A Novel Gene Found for Childhood-Onset Asthma

Pediatric investigators have identified a novel gene involved in childhood asthma, in one of the largest gene studies to date of the common respiratory disease. Because the gene, called DENND1B, affects cells and signaling molecules thought to be instrumental in the immune system overreaction that occurs in asthma, the discovery may have singled out an important target for new treatments.

A research team led by Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics at The Children’s Hospital of Philadelphia Research Institute, implicated a location on chromosome 1 associated with moderate-to-severe childhood-onset asthma. The study appeared on the Online First Web site of the New England Journal of Medicine and was published in the journal’s print issue on Jan. 7.

Asthma is a complex disease, in which a large number of genes, as yet mostly undiscovered, are thought to interact with each other and with environmental factors to produce asthma’s characteristic wheezing, coughing, and shortness of breath. It also is highly heterogeneous, manifesting differently in different patients, and appears to operate differently in childhood-onset asthma compared to adult-onset asthma.

Previously, researchers had identified only one other asthma-susceptibility gene using a genome-wide association study (GWAS), in which automated genotyping tools scan the entire human genome seeking gene variants that contribute to disease risk. That gene, ORMDL3, on chromosome 17, was discovered in 2007 by U.K. researcher William O.C. Cookson, M.D., who collaborated with Dr. Hakonarson in the current study.

In the current study, Dr. Hakonarson’s team performed GWAS on a sample of 793 white North American children with persistent asthma, and a control group of 1,988 children. They replicated the study in a separate group of 2,400 European subjects and controls, then did further analyses on a third group of 3,700 African-American children.

“By analyzing a large cohort of children with moderate to severe asthma, all of whom require controller medications on a regular basis, we managed to enrich our study for genetic signals and achieve sufficient statistical power to uncover and replicate a novel asthma gene,” says Dr. Hakonarson.

Dr. Hakonarson’s group found a novel location on chromosome 1q31 with eight single nucleotide polymorphisms (SNPs) associating robustly with asthma. A SNP (pronounced “snip”) is a change to a single chemical base along the DNA helix. In addition, the group observed the previous results for chromosome 17, but unlike other studies, here the researchers found the same gene for asthma susceptibility in children of both European and African-American ancestries.

Within the region on chromosome 1q31 the gene with an apparent role in asthma is DENND1B, already suspected as a player in the body’s immune response. DENND1B expresses a protein of the same name, which is active in particular types of dendritic cells and specific T lymphocytes, including natural killer cells. Both of these immune cell subtypes form cross-talks between them (in a space commonly referred to as the antigen-presenting synapse) and regulate how the body responds to foreign materials such as viruses, bacteria, and allergens.

“We now know that the DENND1B gene and its protein are involved in the release of cytokines, which are signaling molecules that in this case tell the body how it should respond to foreign particles,” says Dr. Hakonarson. “Many of these particles are well-known triggers of asthma. In asthma, patients have an inappropriate immune response in which they develop airway inflammation and overreaction of the airway muscle cells, referred to as airway hyperresponsiveness. The gene mutations in DENND1B appear to lead to overproduction of cytokines that subsequently drive this oversensitive response in asthma patients.”

By identifying an asthma susceptibility gene with a compelling link to the pathobiology of asthma, says Dr. Hakonarson, his team may also have pinpointed a tempting therapeutic target, if researchers can develop drugs to contain this signaling pathway. “Because this gene seems to regulate many different cytokines, intervening in this pathway has great potential for treating asthma,” he adds. “Other asthma-related genes remain to be discovered, but finding a way to target this common gene variant could benefit large numbers of children.”

Grants from Children’s Hospital, the Commonwealth of Pennsylvania, the Cotswold Foundation, the Lundbeck Foundation, and the National Human Genome Research Institute supported this research.
Brain Imaging May Help Diagnose Autism

Children with autism spectrum disorders (ASDs) process sound and language a fraction of a second slower than children without ASDs, and measuring magnetic signals that mark this delay may become a standardized way to diagnose autism.

Researchers at Children's Hospital recently reported their findings in an online article in the journal Autism Research.

"More work needs to be done before this can become a standard tool, but this pattern of delayed brain response may be refined into the first imaging biomarker for autism," says study leader Timothy P.L. Roberts, Ph.D., vice chair of Radiology Research at Children's Hospital.

ASDs are a group of childhood neurodevelopmental disorders that cause impairments in verbal communication, social interaction, and behavior. ASDs are currently estimated to affect as many as one percent of U.S. children, according to a recent Centers for Disease Control and Prevention report.

Like many neurodevelopmental disorders, in the absence of objective biological measurements, psychologists and other caregivers rely on clinical judgments such as observations of behavior to diagnose ASDs, which often does not occur until a child reaches school age. If investigators can develop imaging results into standardized diagnostic tests, they may be able to diagnose ASDs as early as infancy, permitting possible earlier interventions. They also may be able to differentiate types of ASDs, such as classic autism and Asperger's syndrome, in individual patients.

In the current study, Dr. Roberts and his colleagues used magnetoencephalography (MEG), which detects magnetic fields in the brain, similar to the way electroencephalography detects electrical fields. Using a helmet that surrounds the child's head, the team presents a series of recorded beeps, vowels, and sentences. As the child's brain responds to each sound, noninvasive detectors in the MEG machine analyze the brain's changing magnetic fields.

The researchers compared 25 children with ASDs, having a mean age of 10 years, with 17 age-matched, typically developing children. The children with ASDs had an average delay of 11 milliseconds (about 1/100 of a second) in their brain responses to sounds, compared with the control children. Among the group with ASDs, the delays were similar, whether or not the children had language impairments.

"This delayed response suggests that the auditory system may be slower to develop and mature in children with ASDs," says Dr. Roberts. "An 11-millisecond delay is brief, but it means, for instance, that a child with ASD, on hearing the word 'elephant' is still processing the 'el' sound while other children have moved on. The delays may cascade as a conversation progresses, and the child may lag behind typically developing peers."

A 2009 study by Dr. Roberts and his colleagues sheds light on how changes in brain anatomy may account for the delays in sound processing. The study team used MEG to analyze the development of white matter in the brains of 26 typically developing children and adolescents. Because white matter carries electrical signals in the brain, signaling speed improves when neurons are better protected with an insulating sheath of a membrane material called myelin.

In this previous study, the researchers showed that normal age-related development of greater myelination corresponds with faster auditory responses in the brain. "The delayed auditory response that we find in children with ASDs may reflect delayed white matter development in these children," says Dr. Roberts.

He adds that further studies will seek to refine their imaging techniques to determine that the biomarker is specific to ASDs, and his team will investigate other MEG patterns found in children with ASDs in addition to auditory delays.

Grants from National Institutes of Health, the Nancy Lurie Marks Family Foundation, Autism Speaks, and the Pennsylvania Department of Health supported this research. In addition, Dr. Roberts holds the Oberkircher Family Chair in Pediatric Radiology at Children's Hospital.

Leading Oncology Investigator Honored With Penn Medicine Award of Excellence

John Maris, M.D., chief of the Division of Oncology, recently received the Leonard Berwick Memorial Teaching Award, an Award of Excellence from the University of Pennsylvania School of Medicine. Dr. Maris was selected to receive this award by a committee of senior faculty from the School of Medicine in recognition of his reputation as an outstanding teacher who effectively fuses basic science and clinical medicine. He is considered by both his students and colleagues as a true physician-scientist who has a unique ability to teach in diverse forums.

Dr. Maris, an international leader in identifying the molecular genetics of neuroblastoma through basic and clinical research and director of the Center for Childhood Cancer Research, is also an associate professor of pediatrics in the School of Medicine. His teaching approach is not bound by the for Childhood Cancer Research, is also an associate professor of pediatrics in the School of Medicine. His teaching approach is not bound by the...
New Gene Findings Will Help Guide Treatment in Infant Leukemia

Pediatric oncologists have identified specific genes, dubbed partner genes, that fuse with another gene to drive an often-fatal form of leukemia in infants. By more accurately defining specific partner genes, researchers expect to better predict which infants may benefit from particular treatments.

Oncologists also aim to use this latest knowledge to develop new and more effective therapies for this difficult-to-treat type of blood cancer, called acute lymphoblastic leukemia (ALL). Their goal is to target treatments to specific genes and other associated factors that become abnormal because of the gene fusions.

CHOP Research investigator Blaine W. Robinson, Ph.D., presented research findings in infant ALL at the annual meeting of the American Society of Hematology on Dec. 8. His group collaborated on this research with the Children's Oncology Group (COG), a cooperative, multicenter research organization.

ALL is the commonest of the pediatric cancers. While the survival rate for children older than one year with ALL has increased over time with advances in chemotherapy, the outlook for infants, children younger than one year, with the disease generally has been grim. Infants with ALL have a poor prognosis and a much higher mortality rate compared with other children, and curative treatments for infants are far behind the therapy for childhood ALL.

For the majority of these high-risk infants, the problem is within the structure of a specific chromosome. In an abnormality called the MLL translocation, the MLL gene on chromosome 11 breaks and joins with any one of many different “partner” genes from other chromosomes. The rearranged genetic region, called a translocation, leads to the production of a fusion gene and an abnormal protein and, ultimately, to leukemia.

The current study covered 221 infants with ALL in a COG clinical trial. Researchers detected MLL translocations in the ALL cells of 74 percent of the patients. The two most common partner genes that fused with the MLL gene were AF4 on chromosome 4 and ENL on chromosome 19. Both of these translocations were associated with a very poor prognosis: event-free survival (EFS) rates were 34 percent with AF4 and 29 percent with ENL, compared with the overall EFS rate of 46 percent among all infants in the study — still far inferior to survival rates that are seen in children older than one year.

The EFS rates with these two partner genes were even lower when the infants were less than 90 days of age at diagnosis. Conversely, the survival rates were better when these partner genes fused to MLL in the leukemia cells of older infants. Though age was already known to be a classic prognostic factor in infant ALL, the differences in survival according to age when these specific partner genes are involved had not been so clear.

In contrast, outcomes were better for infants with ALL when the third most common partner gene, AF9, fused to MLL, or when the MLL gene was unaffected. In these patients, the respective EFS rates were 68 and 66 percent. The researchers also analyzed white blood cell counts (WBC) — another classic prognostic factor in leukemia. They found that when MLL was fused to AF4, the infants were far more likely to have higher WBC, while the WBC was lower when MLL fused to AF9.

More refined knowledge of how the different partner genes of MLL in infant ALL are connected to the underlying molecular biology of the disease may guide the researchers to more appropriate treatment decisions. “Our ability to classify ALL based on specific partner genes of MLL may provide a new way to categorize which infants might benefit from specific types of treatment,” says senior author Carolyn A. Felix, M.D., a pediatric oncologist and expert in infant leukemia at Children's Hospital, and a professor of pediatrics at the University of Pennsylvania School of Medicine. “We also hope these findings will contribute to the development of new, molecularly targeted therapies for infants with this grim form of cancer that we seek to conquer.”

Gregory Reaman, M.D., chair of COG, adds, “As infants with ALL represent the group of children with the highest risk of treatment failure, despite successive attempts to intensify conventional therapy, these clues to potentially tailoring molecularly targeted treatment approaches are very exciting.”

Major grant support for this research is from a Specialized Center of Research grant from The Leukemia & Lymphoma Society. Other major support came from a National Cancer Institute grant to COG.

20th Annual CHOP Research Poster Day
Abstract Submission Site Now Open

The Research Institute will celebrate the 20th anniversary of the annual CHOP Research Poster Day on Wednesday, February 24. The event will be held from 9 a.m. to 4 p.m. in the atrium of the Abramson Research Center. All are welcome to join us as we honor the groundbreaking research conducted at CHOP throughout the past year.

All members of the Children's Hospital community (e.g., physician fellows, pre-and postdoctoral researchers, residents, nurse researchers, respiratory therapists, etc.) who are conducting research may now submit their abstracts on the Poster Day Web site at http://www.research.chop.edu/posterday/. Abstracts will be accepted on a first-come, first-served basis. Please note that presenters who have not pre-registered cannot be accommodated.

Presenters should set-up their posters by 8:45 a.m. on the day of the event and be prepared to attend their posters during the judging portion that will begin at 11 a.m. All participants will be eligible for cash prizes. A reception and awards ceremony will follow the event at 4 p.m. in the Abramson Center cafeteria.

Additional information and a complete schedule of the day’s events will be announced in the coming weeks. Questions may be directed to researchtraining@email.chop.edu.

2010 National Postdoctoral Association Annual Meeting

From March 12 to 14, the 8th annual National Postdoctoral Association (NPA) meeting will be held on the Children’s Hospital and University of Pennsylvania campuses.

Providing a combination of professional development seminars, advocacy-themed events, and multiple opportunities to network, the NPA Annual Meeting is an unparalleled venue for postdoctoral fellows and graduate students to advance their skill-sets and marketability. In addition, the NPA has announced that National Institutes of Health Director Francis Collins, M.D., Ph.D., will serve as the 2010 keynote speaker.

Please visit http://nationalpostdoc.org/meetings-and-events/annual-meeting/2010-annual-meeting for more information and a tentative agenda. A limited number of registration discounts are available for CHOP Research postdocs. To reserve a discount, please contact David Taylor at taylord@email.chop.edu.

The 8th annual meeting of the National Postdoctoral Association is hosted by CHOP Research Institute, the University of Pennsylvania, Thomas Jefferson University, Drexel University, and Temple University.
Neurology researchers have shown that feeding amino acids to brain-injured animals restores their cognitive abilities and may set the stage for the first effective treatment for cognitive impairments suffered by people with traumatic brain injuries (TBIs).

“We have shown in an animal model that dietary intervention can restore a proper balance of neurochemicals in the injured part of the brain, and simultaneously improve cognitive performance,” says neuroscientist and study leader Akiva S. Cohen, Ph.D.

The study recently appeared in the online issue of the Proceedings of the National Academy of Sciences.

If these results in mice can be translated to human medicine, there would be a broad clinical benefit. Every 23 seconds, a man, woman, or child in the United States suffers a TBI. The primary cause of death and disability in children and young adults, TBIs also account for permanent disabilities in more than 5 million Americans. The majority of those cases are from motor vehicle injuries, along with a rising incidence of battlefield casualties.

Although physicians can relieve the dangerous swelling that occurs after a TBI, there are currently no treatments for the underlying brain damage that brings in its wake cognitive losses in memory, learning, and other functions.

The animals in the current study received a cocktail of three branched chain amino acids (BCAAs), specifically leucine, isoleucine, and valine, in their drinking water. Previous researchers had shown that people with severe brain injuries showed mild functional improvements after receiving BCAAs through an intravenous (IV) line.

BCAAs are crucial precursors of two neurotransmitters — glutamate and gamma-aminobutyric acid, or GABA — which function together to maintain an appropriate balance of brain activity. Glutamate excites neurons, stimulating them to fire, while GABA inhibits the firing. Too much excitement, or too little, and the brain doesn't work properly. A TBI upsets the balance.

In particular, a TBI frequently damages the hippocampus, a structure deep in the brain involved in higher learning and memory. In the current study, the researchers found that an injury to the hippocampus reduced levels of BCAAs. Although overall levels of glutamate and GABA were unchanged, the loss of BCAAs disturbed the critical balance of neurotransmitters in the hippocampus, making some localized regions more excitable and others less excitable. Dr. Cohen's team tested the hypothesis that providing dietary BCAAs would restore the balance in neural response.

In this study, Dr. Cohen's study team first created standardized brain injuries in mice, and one week later compared the animals' conditioned fear response to that of uninjured mice. A week after receiving a mild electric shock in a specific cage, normal mice tend to “freeze” when placed in the same cage, anticipating another shock. The brain-injured mice demonstrated fewer freezing responses — a sign that they had partially lost that piece of learning.

On the other hand, brain-injured mice that received a diet of BCAAs showed the same normal response as the uninjured mice. The BCAA cocktail had restored their learning ability.

In addition to the behavioral results, the team conducted electrophysiological experiments in slices of hippocampus from brain-injured and non-injured mice, and showed that BCAAs restored a normal balance of neural activity. “The electrophysiological results were consistent with what we saw in the animals’ functional recovery,” says Dr. Cohen.

If the results in mice can be reproduced in people, patients with traumatic brain injuries could receive the BCAAs in a drink. Dr. Cohen suggests that BCAAs as a dietary supplement could have a more sustained, measured benefit than that seen when patients receive BCAAs intravenously, in which the large IV dose may flood brain receptors and have more limited benefits.

Although much work remains to be done to translate the finding into a therapy, Dr. Cohen expects to collaborate over the next year with other researchers in an early-phase clinical trial of dietary BCAAs in patients with mild to moderate TBIs.

The National Institutes of Health provided funding for this study. Dr. Cohen's co-authors were Jeffrey Cole, Ph.D., Christina M. Mitala, Ph.D., Suhali Kundu, and Itzhak Nissim, Ph.D., all of Children's Hospital; Jaclynn A. Elkind of the University of Pennsylvania; and Ajay Verma, M.D., Ph.D., of the Uniformed Services University of the Health Sciences in Bethesda, Md.
Stimulus Bill Funding Opportunities Announced

The National Institutes of Health (NIH) has announced several more funding opportunities under the American Recovery & Reinvestment Act of 2009, also called the Recovery Act or Stimulus Bill.

Details on each funding opportunity, as well as links to additional information, are provided below.

NIH Director’s Opportunity for Research in Five Thematic Areas (RC4) is aimed at research endeavors that address one or more of the following thematic areas: applying genomics and other high throughput technologies, translating basic science discoveries into new and better treatments, using science to enable healthcare reform, focusing on global health, and reinvigorating the biomedical research community. This program will support projects that will benefit from significant three-year funds without the expectation of continued NIH funding. The research supported by the program should have high, short-term impact, and a great likelihood of enabling growth and investment in biomedical research and development, public health, and healthcare delivery. Applications may be submitted beginning Feb. 15. The deadline for submissions is March 15. The full announcement is available at http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-10-005.html.

Behavioral Economics for Nudging the Implementation of Comparative Effectiveness Research: Clinical Trials (RC4) will support large-scale clinical trials with a primary outcome to determine whether a specific approach to changing provider behavior based on the principles of behavioral economics could enhance the uptake of comparative effectiveness research (CER) results among healthcare providers in their practice. In addition, as a secondary outcome, such trials could examine levels of patient compliance resulting from the level of CER uptake during a brief (e.g., 6 month) interval. Applications may be submitted beginning March 7. The deadline is April 7. The full announcement is available at http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-10-001.html.

Behavioral Economics for Nudging the Implementation of Comparative Effectiveness Research: Pilot Research (RC4) will support projects aimed at achieving a better understanding of how the principles of behavioral economics could be used to enhance the uptake of the results of CER among healthcare providers in their practice. The projects could also be designed to understand the maintenance of CER-supported treatments and procedures once prescribed in patient populations. Applications may be submitted beginning Feb. 19. The deadline is March 19. The full announcement is available at http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-10-002.html.

Comparative Effectiveness Research on Upper Endoscopy in Gastroesophageal Reflux Disease, Eradication Methods for Methicillin Resistant Staphylococcus aureus and Dementia Detection and Management Strategies (RC4) will fund initial or preliminary CER projects in targeted, high-priority areas in which such efforts have been lacking. Applications may be submitted beginning Jan. 26. The deadline for submissions is Feb. 26. The full announcement is available at http://grants.nih.gov/grants/grants/guide/rfa-files/RFA-OD-10-008.html.


In addition, the National Heart, Lung and Blood Institute has announced its intention to issue a program announcement to support studies that develop innovative dissemination and implementation approaches to translating efficacious treatments for heart, lung, and blood diseases and sleep disorders to the clinic, community, and other real-world settings, including testing the sustainability, feasibility, and cost-effectiveness of these approaches. The program announcement is expected to be published in the winter of 2010 with expected receipt dates beginning in May 2010. The full announcement is available at http://grants.nih.gov/grants/guide/notice-files/NOT-HL-11-102.html.

For more information on any of these funding opportunities, visit the Sponsored Projects intranet page at https://intranet.research.chop.edu/display/depts/pbm/Stimulus+Bill+Funding.

2010 Junior Investigator Pilot Grant Program Announced

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

The primary goal of the CTRC’s JIPGP is to encourage junior investigators at Children’s Hospital and the University of Pennsylvania Medical Center to develop clinical research projects that will ultimately lead to extramural NIH funding. The JIPGP assists junior faculty members, clinical fellows, and M.D. and Ph.D. post-doctoral trainees with appropriate mentors by providing funds for investigator-initiated, human-based, CTRC pilot studies that will produce preliminary data for a K23 or R03 grant submission.

It is anticipated that the award will lead to a competitive extramural grant application and to a career in CTRC-focused clinical investigations.

At least two $10,000 to $20,000 grants will be available at each institution effective July 1, 2010.

The application deadline is March 1, 2010 and award recipients will be notified on April 2, 2010. The funding period will be from July 1, 2010 to June 30, 2011.

Please see https://intranet.research.chop.edu/pages/viewpage.action?title=All+News&spaceKey=main&id=34571252 or contact Veronica Mazzaccaro at 215-590-2215 for eligibility criteria, proposal instructions, and additional details.