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RESEARCH AT THE CHILDREN'S HOSPITAL OF PHILADELPHIA January 2013

New Autism-Related Gene Variants Discovered

Genetics researchers have identified 25 additional copy number variations (CNVs) — missing or duplicated stretches of DNA — that occur in some patients with autism. According to the researchers, these are "high impact" CNVs: although individually rare, each has a strong effect in raising an individual's risk for autism.

"Many of these gene variants may serve as valuable predictive markers," said the study's corresponding author, Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics at The Children's Hospital of Philadelphia. "If so, they may become part of a clinical test that will help evaluate whether a child has an autism spectrum disorder."

The study, which was published recently in *PLOS ONE*, builds on and extends previous gene research by on autism spectrum disorders (ASDs). Estimated by the CDC to affect as many as one in 88 U.S. children, ASDs are known from family studies to be strongly influenced by genetics.

The researchers first analyzed DNA from 55 individuals from Utah families with multiple members diagnosed with ASDs, which co-author Mark Leppert, Ph.D., of the University of Utah, had collected the data from these high-risk families. The team identified 153 CNVs as potentially specific to autism.

To investigate these CNVs in a broader ASD population, the study team custom-designed a DNA array with probes for those 153 CNVs, as well as for another 185 CNVs previously reported to be associated with autism. They then analyzed the actual prevalence of all the CNVs in a larger sample set of 3,000 ASD cases and 6,000 control subjects previously gathered in studies by The Children's Hospital of Philadelphia.

The researchers found that 15 of the CNVs found in the family studies, in addition to nine other CNVs found by their custom array, all had odds ratios greater than 2.0, meaning that subjects with those variants had at least two-fold increased risk of having an ASD, compared to controls. Another 31 CNVs previously reported to be associated with autism also had odds ratios above 2.0.

These findings, noted Dr. Hakonarson, could be incorporated into clinical tests for evaluating children for ASDs. "These high-impact variants could be most useful in advising parents who already have one child with an ASD," said Dr. Hakonarson. "If a second child has delays in reaching developmental milestones, testing for these CNVs could help predict whether that child is also likely to develop an ASD." He added that the newly identified variants would need to be added to the existing commercially available diagnostic array in current use.

The CNVs detected in the current study, Dr. Hakonarson said, occur in genes involved in neuronal development and signaling pathways — reinforcing earlier findings by Dr. Hakonarson and colleagues.

"Many of these gene pathways active in ASDs overlap with those in other nervous system disorders, such as schizophrenia and epilepsy," he added. "At the same time, our results are consistent with other studies suggesting that many different biological pathways, when disrupted, can lead to ASDs."

Further research may help establish whether the CNVs reported in the current study may be categorized by how they contribute to specific clinical subtypes of ASDs, Dr. Hakonarson concluded.

CHOP Receives Nearly $2 Million to Lead Antibiotic Study

Ron Keren, M.D., M.P.H., director of the Center for Pediatric Clinical Effectiveness (CPCE), was recently awarded nearly $2 million dollars from the Patient-Centered Outcomes Research Institute (PCORI) to lead a study of antibiotic delivery methods.

The three-year award will support a project examining whether children who have a serious bacterial infection that requires prolonged antibiotic therapy (greater than one week) do as well taking the antibiotics by mouth as they would if they received them via an intravenous (IV) catheter, specifically a peripherally inserted central catheter, or PICC line.

A PICC line is a long, flexible tube that is inserted in a peripheral vein, often in the arm or neck, and advanced until its tip rests near the heart. Because they tap directly into the circulatory system, PICC lines offer maximum drug delivery, and are preferred by many clinicians for long-term antibiotics treatment of severe infections.

Unlike regular IV catheters, PICC lines can stay in the body for weeks to months, but they require regular maintenance. PICC lines must be flushed daily, their dressings have to be inspected and changed, and patients with PICC lines must avoid getting them wet or dirty — a tall order for some active pediatric patients and their families. In addition, a variety of medical equipment is required to use and maintain PICC lines, including infusion pumps, IV antibiotic solutions, dressings, and portable IV poles.

PICC lines also have some risks. They can clot, break, or become dislodged. And because they sit in large blood vessels directly above the heart, any bacteria that are inadvertently introduced into the catheter go directly to the heart and are pumped throughout the body, which can lead to a dangerous infection called sepsis.

Oral antibiotics, on the other hand, are much easier for patients to take and caregivers to manage. However, because oral medications must pass through the digestive system, to have the same efficacy as IV medications oral antibiotics must have high "bioavailability" — the percentage of the drug that reaches the blood. Drugs administered via PICC lines have, by definition, 100 percent bioavailability.

"These two antibiotic treatment options have major implications for the overall experience of the child, families and caregivers, but there is a lack of real-world evidence on their benefits and drawbacks to help clinicians and patient families make an informed choice," said Dr. Keren.

Study Design

Dr. Keren's study will be conducted in two parts, the first of which will utilize Pediatric Health Information System (PHIS) data. The PHIS includes data on more than 30 million patient encounters from 43 children's hospitals associated with the Children's Hospital Association. Using PHIS data, Dr. Keren and his research group will conduct retrospective studies of three conditions — acute osteomyelitis, perforated appendicitis, and complicated pneumonia — to compare the efficacy of oral antibiotics versus those delivered through a PICC line.

Osteomyelitis, or an infection of the bone, affects approximately 1 in 5000 children per year, while nearly 70,000 children a year experience appendicitis, or swelling of the appendix. Of these, 20 to 25 percent progress to perforation — a condition in which an infected appendix ruptures and spills intestinal bacteria into the stomach.

Complicated pneumonia, meanwhile, affects 30,000 pediatric patients a year, or some 15 percent of those children hospitalized with pneumonia each year. All three conditions require extended treatment with antibiotics.

Though there is, for the most part, a dearth of evidence to support the use of oral antibiotics to treat these conditions, a 2009 study led by the CPCE's Theoklis Zaoutis, M.D., M.S.C.E., hints at what Dr. Keren's new investigation might find. In that study, Dr. Zaoutis used PHIS data to examine nearly 2000 children who between 2000 and 2005 were treated for osteomyelitis with IV therapy or oral antibiotics. While the researchers found no difference in the failure rate for both methods of treatment, they did find that approximately 3.4 percent of the children who received IV therapy were readmitted for complications.

Following this, in the second part of his study Dr. Keren will lead a consortium of children's hospitals to recruit and survey patients who have been treated for one of the three conditions. In addition to CHOP, the participating hospitals are University of Utah and Primary Children's Medical Center, Cincinnati Children's Hospital Medical Center, and Children's Hospital Boston. With the second study, the investigators seek to compare quality of life and adherence to treatment associated with both methods of receiving antibiotics.

"If we find that the prolonged IV option is no better than the oral route, we think that most families would prefer for their child to take oral antibiotics," Dr. Keren noted. "However, if IV antibiotics are marginally better than oral antibiotics, then that benefit will need to be weighed against any reduction in quality of life and complications that we anticipate with the PICC lines."

Dr. Keren's project is one of 25 awards recently announced by the PCORI, totaling more than $40 million. A relatively young organization, the PCORI was established by 2010's Affordable Care Act — also known as "Obamacare" — to fund and carry out comparative effectiveness research. Last year the PCORI awarded another CHOP Researcher, Katherine Bevans, Ph.D., more than $500,000 to examine ways to incorporate children's views into research decisions.

"The announcement of funding for studies like this one mark a major milestone in our work as we build a portfolio of comparative clinical effectiveness research that will provide patients and those who care for them better information about the health care decisions they face," said PCORI Executive Director Joe Selby, M.D., M.P.H. "These research projects reflect PCORI's patient-centered research agenda, emphasizing the inclusion of patients and caregivers at all stages of the research."

PolicyLab Studies Underscore Importance of Development Screening

By pointing out the importance of standardized screening and communication between clinicians and caregivers, a pair of new studies from CHOP's PolicyLab can help physicians and families better support children with developmental disorders.

James Guevara, M.D., M.P.H., director of Interdisciplinary Initiatives at PolicyLab, led a study of developmental screening that was published recently in *Pediatrics*. In addition to Dr. Guevara, PolicyLab staff members Marsha Gerdes, Ph.D., and Vera Huang, M.S., contributed to the study.

With this study, the investigators sought to determine how effective standardized early childhood developmental screening — which makes use of questionnaires and other tools — was in identifying developmental delays, and in referring children with those delays. While standardized developmental screening has previously been shown to improve developmental delay identification rates and referrals, prior to Dr. Guevara's study little was known about how effective standardized screening was among a high-risk urban population.

From December 2008 to June 2010, the research team surveyed 2,103 children, most of whom were African-American and from families making less than $30,000 a year. The patients were randomized into three groups: one receiving developmental screening with office support, another receiving developmental screening without office support, and a group participating in non-standard "surveillance" conversations with clinicians.

The study found that not only is standardized screening feasible among urban populations, but also that it is twice as likely to identify developmental delays than non-standard surveillance. However, standardized screening does not ensure that children in need will receive aid, as only 58 percent of the children studied were referred to early intervention services.

Obstacles to Early Intervention

Following these findings, a separate study by PolicyLab's Manuel Jimenez, M.D., M.S., examined barriers to early intervention (EI) evaluation among referred children.

2004's Individuals with Disabilities Education Act authorized the creation of a federally funded, statewide system of "early intervention services for infants and toddlers with disabilities and their families." In short, EI programs provide a variety of support for children with disabilities and developmental delays, often at little or no cost to families.

However, up to 90 percent of eligible children do not receive EI services, according Dr. Jimenez's study, which was published in *Academic Pediatrics*. The researchers conducted interviews with parents of referred children and with EI staff members to better understand why some families forgo services.

The researchers discovered a variety of reasons why EI services may be underutilized. Some parents reported communications issues, such as not understanding the referral process, while others cited time constraints and other practical matters. For their part, EI staff members reported that they felt some families avoided EI services because they mistook them for child protective services.

Dr. Jimenez and his team, which included PolicyLab's Alexander Fiks, M.D., M.S.C.E., concluded that effective communication between physicians and caregivers — that addresses practical concerns and reinforces the need to address issues — may improve EI referral success.

Overall, both studies can help early intervention staff and physicians make sure that children with developmental needs receive the support they need to grow and succeed.

To learn more about the important research being done at PolicyLab every day, see the PolicyLab website.

Proposals for Junior Investigator Preliminary, Feasibility Grant Program Announced

The Clinical and Translational Research Center (CTRC) is now accepting research proposals to be considered for the Junior Investigator Preliminary/Feasibility Grant Program (JIPGP).

The primary goal of the Clinical Translational Research Center (CTRC) Junior Investigator Preliminary/Feasibility Grant Program (JIPGP) is to encourage junior investigators to develop clinical research projects that will ultimately lead to extramural NIH funding. The awards are designed to allow junior faculty members, clinical fellows and both M.D. and Ph.D. post-doctoral trainees with appropriate mentors to obtain funds for pilot projects that are investigator-initiated, human-based, CTRC studies that will enable an applicant to obtain preliminary data for an NIH K or R grant submission.

It is anticipated that the award will lead to a competitive extramural grant application and to a career in Clinical Translational Research Center-focused clinical investigation.

The grants will be available at each institution effective July 1, 2013.

AWARD DATES:

- Application Receipt Deadline: February 22, 2013
- Notification of Award: April 5, 2013
- Funding Period: 7-1-13 to 6-30-14

For eligibility criteria, proposal instructions, and additional details, please see the full announcement at https://intranet.research.chop.edu/pages/viewpage.action?title=All+News&spaceKey=main&id=62357584.

Gene Therapy Offers Hope for Children with Canavan Disease

A rare inherited neurological disorder, Canavan disease has a devastating effect on patients and families. The lack of a specific enzyme — known as aspartoacylase — causes the body's central nervous system to break down. Complications associated with the disease include mental retardation, blindness, and an inability to walk. In addition, Canavan disease is often fatal, with many patients dying before they reach 18 months of age, according to the NIH.

Moreover, there is no cure or standard treatment for Canavan disease. But a new study, performed in part by The Children's Hospital of Philadelphia researchers, could offer treatment hopes.

Children's Hospital's neuroradiologist Larissa Bilaniuk, M.D., along with Dah-Jyuu Wang, Ph.D., CHOP's chief of Magnetic Resonance Spectroscopy, were among the co-authors of a new scientific study that reported on the long-term results of gene therapy for this disorder.

Led by Paola Leone, Ph.D., from the University of Medicine & Dentistry of New Jersey, the investigators performed highly specialized imaging studies on patients in a Phase I / Phase II clinical trial. The study, published Dec. 19 in *Science Translational Medicine*, was the first clinical application of a viral-based gene therapy for a neurodegenerative disorder.

The patients received gene therapy between 2001 and 2005. While not a cure, the study showed that the gene therapy was safe, reduced the frequency of the patients' seizures, and stabilized their conditions, especially in the youngest patients. The research team concluded that early detection and gene therapy may offer the best results among infants diagnosed with Canavan disease.

To learn more about CHOP's Radiology Department, click here.

CHOP, BGI Strengthen Partnership with Brain Tumor Collaboration

The Children's Hospital of Philadelphia (CHOP) and BGI-Shenzhen recently announced an agreement to collaborate on research into next-generation sequencing and analysis of pediatric brain tumors, in support of the Childhood Brain Tumor Tissue Consortium (CBTTC). The research initiative will draw on the resources of the state-of-the-art Joint Genome Center BGI@CHOP, which provides next-generation sequencing under CAP/CLIA guidelines, the gold standard of quality in clinical laboratory testing.

A collaborative pediatric research group that brings together four institutions, the CBTTB is made up of The Children's Hospital of Philadelphia (which houses the consortium's operations center), the Children's Hospital of Pittsburgh, Seattle Children's Hospital, and Lurie Children's Hospital of Chicago. The consortium is dedicated to the collection, annotation, and molecular analyses of children's brain tumors.

Next-generation sequencing of pediatric brain tumors offers a deep and comprehensive view into the genetic underpinnings of these often-devastating solid tumors. In collaboration with BGI's genomics platforms, the new project will support the development of new and more effective forms of therapy targeted to each patient's specific subtype of brain tumor.

"These important efforts are made possible through the further extension of CHOP's productive collaboration with BGI, a world-class institution in the global genome sequencing arena that is using its scientific expertise and technological know-how to improve medical research," said Tom Curran, Ph.D., F.R.S., deputy science director of CHOP Research.

"BGI is pleased to have deepened its relationship with The Children's Hospital of Philadelphia, a global leader in pediatric care and research," said Dr. Jun Wang, executive director of BGI-Shenzhen. "We look forward to a productive partnership that will accelerate advances in the research and treatment of pediatric brain tumors."

Clinical Research Coordinator Training Requirement Now in Effect

All existing clinical research coordinators, regardless of job title, were asked to complete the revised Clinical Research Coordinator Education Program by December 31, 2012. New clinical research coordinators, regardless of job title, are expected to complete this training within 90 days of their hire date or before being listed as a coordinator on an active IRB protocol. Approval of new or continuing IRB submission is contingent on this training requirement being met.

Completion of the Clinical Research Coordinator Education Program includes reviewing the content in all seven chapters and passing each corresponding quiz. Additional information and FAQs can be found on the Responsible Research Training website.

This training is managed and tracked by the Office of Responsible Research Training. Questions may be directed to researchtraining@email.chop.edu.

Two Center for Autism Research 2012 Studies Highlighted

The Children's Hospital of Philadelphia's Center for Autism Research (CAR) produced a number of breakthrough studies in 2012, two of which were recently highlighted by the scientific community. The advocacy organization Autism Speaks selected a CAR study as one of its top discoveries of 2012, while another study, published in *Trends in Cognitive Science*, was one of the five most popular articles published in that journal in 2012.

The "world's leading autism science and advocacy organization," Autism Speaks named a study of brain differences in children with autism one of its top 10 discoveries of 2012. The study from the Infant Brain Imaging Network, which includes CAR investigators, found significant differences in brain development starting at age 6 months in infants who later developed autism.

Sarah Paterson, Ph.D., director of the CAR's Infant Neuroimaging Lab, and Robert Schultz, Ph.D., CAR director, were co-authors of the study, which appeared in the *American Journal of Psychiatry*. Drs. Paterson and Schultz are leaders of the Infant Brain Imaging Study at CHOP.

The researchers examined infants who were considered to be at increased risk for autism. After performing brain imaging scans at 6 months and behavioral assessments at 24 months, the investigators found that the brains of infants who went on to develop autism underwent physical changes before behavioral symptoms arose.

"It's a tremendously exciting finding," said Dr. Paterson, who added that the research "raises the possibility that we might be able to intervene even before a child is 6 months old, to blunt or prevent the development of some autism symptoms."

Meanwhile, the *Trends in Cognitive Science* study, which was led by Coralie Chevallier, Ph.D., of CAR's Developmental Neuroimaging Laboratory, investigated the social motivation theory of autism. The theory that social motivation, or the drive to interact and bond with others in society, could play a role in autism is a relatively recently development, and is a move away from an examination of autism rooted in cognitive issues.

In addition to Dr. Chevallier, CAR investigators Gregor Kohls, Ph.D., Vanessa Troiani, and Edward Brodkin, M.D., took part in the study. According to the editors of *Trends in Cognitive Science*, the study was one of the five most read articles of 2012, with more than 3,000 full-text downloads and 1,000 views.

To learn more about the innovative work being done at CAR, see the Center's website.

Medals4Mettle — Racing for Life

The Children's Hospital of Philadelphia Research Institute is a big place, with a staff in the thousands working every day to improve the health of children. As such, CHOP Research is the source of a lot of big stories, about big advances against big diseases. But CHOP Research is also a place where individuals quietly work on their own to better children's lives, often volunteering their time.

One of these is Sharan Kaur, the manager of Corporate Sponsored Research in the Office of Technology Transfer. For the past several years, Kaur has been a volunteer for Medals4Mettle (M4M), a non-profit organization that collects and distributes runners' marathon and triathlon medals to patients "fighting debilitating illnesses who might not be able to run a race, but are in a race of their own just to continue to live," according to the M4M website.

Kaur, a runner and triathlete herself, first became involved with M4M after reading about the organization in *Runner's World*. Though she began as a chapter coordinator, Kaur recently took on the role of president of M4M, which has expanded widely since it was founded in 2005. M4M has spread to a total of 31 states, and has chapters in Canada, Japan, and Mexico; the organization also recently opened a chapter in South Korea on a U.S. Air Force base.

To date, M4M has distributed approximately 23,000 medals, Kaur said.

While many M4M chapters hand out medals at events, at Children's Hospital medals are given to bone marrow transplant patients on transplant day, so clinical staff and caregivers give out the medals rather than M4M volunteers. Kaur has partnered with CHOP's child life specialists — specially trained staff members who help families and patients cope with treatment — to distribute 20-25 medals to patients every few months.

Stephanie Fooks-Parker M.S.W., L.S.W., a CHOP social worker, works with Kaur to distribute the medals to bone marrow patients on their transplant day. She tries to match specific medals to individual patients — such as a Liberty Bell medal for an international patient visiting Philadelphia, or a "Rock Star" medal for a patient who had gone through a particularly grueling course of treatment. Each patient receives a medal and a card explaining its significance.

Working with M4M has been "such a small gesture, but it has been so rewarding for me," Kaur said.

To learn more about Medals4Mettle, see the M4M website. If you're interested in getting involved, contact Sharan Kaur.

Nominations for 2013 CHOP Mentor Award Invited

We invite faculty at the rank of assistant professor or higher to nominate colleagues for the 2013 CHOP Mentor Award. The award recognizes faculty mentors who, during the past three years, demonstrated extraordinary dedication to fostering the professional development of other members of the CHOP faculty (not trainees). Up to three awards are presented annually, including an honorarium, an individual commemorative plaque and a celebration dinner. Nominations are due by Friday, February 15.

2013 CHOP Mentor Award — Guidelines and Instructions for Submitting Letters of Nomination

Guidelines

- Mentor Award recipients must have a Perelman School of Medicine faculty appointment and be based in one of the CHOP departments:
- Anesthesiology & Critical Care Medicine, Child and Adolescent Psychiatry, Pathology and Laboratory Medicine, Pediatrics, Radiology, and Surgery
- A minimum of 3 signed nomination letters are required from other faculty members (not trainees)
- The award is designed to honor:
- Faculty mentoring of faculty (not trainees)
- Activities during the past three years of activity (not life-time achievement award
- Excellence in mentoring in some, but not necessarily all, aspects of academic careers such as research, clinical care, administration, teaching, advocacy, promotion and career management, and local and national/international career development

Instructions

- Please submit signed nomination letters to: Mary Field, Office of Faculty Development, CHOP Research Institute via e-mail, fax, or interoffice mail:
- E-mail: fieldm@email.chop.edu
- Fax: 215-590-0604
- Interoffice Mail:
- Mary Blitzer Field, Assistant Director
  Office of Faculty Development, CHOP Research Institute
  3535 Market Street, Room 1552
- DEADLINE: Friday, February 15, 2013
- For questions concerning the Mentor Award, contact Mary Field at fieldm@email.chop.edu or 267-426-9334.

HAVE NEWS? Contact Jennifer Long at ext. 4-2105 or by e-mail at longj@email.chop.edu.

Read this and previous versions of *Bench to Bedside* online at http://www.research.chop.edu/publications/.

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