SPRING/SUMMER 2012

Collaborations

MID-ATLANTIC CONSORTIUM

Meet the Mid-Atlantic Consortium

Children's National Medical Center
Children's Hospital of Philadelphia
Kennedy Krieger Institute/Johns Hopkins University
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Letter from the Directors

Welcome to the inaugural issue of *Collaborations*, a newsletter showcasing developmental disabilities research at the Intellectual and Developmental Disabilities Research Centers (IDDRCs) of Children's Hospital of Philadelphia, Children's National Medical Center in Washington and Kennedy Krieger Institute/ Johns Hopkins University in Baltimore.

Our centers, which formed a Mid-Atlantic Consortium in 2007, have resulted in thousands of studies over several decades to better understand developmental disabilities. Our discoveries often have led to improved treatment of affected children and adults, resulting in a better quality of life.

Although intellectual and developmental disabilities are extremely complex, scientific and technological developments provide tools for making even more progress. Each issue of *Collaborations* will highlight collaborative efforts supported by our centers. This time out we're featuring studies about early developmental changes in Fragile X Syndrome, and new candidate genes and genomic variants contributing to autism.

Our IDDRCs leverage what investigators in each center can do by providing them with equipment, services and innovative ideas that otherwise might not be accessible. These include analytical neurochemistry; expertise in biostatistics and bioinformatics; cellular neuroscience tools and neuroimaging; and sophisticated methods for assessing learning and performance. These resources are available both for established scientists and young investigators, who will produce the next generation of advances in our field.

We hope you enjoy *Collaborations* and find it useful. We invite your comments and suggestions. Contact us any time at collaborations@kennedykrieger.org.

Michael F. Cataldo, Ph.D.,
Kennedy Krieger Institute/ Johns Hopkins University

Vittorio Gallo, Ph.D.,
Children's National Medical Center

Marc Yudkoff, M.D.,
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Want to receive Collaborations *and other news from the Consortium? Send an e-mail to* **collaborations@kennedykrieger.org**

Computer Games

A Potential Strategy for Helping Children with Epilepsy Improve Thinking Skills

Investigators at Children's National Medical Center (CNMC) hope that a series of specialized computer games can help children with epilepsy improve their ability to keep information in mind while doing work, a skill called 'working memory.'

"Many kids with epilepsy have learning problems, and a lot of them have the inattentive form of attention-deficit hyperactivity disorder," explains Madison Berl, Ph.D., principal investigator at the Children's Research Institute, part of the Center for Neuroscience Research at CNMC. These children have good intelligence, she says, but as academic demands and need for listening skills increase throughout elementary school, problems may become evident.

"It's not so much that they can't understand the information, but that they lack the ability to keep all information in mind," Berl says.

To help them, she and her colleagues are applying a computerized cognitive training program designed to improve working memory by featuring computer games with thinking tasks, such as remembering sequences. For the first time, the five-week program, originally designed for children with ADHD, is being assessed for use at home in pediatric epilepsy patients ages 8 to 15.

The CNMC team has an ongoing pilot study to measure the effects of the games performed for 30 minutes at a time, five times a week. Preliminary results show that "even a few times a week makes a difference," Berl says. "It doesn't work for everyone, but in those it helps, we see results relatively quickly."

To evaluate the games' impact, researchers will compare neuropsychological tests, parent reports of attention, and brain images taken with diffusion tensor imaging (DTI) before and after the intervention, and three months later. DTI studies the brain's white matter, what Berl refers to as "the brain's highway for communicating information." While Berl's current DTI studies are in collaboration with scientists at NIH, the early development of the DTI approach resulted from the pioneering work of Susumu Mori, Ph.D., at the Kennedy Krieger Institute/Johns Hopkins IDDRC.

The premise is similar to a traditional exercise program, says Berl: Working the thinking "muscle"—the brain—daily can build its strength. Though hers is a regimented program, applying the same basic skills can be done with games. ◆

For more information on Berl's studies, contact mberl@childrensnational.org.

Understanding Fragile X Syndrome
May Lead to Treatment for Autism As Well

It was a guest lecture from the director of Kennedy Krieger Institute's (KKI) Fragile X Syndrome clinic that turned Joshua Corbin, Ph.D., on to studying the Fragile X brain.

Corbin, an associate professor of pediatrics, pharmacology and physiology at Children's National Medical Center (CNMC), had long been interested in basic mechanisms of brain development — specifically the amygdala, an almond-shaped mass involved in emotional processing and memory. The amygdala also is implicated in the fear response known as "fight or flight;" its dysfunction is tied to many emotional and social defects associated with autism.

But when KKI's Walter Kaufmann (now at Children's Hospital in Boston) came to speak at CNMC six years ago as part of the IDDRC lecture series, "He directly brought to my attention that no one had been looking at Fragile X in a way that focused on social and emotional factors." Corbin says.

He has since directed half of his lab's efforts to uncovering brain mechanics in animal models of Fragile X Syndrome, a genetic condition caused by an alteration in a single gene. The mutation decreases the amount of a protein vital to normal intellectual development. Fragile X is the most common inherited cause of intellectual disability and the leading known genetic cause of autism.

Using mouse models of Fragile X, made by knocking out the gene Fmr1, Corbin and colleagues have expanded understanding of brain development and dysfunction seen in Fragile X and autism spectrum disorders. In 2010, Corbin's team published a report in the *Journal of Neuroscience* describing a significant decrease in a chemical pathway in the amygdala that they believe is responsible for many social and emotional problems associated with Fragile X, a hypothesis they're now testing. And they demonstrated the effectiveness of a compound, gaboxadol, that re-activates the pathway, suggesting drugs targeting this pathway could treat specific behavioral abnormalities.

The discoveries resulted from a three-year collaboration of Corbin's lab, Kaufmann's lab, and a third lab directed by CNMC neuroscientist Molly Huntsman, Ph.D. Their studies found too little of the inhibitory chemical GABA, rendering interactions among neurons too excitable. Gaboxadol restored the balance in nerve cell communications.

In unrelated clinical trials of GABA-enhancing medications in people with Fragile X, social behaviors appear to get better, Corbin says: "Our work gives a biological explanation for why this might work."

Corbin and his collaborators also have learned that there is a period during which the deficient inhibitory pathway tries to correct itself but it doesn't hold. "A future quest is to understand why," he says. He and Huntsman have funding from Autism Speaks for this purpose. "If you can significantly decrease the symptoms in Fragile X, you can probably affect at least a subpopulation of other types of autism."

Corbin began his Fragile X work as a junior investigator. CNMC's IDDRC provided immediate access to research resources for cellular imaging and biostatistics, and later to the Fragile X clinics. Through the Center's lecture series and links to other centers, a gateway to the larger Fragile X community opened.

"It's an incredibly exciting time," he says. "It's likely that more directed therapeutics will become available, and there is a tremendous amount of optimism." ◆

ⓘ *For more information about Corbin's work, see http://www.childrensnational.org/research/faculty/bios/cnr/corbin_j.aspx. For more information on Fragile X, see the FRAXA Research Foundation's Web site: www.fraxa.org.*

Ask the Expert: **David Valle, MD**

Director, Genetics Core, Hopkins/KKI IDDRC
Henry J. Knott Professor and Director, McKusick-Nathans Institute of Genetic Medicine
Johns Hopkins University School of Medicine

David Valle is on the hunt for yet-unknown Mendelian disorders

David Valle has been interested in biology almost as long as he can remember. He recalled in an interview recently that when he was in fourth grade in upstate New York, he learned with "excitement" that in seventh grade, he could take a biology class!

With help from a series of "great science teachers," Valle says, he turned to the study of genetics in college and later in medical school, after which, on the advice of his medical school mentor, he came to Johns Hopkins in 1969 for a pediatrics residency. He joined the faculty in 1975 and made Hopkins his lifetime professional home.

An international authority on inborn errors of metabolism, Valle has published more than 200 research papers and is a recognized leader and heir to deep-bench genetics research, teaching and clinical enterprise. In addition to his work at the Institute that bears the names of legendary geneticist Victor McKusick and Nobel prize-winning molecular biologist Dan Nathans, Valle has directed the Center for Inherited Disease Research and led a predoctoral training program in human genetics.

In December, the National Human Genome Research Institute awarded a four-year, $16 million grant to Valle and colleagues at Hopkins and Baylor College of Medicine in Houston to more fully identify the causes of genetic disease. The new Baylor-Hopkins Center for Mendelian Genomics aims to define genetic causes of so-called Mendelian disorders – inherited diseases caused by a defect in a single gene. An estimated 25 million Americans are affected by these conditions, most of which are relatively rare. Many of the disorders, like cystic fibrosis and muscular dystrophy, are well known; others may affect only a handful of families around the world.

Recently, he spoke to Collaborations about the work to be done with the new grant.

Q: Do you have an estimate of how many Mendelian disorders there are?

A: I don't, but there's no reason why we could not expect a Mendelian phenotype (observable characteristics) for every one of our 22,000 genes. Usually when you have a mutation of a particular gene, and it results in a particular phenotype, there's a one-to-one relationship between the gene and phenotype. In other cases, a particular kind of mutation in a gene could cause one phenotype, and another kind of mutation in the same gene may cause a second phenotype. One could ask, of all the patients, are we going to find the one-to-one correlation, multiple correlations, or something in between? The answer almost certainly is going to be something in-between.

Q: How many disease-causing genes do you think you will find during the four-year study?

A: I hope that in aggregate we would increase the number of known disease genes to something over 50 percent of the total number of genes. That would mean going from roughly 2,500 now to 10,000. If we succeed, it will be an enormous boost.

Q: What are the implications for patients and families?

A: We think the study will have a lot of important consequences for the diagnosis and care of patients. It will lead to precise molecular diagnoses so instead of patients going through what seems like endless testing, we will get to the genetic definition of the disorder as quickly as possible. Identification of the responsible gene and the information that will come from that will inform the way we take care of patients. It may also inform us about ways to prevent problems they might be susceptible to, and about potential treatment strategies and better medicines. And it will improve genetic counseling for families as well.

Children and their families will ultimately benefit from our research, but only as we begin to translate our findings from the basic cellular level to studies of problems with known or suspected genetic origins. That process requires close working relations with the clinicians and clinical investigators that have been occurring through our IDDRC here, and now with the two other centers that are part of the MAC Consortium. ◆

For more information: McKusick-Nathans Institute of Genetic Medicine http://www.hopkinsmedicine.org/geneticmedicine/OnlineMendelian Inheritance in Man http://www.omim.org

Autism More Common, CDC Study Shows

One in 88 American children have been identified as having an autism spectrum disorder (ASD), according a study released in March by the federal Centers for Disease Control and Prevention.

Results from a survey of autism prevalence among children in 14 areas of the nation showed that 11 of every 1,000 8-year-olds have been identified as having ASD – a 23 percent increase since the last report three years ago. Some of the increase is due to the way children are screened, diagnosed and cared for in their communities, the researchers said. The study also found that more children are diagnosed by age 3 these days, an increase of six percent between those born in 1994 and those born in 2000.

The number of children with an ASD ranged from one in 210 children in Alabama to one in 47 children in Utah. The largest increases were among Hispanic and African-American children. Across the three IDDRCs of the MAC Consortium, more than 100 scientists are working to better understand and treat ASD. ◆

For more information, see http://www.cdc.gov/media/releases/2012/p0329_autism_disorder.html

Children With Seizures Prefer Bacon to Candy, Puzzling Parents

It may be easier than parents think to get children with intractable seizures to follow a high-fat, high-protein, ultra low-carbohydrate diet, according to researchers at Kennedy Krieger Institute (KKI) and Johns Hopkins.

Physicians and parents of children with difficult-to-control seizures are often reluctant to start them on the strict ketogenic diet, which, although a proven non-drug therapy, is often perceived as unpalatable over the long haul. But when investigators tested children with epilepsy, the facts suggested that even 2-year-olds, when given a choice, often select high-fat foods like bacon, butter, cream cheese and mayonnaise over candy or chips.

A team led by Adrianna Amari, Ph.D., a licensed psychologist at KKI and an assistant professor at Johns Hopkins University, compared the food preferences of 29 children ages 2 to 17, all with seizures, to 30 same-aged children without seizures. The team offered small tastes of seven high-fat foods, and seven high-carbohydrate foods in various paired combinations. They also asked parents to predict which foods their children would select.

Overall, children with seizure disorders had significantly higher preferences for high-fat versus high-carbohydrate foods, while children without seizure disorders had the opposite preferences. One child with epilepsy scooped up butter and said, "This one makes me feel better," Amari says. Parents were rarely accurate in predicting their childrens' choices.

"We were quite surprised to find that children with seizure disorders preferred atypical items like mayonnaise and cream cheese," Amari says. "Parents were also surprised by these preferences. In fact, some children in this study were started on the ketogenic diet after parents saw their children eating the high-fat foods without difficulty."

Amari says her research was made possible through the collaborative environment of the KKI/Hopkins IDDRC, which allowed her to adapt the efficient methods of the KKI NeuroBehavioral Clinical Program for quantifying preferences of children with the high-fat diet employed by the Hopkins Epilepsy Program.

Amari and colleagues at Hopkins are analyzing results of a follow-up study to see whether preferences for high-fat foods compatible with the ketogenic and modified Atkins diets correlate with likelihood of seizure control once these diets are actually started. If true, food preferences could help predict the children most likely to benefit from these diets.

Her original report on food preferences was published in 2007 in the journal *Epilepsy & Behavior.* ◆

For more information on Amari's studies, contact amari@kennedykrieger.org.

The Genetics of Autism: New Research Suggests Role for Multiple Genes

New research on autism indicates that common biological themes underlie the complexity of the condition's genetic roots.

A study by researchers at The Children's Hospital of Pennsylvania (CHOP) has implicated several new candidate genes and genomic variants as contributors to autism, concluding that many more remain to be discovered. While gene alterations individually are very rare, they mostly appear to disrupt processes that play important roles in brain development and nerve signaling.

"This study is the first to demonstrate a statistically significant connection between genomic variants in autism and both synaptic function and neurotransmission," said senior author Peter S. White, Ph.D., a molecular geneticist and director of the Center for Biomedical Informatics at CHOP. Synapses are the contact points at which nerve cells communicate with other nerve cells; neurotransmitters are the chemical messengers carrying those signals.

"Prior genomic studies of autism have successfully identified several genes that appear to confer risk for autism, but each gene appears to contribute to only a small percentage of cases," said the study's lead author, Xiaowu Gai, Ph.D. "Our approach considered whether groups of genes with common biological functions collectively accounted for a greater percentage of autism risk."

In the study, published in the journal *Molecular Psychiatry*, researchers compared the DNA of more than 1,000 children with autism to DNA from typically developing children, searching for gene variants called copy number variations (CNVs) within the genomes of autistic individuals and their families. Members of the study team reinforced their findings using information from these mouse models, showing that mice with abnormal motor and learning behaviors similar to human autistic behaviors were more likely to have CNVs in genes similar to human autism-associated genes.

"Because the gene alterations that we found influence brain development, our hope is that they may eventually provide clues to developing diagnostic tests as well as treatments for children with autism," said study co-author and lead clinician Josephine Elia, M.D., a child psychiatrist at CHOP.

White and colleagues found more than 400 inherited CNVs in autism subjects that did not occur in typical children. There are more than 100 scientists at the three IDDRCs working on a better understanding of autism. ◆

Note: *CHOP's IDDRC remains sharply focused on autism research and the tools of bioinformatics to amass useful information from microarray analyses of the genome. In addition to White, associate director of Biostatistics and Bioinformatics Core, other key faculty in CHOP's IDDRC autism program are Robert Schultz, Ph.D., Director of the Center for Autism Reseach and associate director of the Neuroimaging Core; and Josephine Elia, M.D. a lead clinician and study co-author, supported by the New Program Development enterprise. This article excerpted from a CHOP news release.*

ⓘ *For more information on White's work, see http://stokes.chop.edu/research/profiles/index.php?ID=731976.*

Proposed Changes to Psychiatry's "Diagnostic Bible" Narrow Criteria for Some Autism Spectrum Disorders

The manual used by psychiatrists and others to match symptoms to a specific diagnosis within the broad category of autism spectrum disorders may soon be changing some ASD criteria.

A panel of doctors appointed by the American Psychiatric Association, while mulling revisions for the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (known as the DSM-V), has proposed changes that may seriously alter or eliminate the diagnostic criteria for Asperger's syndrome and pervasive developmental disorders not otherwise specified (PDD-NOS), potentially changing the diagnosis of tens of thousands of children and adults.

Currently, a person qualifies for a diagnosis of ASD by exhibiting six of 12 behaviors on the criteria list, which include failure to develop peer relationships, inflexible adherence to a routine, or delays in communication or imaginative play. The proposed changes call for a much narrower set of criteria: three deficits in social interaction and at least two repetitive behaviors.

Some experts and parents are worried that many people currently diagnosed under current definitions may be locked out of state and insurance benefits. But an unpublished study of 300 children, presented in May at the APA's annual meeting, suggests the proposed definition would exclude very few who have a diagnosis of autism or a related disorder.

The APA panel has posted its recommendations online, and will accept public comments until June 15. The fifth edition is scheduled for release in May 2013. ◆

ⓘ *For more information, go to http://www.dsm5.org/proposedrevisions/pages/proposedrevision.aspx?rid=94.*

To Protect Those Who Serve

There are protections and oversight at all university medical centers for those who serve as volunteers in research studies. Without their desire to help others, the scientific road from problems to solutions would not be possible.

Research studies at the Intellectual and Developmental Disabilities Research Centers aim to treat or prevent medical and other complications affecting people with developmental disabilities. Research leaders are looking for volunteers affected by these conditions to participate in studies to advance knowledge and care, but always with extreme concerns for protecting volunteers' rights and welfare.

The United States federal government has established a human research protection program to help scientists meet their ethical responsibilities in every study. Today, all researchers conducting government-funded human subject research must seek review and approval of their plans by Internal Review Boards (IRBs). The reviews consider the rights and welfare of volunteers, as well as the way investigators obtain volunteer consent to take part in studies, and the risks and potential benefits of the research.

These reviews focus on three basic principles:

1. Respect for Persons – Respect is given by informing those thinking about volunteering for a research study about everything that will happen, including all risks and benefits; and by obtaining informed consent.

2. Beneficence – Research projects protect study participants by maximizing the potential benefits to them, and minimizing possible harms.

3. Justice – Scientists treat research participants fairly by ensuring that they, or the group they represent, would benefit from the expected findings. ◆

Research Studies

Collaborations is dedicated to bringing readers information about the Consortium's pace-setting research projects. Some are highlighted in the newsletter's featured articles. Listed in the section below are brief descriptions of many other projects of potential interested to patients and families.

Learn further details about them by calling 1-443-923-3826, listening to the greeting, and then entering the Code Number accompanying the listing of interest or by going online to **www.maccollaborations.org/current-research.**

ADHD

Kennedy Krieger researchers are studying brain structure differences between children with and without ADHD aged 8-12. Children participate in IQ testing, computer tasks, paper/pencil tasks, and an MRI brain scan. PI: Stewart Mostofsky, M.D. ***Code 203.***

Kennedy Krieger researchers are conducting a new research study of processing speed and memory in children aged 5-9 to further understanding of ADHD. The study involves paper and pencil tasks, computer activities, and Magnetic Resonance Imaging (MRI) of the brain, as well as parent questionnaires and interviews. P.I. E. Mark Mahone, Ph.D. ***Code 205.***

Kennedy Krieger researchers are studying brain development and learning in boys and girls aged 4-5 to understand early indications of ADHD. The study involves IQ, language and behavioral tests, as well as a Magnetic Resonance Imaging (MRI) scan of the brain. None of these tests are harmful or painful. P.I. :E. Mark Mahone, Ph.D. ***Code 206.***

Kennedy Krieger researchers are studying how accommodations for children in 6th, 7th and 8th grades with ADHD affects standardized testing. The study involves a 10-minute interview with the parents of affected children and permission to access academic information and children's educational testing results. P.I.: Alison E. Pritchard, Ph.D. ***Code 207.***

Autism

Researchers at the Children's Hospital of Philadelphia are conducting a functional neuroimaging study to further understanding of how autism affects brain development and functioning. Participants include people from six months of age to adulthood with an autism spectrum disorder (ASD). P.I.: Sarah Paterson, Ph.D. ***Code 102.***

Kennedy Krieger researchers are studying motor differences between children with and without high-functioning autism aged 8-12. Children participate in IQ testing, computer tasks, paper/pencil tasks, and an MRI brain scan. PI: Stewart Mostofsky, M.D. ***Code 202.***

Children's National Medical Center investigators are studying the genetic, neurocognitive, behavioral and social factors in children with autism, compared to typically developing peers, aged 6-21. Children participate in behavioral and cognitive testing and MRI scans. PIs: Chandan Vaidya, PhD, and Lauren Kenworthy, Ph.D. ***Code 301.***

Dyslexia

Researchers at Kennedy Krieger are working on developing a simple, accurate and inexpensive screening test for dyslexia by examining the connection between genes and reading, especially for African American or Hispanic children between the ages of 8 and 15.The study involves taking some school-like tests and collecting saliva for genetic studies. Both children and their parents participate. P.I. E. Mark Mahone, Ph.D. ***Code 208.***

Epilepsy

Children's National Medical Center investigators are studying the effects of co-morbidities on the functional anatomy of separate cognitive domains in childhood focal epilepsy. Children with focal epilepsy and typically developing peers aged 8-15 will have detailed cognitive testing and MRI scans. PI: Madison M. Berl, Ph.D. ***Code 303.***

Rett syndrome

Kennedy Krieger/Johns Hopkins researchers are studying the effects of a placebo-controlled trial of Dextromethorphan in girls aged 2-9 with Rett syndrome (identified by a positive mutation in the MECP2 gene). PI: Sakkubai Naidu, M.D. ***Code 201.***

Tourette's syndrome

Kennedy Krieger researchers are studying brain structure differences between children with and without Tourette's syndrome aged 9-14. Children participate in IQ testing, computer tasks, paper/pencil tasks, and an MRI brain scan. PI: Stewart Mostofsky, M.D. ***Code 204.***

Other

Researchers at the Children's Hospital of Philadelphia are conducting a study of Carbaglu, a drug to treat high blood ammonia levels, in people ages 3 and older with propionic acidemia, methylmalonic acidemia, ornithine transcarbamylase deficiency, NAGS deficiency, or CPS deficiency. P.I. Mendel Tuchman, M.D. ***Code 101.***

Researchers at the Children's Hospital of Philadelphia are conducting a research study of Parkinsonism and Gaucher disease using state-of-the-art PET imaging to examine brain activity. Adults (18 years of age and older) with Gaucher disease and carriers at risk for Gaucher disease participate. P.I.: Jaya Ganesh, M.D. ***Code 103.***

Researchers at the Children's Hospital of Philadelphia are studying new treatments for Friedreich's ataxia. This research is a clinical drug trial, and participants include affected adults (aged 18 and older). P.I.: David Lynch, M.D. ***Code 104.***

Children's National Medical Center investigators are conducting studies of the neurological effects of ornithine transcarbamylase deficiency (OTCD). Tests include cognitive testing and MRI scans in patients with OTCD and controls 7-60 years old. PI: Andrea Gropman, M.D. ***Code 302.***

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