

New Gene Variants Found to Raise Neuroblastoma Risk

The Children's Hospital of Philadelphia researchers have discovered two gene variants that raise the risk of the pediatric cancer neuroblastoma. The study, which draws on genome-wide association studies on DNA from thousands of subjects, broadens our understanding of how gene changes can make a child susceptible to this early childhood cancer and how those changes can cause a tumor to progress.

"We discovered common variants in the HACE1 and LIN28B genes that increase the risk of developing neuroblastoma. For LIN28B, these variants also appear to contribute to the tumor's progression once it forms," said first author Sharon J. Diskin, Ph.D., a pediatric cancer researcher at Children's Hospital. "HACE1 and LIN28B are both known cancer-related genes, but this is the first study to link them to neuroblastoma."

Dr. Diskin and her colleagues, including senior author John M. Maris, M.D., director of the Center for Childhood Cancer Research, published their study Sept. 2 in Nature Genetics.

Affecting the peripheral nervous system, neuroblastoma usually appears as a solid tumor in the chest or abdomen. It accounts for 7 percent of all childhood cancers, and 10 to 15 percent of all childhood cancer deaths.

The study team performed a genome-wide association study (GWAS), comparing DNA from 2,800 neuroblastoma patients with that of nearly

7,500 healthy children. They found two common gene variants associated with neuroblastoma, both in the 6q16 region of chromosome 6. One variant is within the HACE1 gene, the other in the LIN28B gene. They exert opposite effects: HACE1 functions as a tumor suppressor gene, hindering cancer, while LIN28B is an oncogene, driving cancer development.

The current study showed that low expression of HACE1, a tumor suppressor gene, and high expression of LIN28B, an oncogene, correlated with worse patient survival. To further investigate the gene's role, the researchers used genetic tools to decrease LIN28B's activity, and showed that this inhibited the growth of neuroblastoma cells in culture.

The new research builds on previous work by Children's Hospital investigators implicating other common gene variants as neuroblastoma oncogenes. As in the current study, these gene variants show a double-barreled effect, both initiating cancer and provoking its progression.

"In addition to broadening our understanding of the heritable component of neuroblastoma susceptibility, we think this research may suggest new therapies," Dr. Diskin noted. "Our follow-up studies will focus on how we may intervene on these genes' biological pathways to develop more effective treatments."

Center for Autism Research Receives \$2.2 Million NIH Grant

Supported by a grant through the National Institutes of Health's Autism Centers of Excellence program, the Children's Hospital of Philadelphia's Center for Autism Research will continue to work to identify early signs of autism spectrum disorders. Children's Hospital will share more than \$100 million in NIH funding for autism research, which is distributed across nine Autism Centers of Excellence (ACE) grants.

"Being able to identify the earliest behavioral and biological signals of autism will help us better understand how autism develops, how to maximize long term outcomes, and how to develop new treatments," said Robert Schultz, Ph.D., director of the Center for Autism Research (CAR). According to the Centers for Diseases Control and Prevention, autism currently affects one in 88 children in the United States.

Under the recently announced five-year, \$2.2 million grant, CAR is part of a network of four research sites that will use advanced brain imaging techniques to study brain development in 200 infants beginning at three months of age. Researchers will follow infants every three months, through 24 months of age in order to carefully chart brain development.

The research team plans to conduct follow-up behavioral and diagnostic testing of these children at 36 to 60 months, the age at which a diagnosis of autism is considered to be more stable. The study will also evaluate child and family-level characteristics to learn which are predictors for a later autism diagnosis.

"We have initial findings suggesting that we can detect brain features as early as six months of age that help predict which infants will go onto to develop autism in the second or third year of life," said Sarah Paterson, Ph.D., director of the Infant Neuroimaging Lab at CAR and co-leader with Schultz of CHOP's study team.

The current grant is a continuation of an earlier ACE-funded brain imaging study conducted by CAR in collaboration with four other autism research centers throughout the country. This research network published a study earlier this year demonstrating significant differences in brain development as early as six months of age — well before the appearance of behavioral or "outward" symptoms of autism.

Autism is typically diagnosed around age two or three, and a growing body of research shows that early intervention yields better outcomes for individuals with autism. The new research grant will allow CHOP researchers to study children's brain development at even earlier ages, in the hope of finding an earlier starting point.

"We are excited by the opportunity the ACE grant affords us to advance the current understanding of autism and early brain development, with the goal of being able to identify biomarkers for autism at as early as three months of age," noted Dr. Paterson.

Epilepsy Researcher Selected for Administration Fellowship

The Office of Postdoctoral Affairs recently announced the selection of a new Research Administration Fellow. Paulette McRae, Ph.D., a research associate in the laboratory of Brenda Porter, M.D., Ph.D., began the administration fellowship in early August.

After receiving a bachelor's degree from Rutgers, Dr. McRae went on to receive her doctorate from Yale in 2007. Notably, Dr. McRae was the first African American to earn a Ph.D. in neurobiology from Yale, something that has given her "the courage and the strength to tackle new challenges." It has also "made me more aware of mentoring and making sure other students have the same opportunities," Dr. McRae said. She joined CHOP as a postdoctoral fellow in 2007.

Dr. McRae's current research investigates the role of the extracellular matrix in the development of epilepsy. While many epilepsy researchers focus on specific regions of the brain or cells, Dr. Rae's work examines the surrounding environment to see "how certain changes lead it to be more permissive to the development of epilepsy," she explained.

"I think the brain is one of the most fascinating frontiers in modern science," Dr. McRae added.

During her research administration fellowship, Dr. McRae hopes to better "understand the complexities that come with running a tier-one research institute," to prepare her for future positions in medical research, whether they be administrative or investigative.

The Research Administration Fellowship is a part-time, unpaid, six-month program that fellows complete concurrently with their research duties. The overall goal of the fellowship is to provide the fellow with a broad overview of CHOP Research Administration through rotations with administrative directors in the fellows' areas of interest.

For more information about the Research Administration Fellowship, visit https://intranet.research.chop.edu/display/deptpda/Research+Administration+Fellows or contact David Taylor at taylord@email.chop.edu.

Future Scientists At Work

Eight students from colleges across the country spent 10 weeks over the summer working side-by-side with the Center for Injury Research and Prevention (CIRP) team. Now in its second year, the Center's unique Research Experiences for Undergraduates (REU) program, sponsored by the National Science Foundation (NSF), offers a diverse group of student scholars hands-on research experience in the fields of Engineering, Behavioral Science, Education, Population Science, and Statistics. Each student is also paired with a CIRP mentor to work on specific projects and receives formal training in research ethics, conducting studies, and presenting research findings.

"The National Science Foundation spends over \$160 million annually to support numerous REU sites across the country. Last year, we received one of these REU site grants that covers stipends and assistance with housing and travel, removing any barriers to participation for our summer scholars. As a former beneficiary of an undergraduate research program, I know how important an experience like this was in shaping my research career," said Flaura K. Winston, M.D., Ph.D., founder and scientific co-director of CIRP and director of the Injury Science REU site at the Center.

"We at CIRP feel fortunate for the opportunity to mentor and work with these exceptional students. I hope that we will inspire them to pursue careers in injury science," Dr. Winston added.

Over 320 applications were received for the Center's 2012 REU program. After a rigorous selection process, this year's class included recruits from the following schools: the University of South Florida;

the University of Delaware; Cornell University; Wellesley College; Cheyney University; Tufts University; University of Maryland College Park; and the University of Pennsylvania. The CIRP REU site is coordinated by Carol Murray and co-directed by Dr. Winston and Meghan Marsac, Ph.D.

Danielle Grams, an REU student who will be beginning her senior year at the University of South Florida this fall, pursuing a B.S. in Biology with a concentration in Cellular and Molecular Biology, worked under the direction of Jessica H. Mirman, Ph.D., lead behavioral scientist on the Young Driver Research team at CIRP, on a project that involved studying the barriers to proper car seat use.

"Through this study, we are seeking to understand how to improve the installation of car seats," said Grams. "During my time at CIRP, I gained experience with a variety of components of the research project including survey design, recruitment, data management, and data collection. I have enjoyed the opportunity to work at such a highly collaborative and interdisciplinary center."

At CIRP Student Research Day, held on August 9th in Philadelphia, Grams won first place in the presentation competition, which includes a \$1,000 stipend to be used to present her work at a conference of her choice. She plans to become an academic physician and to work with underserved populations within and outside the U.S.

For more information on the CIRP REU program and other undergraduate and graduate student research opportunities at the Center, click here.

Prestigious Award Honors CHOP Nurse-Scientist

Nurses are far more than hard-working and compassionate caregivers, meeting the moment-to-moment needs of patients and their families. Their critical roles on the front lines of patient care put them in an optimal position to observe the effects of treatments and procedures, often leading to new research questions that can improve healthcare and advance science.

Three decades of innovative research has led the Council for the Advancement of Nursing Science to honor nurse-scientist Barbara Medoff-Cooper, Ph.D., R.N., F.A.A.N., with its Outstanding Nursing Scientist Award.

The Council is the country's leading scientific organization for nurse-scientists. The award acknowledges Council members whose research studies have had significant impact on nursing and healthcare knowledge and practice.

Dr. Medoff-Cooper is a nationally and internationally known expert on developmental outcomes, feeding behaviors and infant temperament in high-risk infants. She has received six grant awards from the National Institutes of Health to support her research,

including her latest study that uses state-of-the art telehealth technology for in-home monitoring of infants who underwent neonatal cardiac surgery.

"This ongoing study has the potential to change the paradigm of home monitoring care for extremely vulnerable populations," says Dr. Medoff-Cooper, who has published more than 70 journal articles and is the co-inventor of Neonur, a feeding device allowing researchers and clinicians to objectively measure feeding behaviors in neonate and young infants.

Her work extends outside of patient care and includes participation in many NIH review groups and serving as the chair of a national task force to develop protocols for the care of preterm infants.

Dr. Medoff-Cooper holds the Ruth M. Colket Endowed Chair in Pediatric Nursing at CHOP, the first endowed chair for nursing in a children's hospital. She also serves as a professor at the University of Pennsylvania School of Nursing and previously served as the director for the Center for Nursing Research at Penn.

Investigators Discover New Cornelia deLange Syndrome Gene

Genetics researchers have identified a key gene that, when mutated, causes the rare multisystem disorder Cornelia deLange syndrome (CdLS). By revealing how mutations in the *HDAC8* gene disrupt the biology of proteins that control gene expression and cell division, the research sheds light on this disease. CdLS causes intellectual disability, limb deformations, and other disabilities resulting from impairments in early development.

"As we better understand how CdLS operates at the level of cell biology, we will be better able to define strategies for devising treatments for CdLS, and possibly for related disorders," said study leader Matthew A. Deardorff, M.D., Ph.D., a pediatric genetics clinician and researcher at The Children's Hospital of Philadelphia.

Deardorff and co-corresponding author Katsuhiko Shirahige, Ph.D., of the Research Center for Epigenetic Disease at the University of Tokyo, recently published their study in Nature.

The new findings add to previous discoveries by Children's Hospital researchers. A group led by Ian Krantz, M.D., and Laird Jackson, M.D., announced in 2004 that mutations in the *NIPBL* gene are the primary cause of CdLS, accounting for roughly 60 percent of the "classical" cases of the disease. In 2007, Deardorff joined them to describe mutations in two additional genes, *SMC1A* and *SMC3*. First described in 1933, CdLS affects an estimated 1 in 10,000 children.

The CdLS research team at Children's Hospital has focused on the cohesin complex, a group of proteins that form a bracelet-like structure that encircles pairs of chromosomes, called sister chromatids. "Cohesin has two roles. It keeps sister chromatids together during cell division, and it allows normal transcription — the transmission of information from DNA to RNA," noted Deardorff.

Deardorff added that mutations that perturb normal cohesin function can interfere with normal human development. Such is the case in CdLS, which exemplifies a newly recognized class of diseases called cohesinopathies.

In the current study, the scientists investigated both acetylation — how an acetyl molecule is attached to part of the cohesin complex — and deactylation, the removal of that molecule. Normally, deactylation helps recycle cohesin to make it available during successive rounds of cell division. The study team found that mutations in the *HDAC8* gene threw off normal cellular recycling of cohesin.

Mutations in the gene cause loss of HDAC8 protein activity, and consequently decrease the amount of "recharged" cohesin available to properly regulate gene transcription. This, in turn, the researchers suggest, impairs normal embryonic development and gives rise to CdLS.

The researchers showed in cell cultures that mutations in *HDAC8* lead to a decrease in cohesin binding to genes, similar to that seen for cells deficient in the *NIPBL* gene. They also identified *HDAC8* mutations in approximately 5 percent of patients with CdLS.

Because mothers of children with CdLS may carry mutations in the *HDAC8* gene, identifying these mutations will be very useful in accurately counseling families of their recurrence risk — the likelihood of having a subsequent child with CdLS.

Furthermore, added Deardorff, by providing biological details of the underlying defect in CdLS, the current research suggests future approaches to treating the genetic disease. "By concentrating downstream on the biological pathway in the cohesin cycle rather than focusing on the defective gene, we may be able to eventually screen for small-molecule drugs that could be used to intervene in CdLS."

Deardorff and colleagues plan to continue to investigate CdLS and possible therapies. In June, the Doris Duke Charitable Foundation chose Deardorff to receive a Clinical Scientist Development Award. This three-year award, totaling \$486,000, is directed to further studies of cohesin abnormalities in human disease.

First Ellen Hyman-Browne Memorial Lecture Scheduled for October 4th

To honor the memory of The Children's Hospital of Philadelphia Research Institute's first director of Research Compliance, Ellen Hyman-Browne, J.D., Children's Hospital will hold the first annual Ellen Hyman-Browne Memorial Lecture on October 4, 2012. The goal of this event is to promote discussion and awareness of ethical and compliance-related issues.

The 2012 Ellen Hyman-Browne Memorial Lecture, originally scheduled for last March, has been rescheduled for Thursday, October 4, 2012 at 4 pm in the Colket Translational Research Building (1st Floor, Conference Room 1200 A/B). Katie Watson, J.D., Assistant Professor, Medical Humanities & Bioethics Program at the Feinberg School of Medicine, Northwestern University will join us to present a lecture titled "The Atticus Finch Problem: Navigating Conflicts Between Law and Ethics." Ms. Watson will address provocative

questions by considering the ethical dilemmas law occasionally creates for clinicians and researchers, and exploring whether violating the law to advance healthcare is ever an ethical choice. A reception in the Colket Atrium will follow the talk.

Ellen Hyman-Browne served for five years as CHOP's first director of Research Compliance. She approached her work with the highest standards of integrity and professionalism and contributed in countless ways to helping the organization address compliance issues. Ellen especially loved being around scientists and helping to support their work. Sadly, Ellen passed away in 2011 after battling cancer.

All are welcome to attend this event. Please visit http://www.research.chop.edu/ehblecture to review the talk abstract, find out more about Ms. Watson and RSVP to attend the session. Please direct any questions to williamsw@email.chop.edu.

PolicyLab's Kathleen Noonan Returns to Children's Hospital

After a two-year stint at the University of Wisconsin Law School, Kathleen Noonan, J.D., recently returned to The Children's Hospital of Philadelphia Research Institute to serve as co-director of PolicyLab, an organization she helped establish.

In 2008, along with current co-Director David Rubin, M.D., M.S.C.E., Noonan founded PolicyLab, which works to develop evidence-based solutions for the most challenging health-related issues affecting children. Trained as a lawyer, Noonan's work has long focused on the intersection of policy and health law, and over the years she has helped a number of government agencies restructure their systems and policies.

Prior to originally joining Children's Hospital, Noonan spent a number of years at the Baltimore, Md.-based Annie E. Casey Foundation, working to produce positive public system change. She is also the former associate director of the University of Pennsylvania's Center for High Impact Philanthropy, where she remains a senior fellow.

In 2010 she left Children's Hospital to join the University of Wisconsin Law School where, in addition to teaching a course on

health law, she headed the development of the school's J.D.-M.P.H. program and its Government and Legislative Law Clinic. "The legal aspects of public health are significant, and there is a growing need for professionals trained in both disciplines," Noonan noted.

Overall, Noonan said her experiences at the University of Wisconsin enriched her "understanding of public health and law, and reaffirmed my conviction that interdisciplinary solutions will be critical to improved health care in this country."

Now that she has returned to PolicyLab, Noonan hopes to expand the Center's understanding of how laws affect health outcomes for children and their families. She also plans to build on PolicyLab's "evidence to action mission," by "expanding our know-how around program and policy implementation in both public and private systems," Noonan noted.

"I am delighted to be back at PolicyLab with founding co-director, David Rubin, and the many talented and dedicated people within our Center and CHOP," Noonan said.

CHOP's National Postdoc Appreciation Week Celebration Begins September 17

During the week of September 17, 2012, the Children's Hospital of Philadelphia Research Institute and the Office of Postdoctoral Affairs will celebrate National Postdoc Appreciation Week, recognizing the accomplishments and contributions of our postdoc community to the success of Children's Hospital.

We will be featuring two distinguished speakers to mark the event: David G. Jensen, Managing Director of Kincannon & Reed Global Executive Search, and author of the popular "Tooling Up" column for monthly career tips at ScienceCareers.org; and Ellen Purpus, Ph.D., director of the CHOP Research Institute Office of Technology Transfer.

On the morning of September 17, David Jensen will discuss the tools and core skills necessary to stand out as you pursue a career in his first talk, "Street Savvy Science: Elements of Job and Career Success," (9:00am, Biomedical Research Building II/III Auditorium). Later that afternoon, he will present "Job Offer Negotiation Strategies for the Scientist" (1:30pm, Abramson Research Center 123ABC), discussing the importance of understanding issues surrounding a prospective job offer and how to maximize a job offer to suit your needs.

On September 20, Dr. Purpus will moderate a Technology Transfer/ Industry career panel titled, "Breaking Into the Business of Science: Tech Transfer, Business Development, Patent Law and Everything In Between." This event, taking place at 3:00pm in the Colket Translational Research Building First Floor Conference Rooms, will include career professionals from throughout the Philadelphia area.

Panellists include Greg Baker, Ph.D., Christopher J. Laing, MRCVS, Ph.D., Timothy J. Pelura, Ph.D., and Kathleen Rigaut, Ph.D., J.D. Postdocs, mentors and colleagues are invited to close out the week immediately afterward with our National Postdoc Appreciation Week Reception at 4:30pm in the Colket Translational Research Building Lobby.

The Office of Postdoctoral Affairs will also be offering giveaways and free coffee for postdocs prior to these special events in the ARC lobby.

More information on these events and speaker/panelist bios can be found at http://www.research.chop.edu/programs/postdoc/index.php/current-trainee-home/events-of-interest/392-2012-national-postdoc-appreciation-week.html



AIDS Researcher Robert W. Doms, Named Chief of Pathology

Longtime University of Pennsylvania professor and AIDS researcher Robert W. Doms, M.D., Ph.D., will soon be joining the Children's Hospital of Philadelphia as pathologist-in-chief and chair of Pathology and Laboratory Medicine. Dr. Doms's new appointment is effective September 15.

Before joining Children's Hospital, Dr. Doms spent over a decade at the University of Pennsylvania, where he will retain a dual appointment. Dr. Doms first joined UPenn in 1992, and in 2001 was named chair of the Department of Microbiology. He received his M.D. and Ph.D. from Yale in 1988, and completed a postdoctoral fellowship at the NIH in 1992.

Much of Dr. Dom's work as a researcher has been focused on AIDS pathogenesis and how viruses enter cells, but more recently his lab has also studied West Nile Virus and other emerging pathogens. He has won a number of awards for his work, including the Elizabeth Glaser Scientist Award from the Pediatric AIDS Foundation. And though his lab currently remains at the University of Pennsylvania, Dr. Doms hopes to eventually move it over to a CHOP facility.

In addition to finding the opportunity to lead the pathology department of the leading pediatric hospital in the country attractive, Dr. Doms decided to join CHOP because he was "looking for new challenges." Because a pathology department is by nature a clinical/research hybrid, his new position will allow him the opportunity to work more closely with his clinical colleagues, Dr. Doms noted.

In his role as the new Chief of Pathology, Dr. Doms plans to work to integrate next generation sequencing (NGS) techniques into the Department of Pathology's work, a project he calls a "big challenge." By reducing sequencing time and costs, NGS can help researchers and clinicians to efficiently identify the genetic variants underlying diseases through whole-exome or whole-genome sequencing.

"I am very pleased that Dr. Doms has agreed to join us at CHOP, and we look forward to his contribution to an exceptional Pathology and Laboratory Medicine program," said Chief Executive Officer of CHOP Steven M. Altschuler, M.D. "Bob is internationally known and recognized for his discoveries in HIV/AIDS research, and his reputation for excellence will certainly enhance our efforts at CHOP."

HAVE NEWS?

Contact Jennifer Long at ext. 4-2105 or by e-mail at longi@email.chop.edu.

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

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34th Street and Civic Center Boulevard, Philadelphia, PA 19104-4399

1-800 TRY CHOP www.chop.edu