and the current realities of providing care for individuals with severe disabilities.
Nicotine, Dopamine, and Behavior Disorders

If a woman smokes while pregnant, she increases her child’s susceptibility to attention deficit/hyperactivity disorder (ADHD) and conduct disorder (CD). Some researchers have speculated that women who smoke during pregnancy are more likely to be impulsive, and it is this genetic predisposition, rather than exposure to nicotine that affects their children. Theodore Beauchaine, Ph.D. and Lisa Gatzke-Kopp, Ph.D. (now at Penn State University), are helping to disentangle these genetic and environmental factors through research that links prenatal exposure to second-hand smoke with risk of ADHD and CD. Recent research for their lab also further illuminates the role of dopamine deficiencies in ADHD and CD.

ADHD is a developmental disorder characterized by inattention, impulsivity, and hyperactivity. The term CD refers to a group of behavioral and emotional problems that can include aggression, serious violations of rules, and destruction of property. ADHD is diagnosed in about 2-5 percent of children between the ages of six and sixteen, about 80 percent of them boys. ADHD and CD often occur together. Almost all children with CD have ADHD. In contrast, only about half of children with ADHD have CD.

Exposure to nicotine before birth increases the risk of ADHD and CD, as well as prematurity, low birth weight, and allergies. In addition, research has shown that women who smoked while pregnant are more likely than non-smokers to have a childhood history of CD. This makes sorting the effects of nicotine from genetic predispositions to ADHD and CD difficult.

Second-Hand Smoke

By studying the effects of second-hand smoke, Kopp and Beauchaine hoped to isolate the effects of nicotine exposure. Like previous research, their study compared children of women who smoked during pregnancy with children of women who did not smoke. Kopp and Beauchaine went further by adding a third group, children of women who did not smoke but were exposed to significant amounts of second-hand smoke during pregnancy. The women who did not smoke during pregnancy, regardless of whether they were exposed to second-hand smoke, tended to be more similar to each other than to women who smoked regarding a variety of demographic characteristics linked to ADHD and CD. These factors included education, household income, and scores on tests of antisocial behaviors. Yet study results revealed that children of non-smoking women who were exposed just to second-hand smoke had the same risk of ADHD and CD as did children of women who smoked.

“This is the very first study to show that even second-hand smoke exposure on the part of mothers who do not smoke themselves, whether that exposure be in the workplace or the home, increases the risk of conduct problems in their children,” said Beauchaine, an associate professor of psychology, and a research affiliate of the Center on Human Development and Disability (CHDD).

Dopamine Connection

The link between nicotine and ADHD/CD appears to be dopamine. Dopamine has many functions in the brain, including roles in motivation, mood regulation, and learning. It acts by linking rewards with behavior, and is associated more with a motivation to seek a reward than with pleasure in the reward itself. Laboratory studies show that exposure to nicotine can reduce the amount of dopamine in some parts of the brain, decreasing responsiveness of neurons that release dopamine. “Children of mothers who smoke are born with dopamine systems that are less active,” said Beauchaine.

In numerous biobehavioral studies, Kopp and Beauchaine have documented low levels of dopamine activity in children with ADHD and CD. For example, during functional magnetic resonance imaging (fMRI), they found that adolescents with ADHD and CD responded differently to rewards (money won while playing a game) than those of typical children. All of the study participants showed activity in the striatum when they won. This region of the brain reacts to rewards and novel or intense experiences. When the game stopped allowing the participants to win, activity in the brains of the typical children “moved forward to the anterior cingulate cortex, an area involved in attentional processes,” said Beauchaine. “However, the adolescents with CD and ADHD kept recruiting the striatum even when the rewards weren’t coming anymore.” Collaborators in this study included Elizabeth Aylward, Ph.D., professor of radiology and CHDD research affiliate.

Mitigating Low Dopamine Levels

This and other research indicates that individuals who have low levels of dopamine may need more stimulation to activate their reward systems. These findings have implications for helping children with ADHD and CD learn. They tend to need more consistent and predictable rewards for behavior than do typical children, said Beauchaine.

Growing understanding about dopamine deficiencies also explains why

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Faculty Members Appointed as New CHDD Research Affiliates

Christine Disteche, Ph.D., a professor of pathology, studies the structure, function, and regulation of the X chromosome. She and her lab focus on X inactivation, a process which silences one of the two X chromosomes in females, and genes that escape regulation by X-inactivation, such as JARID1C. Mutations in JARID1C have been implicated in X-linked intellectual disabilities in males. Disteche’s work is also relevant to the study of Turner Syndrome, a developmental disorder that occurs in females who are missing part or all of one X chromosome, which can cause disabilities in some types of non-verbal learning.

Eliot Brenowitz, Ph.D., is a professor of psychology and biology. Brenowitz studies the song systems of birds as a model for the effect of hormones on neurodevelopment in humans, especially vocal learning, and processes that damage and protect neurons. Song learning in birds is extremely sensitive to fluctuations in steroid sex hormones, with the parts of the brain that control song adding and pruning neurons in response to these fluctuations. Neuron receptors for the hormones that influence song learning in birds are also found in the speech production and perception areas of the human cortex.

Zoran Brkanac, M.D., an assistant professor of psychiatry and behavioral sciences, studies the genetic basis of dyslexia. To identify susceptibility genes for dyslexia, the UW Genetics of Dyslexia group is searching for genes that underlie phonological and orthographic skills needed to translate written words into sounds of language. In addition, Brkanac searches for genes associated with deficits in attention and executive function in persons with dyslexia. Such deficits have also been associated with other inherited disorders, such as attention deficit hyperactivity disorder (ADHD).

David Perkel, Ph.D., is a professor of biology and otolaryngology-head and neck surgery. He studies vocal learning in birds as a model for understanding speech learning in humans. Vocal learning involves learning new communication sounds, such as new words, by listening to others. Perkel and his team study neural circuits, including a major pathway involving the basal ganglia, which allow some songbirds to learn new songs. Since these circuits are similar to those in mammals, study of them may contribute to therapies for persons who have developmental disabilities that affect their ability to speak and learn language.

Marina Guizzetti, Ph.D, is a research scientist in the Department of Environmental and Occupational Health Sciences. Guizzetti studies developmental neurotoxicology, focusing on the effects of prenatal alcohol (ethanol) exposure on interactions between neurons and astrocytes. Astrocytes are glial cells that play an important role during brain development as they regulate neuronal survival, migration, and differentiation. Guizzetti investigates novel mechanisms of astrocyte-neuron interactions relevant to brain development, and how ethanol affects these interactions by influencing the release of proteins and lipids from astrocytes, contributing to the brain injury observed in individuals with Fetal Alcohol Spectrum Disorders.

Bensheng Qiu, Ph.D., a research assistant professor of radiology, studies possible therapies to treat gliomas, cancerous tumors of the brain and spinal cord. Gliomas arise from glial cells, a class of cells that nourish, protect, and support neurons. Current treatments for gliomas can lead to significant cognitive damage, especially in the developing brains of young children. Qiu and his lab are using MRI imaging to develop techniques to label and track the migration of stem cells, which could be used in targeted glioma treatments, including gene, radiation, or chemotherapies.
Amanda Jones, Ph.D., is a research assistant professor of pediatrics. Jones studies group B streptococcus (GBS), which causes half of serious infections in newborns, including meningitis and pneumonia. GBS infections are fatal in about 5 to 15 percent of newborns and developmental disabilities and delays are common in infants that survive. Jones’ lab studies the ways this common type of bacterium, which rarely causes illnesses in adults, evades the neonatal immune system. She and her team have identified several strategies used by this bacterial pathogen to evade microbial peptides in the innate immune response system.

David Morris, Ph.D., is a professor of biochemistry. His laboratory studies the role of RNA-protein complexes in the regulation of gene expression, and ways that these complexes can be used to profile genome-wide expression. One research focus is the role of the RNA-binding protein FMRP and its multiple isoforms (variations), work that is relevant to understanding the biological basis of Fragile X syndrome and ultimately to the design of therapies. Another focus is the development of techniques to tag ribosomes in specific cells and the use of this approach to analyze gene expression in complex tissues, such as the brain.

Ellen M. Wijsman, Ph.D., a professor of medicine and biostatistics, develops statistical methods for analyzing large amounts of genetic data. Currently Wijsman is working with a team of researchers to study the genetics of autism spectrum disorders (ASD). By analyzing the genomes of multiple families with a possible genetic predisposition to ASD, and comparing the genes of family members with and without ASD, she and her colleagues are isolating genetic variants more likely to be found in persons with the disorders. Wijsman has also contributed to successful efforts to isolate genes involved in Werner’s syndrome and familial Alzheimer’s disease.

Jeffrey Chamberlain, Ph.D., is a professor of neurology, biochemistry, and medicine. He researches the muscular dystrophies, primarily Duchenne muscular dystrophy (DMD), to develop a better understanding of the molecular basis of the pathophysiology of the diseases, and to develop gene and cell therapies to correct and treat them. DMD is the most common form of muscular dystrophy, affecting one in 3,500 newborn males, and is caused by mutations in the dystrophin gene. Chamberlain and his associates are studying the structure and function of the dystrophin gene, as well as developing viral vectors to deliver this or other genes to muscle cells for possible gene therapy.

Lucio Costa, Ph.D., is a professor of environmental and occupational health sciences focusing on the area of developmental neurotoxicology. Neurotoxicants can cause long-term changes in the central nervous system. His laboratory uses in vitro and in vivo approaches as well as biochemical, molecular, and imaging techniques to investigate mechanisms of developmental neurotoxicity. Neurotoxicants currently under study include ethanol, organophosphate insecticides, domoic acid, and polybrominated diphenyl ether fire retardants. Costa also investigates genetic variations that can affect susceptibility to neurotoxic compounds.
methylphenidate (Ritalin), a drug that increases dopamine levels, is effective in children with ADHD and CD. “If you think of impulsive behavior as a product of low dopamine activity, when you give children Ritalin, you increase their dopamine activity and that normalizes their behavior, so they get the sort of contentment the rest of us do without drugs,” said Beauchaine.

Beauchaine has also linked ADHD and CD to differences in the function of the autonomic nervous system, which regulates heart rate and other functions not under conscious control. Children with ADHD and CD tend to have lower levels of activity in parasympathetic nervous system (PNS), the part of the autonomic nervous system (ANS) that keeps flight-or-flight responses in check. “The PNS suppresses strong emotional reactions,” said Beauchaine, who measures ANS activity through analysis of heartbeat. “So a lot of PNS activity is a very good thing. It stabilizes our emotions and behavior.” Children with low PNS activity are more likely to act impulsively and aggressively.

“Even second-hand smoke exposure on the part of mothers who do not smoke themselves...increases the risk of conduct problems in their children.”

- Theodore Beauchaine

Beauchaine is also studying interventions for children with ADHD and CD in collaboration with Carolyn Webster-Stratton, Ph.D., a professor of family and child nursing and a CHDD research affiliate. Beauchaine’s team is testing ANS activity of 4-6-year-old children before, during, and after participation in a program for high-risk preschoolers developed by Webster-Stratton. The researchers are looking for biomarkers to predict which children will respond to the intervention, known as the Dino Dinosaur Treatment Program. They also hope to learn if participation changes the ANS activity, “if the treatment actually affects biology,” said Beauchaine.

Beauchaine is also planning an fMRI and genetics study involving the CHDD Genetics and Neuroscience Cores. “We’re looking for genes that give rise to these dopamine deficiencies that lead to ADHD and CD,” said Beauchaine. The proposed study “is very ambitious,” said Beauchaine. “Most neuroimaging studies have just a handful of children and we want to image two hundred." Genetic analysis will focus on interactions in polymorphisms of five genes implicated in dopamine functioning and ADHD. Collaborators in this project will include Sara Webb, Ph.D., research assistant professor of psychiatry and behavioral sciences and a CHDD research affiliate; Elizabeth Aylward, associate director of the Brain Imaging Component of the Neuroscience Core; and Federico Farin, M.D., Ph.D. director of the Microarray Component of the CHDD Genetics Core.

Visit the CHDD web site at www.chdd.washington.edu

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