As New Data Wave Begins, a Gene Study in One Disease Discovers Mutations in an Unrelated Disease

Often enough, in science as in life, unexpected knowledge has a personal impact. Researchers seeking rare gene variants in just a few individuals with attention-deficit hyperactivity disorder (ADHD) discovered that one patient had a novel combination of two mutations. Those mutations caused a different disease, unrelated to ADHD — a blood disorder called idiopathic hemolytic anemia.

Although the man had long contended with the blood disease, “idiopathic” meant that physicians were unable to determine the cause of his particular anemia — until now, say authors of a new study.

As gene-sequencing costs continue to drop as a result of new technology, the authors predict “a coming wave of unrelated findings and the resolution of ‘idiopathic’ diseases.” In its wake will be new ethical and clinical implications — such as how and when to best share these findings with people who provide their own DNA for the research.

Rapid improvements in analytical tools are enabling researchers to more frequently sequence whole genomes of individual patients, says study leader Gholsen J. Lyon, M.D., Ph.D., a psychiatrist and principal investigator in the Center for Applied Genomics at The Children's Hospital of Philadelphia.

“As we sequence whole genomes, we will find new mutations unrelated to the disease under investigation,” he adds. “How do we handle this information, especially when it doesn’t lend itself to immediate action by a patient and physician? This is an issue that is coming to the forefront with current advances in genetic knowledge.”

Dr. Lyon and co-corresponding author Kai Wang, Ph.D., published the study online July 15 in the journal *Discovery Medicine.* (Formerly at The Children's Hospital of Philadelphia, Dr. Wang is now at the University of Southern California.)

In the current study, Dr. Lyon and his colleagues performed genetic analysis in a Utah family in which a father and two sons have a severe form of ADHD. All three had responded to a stimulant drug in a clinical trial, but ADHD is a complex disorder, with many different genes thought to be involved in conferring susceptibility to ADHD. Hence the researchers sought to identify specific mutations affecting this family.

In this collaboration among scientists at Children's Hospital, BGI-Shenzhen, and the University of Utah, the researchers first captured most of the exome, the protein-coding sequences of DNA from each patient’s genome. Then they sequenced and analyzed the exomes to identify gene mutations with a likelihood of causing disease.

The study team identified the family members had several rare gene variants that might contribute to ADHD, but the team has not yet been able to prove clear-cut causation. However, they did find other mutations that appear to cause chronic anemia in one family member.

The man, a young adult, had been plagued his whole life with chronic anemia, had suffered abdominal pain and jaundice, and had undergone surgeries to remove first his gallbladder, then his spleen. “He had been told that he had ‘idiopathic hemolytic anemia,’ which basically means, ‘your red blood cells are bursting open for reasons we do not understand,’” says Dr. Lyon.

The exome sequencing quickly pinpointed two separate, rare mutations in *PKLR,* a gene that makes pyruvate kinase, an enzyme in which defects have previously been implicated as one cause of hemolytic anemia. This form of anemia is recessive, so the man received one mutation from his mother, the other mutation from his father. This is the first scientific report of both mutations occurring in the same person.

After consulting with the University of Utah institutional review board (IRB) that oversees human subject research, Dr. Lyon informed the patient’s hematologist of the results, with a request to follow up the findings and offer genetic counseling.

“If this information had been available many years earlier, the patient may have received treatment or been advised to take preventive measures that could have possibly avoided complications, including the need for surgical removal of his spleen,” says Dr. Lyon, adding, “This illustrates the kind of medical information that will become more widely available as the pace of genetic discovery increases.”

With appropriate genetic counseling, the genetic information can be helpful to this patient, as he is extremely unlikely to pass on anemia to any future children because of the recessive nature of the illness and the rarity of these specific mutations.

“There is considerable debate among medical geneticists and medical ethicists about whether genetic research results should be returned to participating research subjects,” says Dr. Lyon. “In this case, we informed the patient’s doctor so that they could decide how to proceed.”

Medical practice is still evolving on the questions of how to use this information, adds Dr. Lyon. “For now, it remains a challenge to quickly discover causative mutations for complex multigene diseases. However, the whole genetics field is moving toward doing whole-genome sequencing to find disease-causing mutations, and in the future, a person’s full genome sequence will probably be linked to his or her medical records. Researchers and clinicians will be learning how to handle this information.”

Funding support for the study came from The Children’s Hospital of Philadelphia, the University of Utah Department of Psychiatry, and BGI-Shenzhen. Some of Dr. Lyon’s and Dr. Wang’s co-authors included Hakon Hakonarson, M.D., Ph.D., of Children’s Hospital; and Mark Yandell, Ph.D., of the University of Utah.
Treatment Aggressiveness Research Named Article of the Year by AcademyHealth

In today’s news, few topics are as talked about — or as heavily debated — as healthcare reform. The issue of decreasing the cost and social burden of healthcare while improving the quality of care impacts every American, and strategies for addressing the issue are hotly debated in the Congress and media.

Many in the government, research community, and lay press have suggested that an aggressive treatment style is both dangerous and wasteful. The implication of this argument is that cutting healthcare expenditures can be achieved without reducing quality.

Yet just as comparative effectiveness research is needed to establish evidence-based standards of care, outcomes research is essential to understanding the true impact of medical care spending on health. Through research that evaluates cost effectiveness in clinical care, researchers will peel back the issues covering the core sources of spending inefficiencies.

Jeffrey H. Silber, M.D., Ph.D., director of the Center for Outcomes Research at CHOP Research, and Robert Kaestner, Ph.D., from the University of Illinois, received the Article-of-the-Year Award for two papers that evaluate how medical outcomes and financial costs are associated with the intensity, or aggressiveness, of treatment.

Given by AcademyHealth, the nation’s largest health services research professional organization, the award recognizes the best scientific work that the fields of health services research and health policy have produced and published during the previous calendar year. It is awarded for an article that provides new insights into the delivery of health care and advances the knowledge of the field.

In the award winning companion papers, Drs. Silber and Kaestner evaluated the influence of an aggressive treatment style on surgical outcomes using data collected from more than 4.5 million Medicare patients admitted to one of more than 3,000 hospitals for surgery.

The authors examined treatment aggressiveness as defined by the Dartmouth Atlas hospital spending intensity, which has been used in studies that assert aggressiveness increases complications and worsens mortality rates. However, using the same definition of aggressiveness, the current articles indicate that a more aggressive treatment style increases survival, contradicting previous studies and cost-cutting arguments that argue patients would not be harmed by reductions in Medicare spending.

“Previous studies have looked at the end of life care for patients who have died, under the assumption that they are equally sick,” says Dr. Silber, who is also a professor of pediatrics and anesthesiology and critical care medicine at the University of Pennsylvania, a professor of health care management at the Wharton School, and a senior fellow at the Leonard Davis Institute of Health. “But these studies are not looking at everyone. We wanted to know what to do with patients moving forward, when we don’t know what their outcome will be yet. What is the impact of aggressive treatment when a patient is admitted, looking forward?”

In the first paper, published in Health Services Research, Drs. Silber and Kaestner asked whether hospitals with more aggressive treatment had better surgical quality compared to less aggressive hospitals. They found that surgery at more aggressive hospitals had significantly lower mortality and failure-to-rescue rates. They also found that the aggressive treatment style did not lead to increased complications, which can contribute to much of the high cost associated with surgery.

To further explore the issue, Drs. Silber and Kaestner estimated the cost effectiveness of aggressive care by looking at the association between inpatient spending and mortality of Medicare patients admitted to hospitals for surgery. Published in Milbank Quarterly, the research showed that in many types of surgery, a 10 percent increase in expenditure was associated with 4 to 11 percent increase in the number of patients who survived 30 days following surgery. This benefit was stable after the 30-day mark, showing that patients who survive at aggressive hospitals are no more fragile than survivors at less aggressive hospitals.

By identifying improved outcomes at hospitals with a more aggressive treatment style, Drs. Silber and Kaestner found that aggressive treatment does not push beyond the commonly cited “flat of the curve,” the point at which additional healthcare spending cannot provide better quality of care. The conclusion from this research indicates that inefficiencies in health spending are less than conventionally believed, at least for inpatient care.

The award-winning findings should be taken into account when attempting to find cost efficiencies by reducing aggressive care. “In our study the more aggressive hospitals did better, which shows aggressive treatment is not waste or abuse, it is a style of practice,” says Dr. Silber. “While there are opportunities for tremendous savings in health spending, a blunt approach to cutting costs can hurt patients. If you think that aggressiveness is bad, you’ll want to cut it. But if it were your life, you’d be interested in that extra benefit in survival. We need to be careful.”

Free Biostatistics and Data Management Services Available to CHOP Investigators

The CHOP Biostatistics and Data Management Core offers free services for CHOP researchers. These services include:

**Grant Applications** - Collaborating with investigators to develop study design; writing the statistical analysis section of grant applications (including power and sample size calculations), and data management section (including database development and data capture procedures).

**Consulting** - Providing options and guidance for conducting statistical analyses and developing database management systems using tools such as REDCap.

**Analysis** - Performing limited statistical analyses of existing datasets (cost estimates provided if additional analyses are needed).

To make an appointment to discuss your project/proposal, please contact Linda Harrison at 267-426-7201 or harrisonl@email.chop.edu, or complete the web-based form at http://www.research.chop.edu/tools/bdmc/contact.php.
Philadelphia Hyundai Dealers joined Hyundai Motor America in support of childhood cancer research by presenting a $100,000 Hyundai Scholar grant to Children’s Hospital as part of the 2011 Hope on Wheels’ program.

The grant was officially presented to Vandana Batra, M.D., and Lisa Wray, M.D., and to Children’s Hospital and will help fund their research to find better treatments and ultimately cures for both neuroblastoma and acute lymphoblastic leukemia (ALL).

Following the presentation of the $100,000 Hyundai Scholar grant, Philadelphia-area children affected by cancer placed their handprints in colorful paint on a 2011 Hyundai Santa Fe — the official vehicle of the Hope on Wheels tour — to commemorate their brave battles with cancer.

With its Hyundai Scholars grants, Hope on Wheels is awarding research grants to 50 children’s hospitals in 2011. Each of these 50 Hyundai Scholar grants will go toward funding new pediatric cancer research projects and the grant recipients, known as “Hyundai Scholars,” will receive a combined total of $2.7 million from Hyundai Hope on Wheels.

“The Cancer Center is making great strides in pediatric cancer but funding is vital for our continued success,” says John Maris, M.D., director of the Cancer Center and Center for Childhood Cancer Research at Children’s Hospital. “We are grateful for the support of Hyundai Hope on Wheels and its customers, and will remain steadfast in our dedication to find new treatments and ultimately a cure for pediatric cancer.”

The 2011 program marks the 13th straight year of Hope on Wheels’ mission to fight childhood cancer. This year alone, Hyundai and Hope on Wheels have pledged more than $18 million to childhood cancer research. Along the way, Hyundai’s National Youth Ambassador and pediatric cancer survivor, Brianna Commerford, 13, will join Hyundai for a second year at children’s hospital Handprint Ceremonies all over the country. Brianna battled stage IV Hodgkin’s lymphoma, and is now sharing her story with children, families, medical staff, and communities at Hyundai Hope on Wheels ceremonies.

During Childhood Cancer Awareness month, Hyundai will donate additional grants in the amount of $100,000 each through its competitive September Hope Grants program. The September program allows Children’s Oncology Group (COG) member institutions seeking funding in areas of childhood cancer research to apply for the grants, which are then reviewed by Hyundai’s board of medical directors and awarded to hospitals around the United States.

More information and the complete list of 2011 Hyundai Hope on Wheels tour stops is available at www.HyundaiHopeOnWheels.org.

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CHOP’s Genome Center Contributes to Large International Gene Study of Multiple Sclerosis

The Center for Applied Genomics contributed pediatric data to the largest-ever genetic study of multiple sclerosis (MS), published on August 11 in Nature.

Bringing together scientists from 23 research groups in 15 countries, the International MS Genetics Consortium described the genetic architecture of MS and reinforced the central role of immune dysfunction in the disease. The genome-wide association study (GWAS) of samples from nearly 9,800 MS patients and 17,000 healthy control subjects replicated previous genetic findings and identified 29 novel gene variants linked to increased risk of MS patients and 17,000 healthy control subjects replicated previous genetic findings and identified 29 novel gene variants linked to increased risk of MS, with the hope that increased understanding of how the disease occurs may lead to more effective treatments for MS.

The research leaders say the study has established that MS is primarily an immunological disease. Many of the susceptibility genes identified play roles in immune function, particularly in the function of immune cells called T-helper cells, as well as in interleukins, which are signaling molecules. Some of the genes identified have previously been associated with other autoimmune diseases, such as Crohn’s disease and type 1 diabetes. These findings shed light on the underlying causes and biology of MS, with the hope that increased understanding of how the disease occurs may lead to more effective treatments for MS.
CHOP’s Genome Center Helps Build Advanced Genetic Map, Based on African-American DNA

The Center for Applied Genomics at Children's Hospital played an important role in a large international research consortium that just created the world’s most advanced genetic map, published July 20 in the journal Nature.

The center contributed high-density genotypes form nearly 80,000 samples of DNA collected through the Children’s Hospital pediatric network from healthy African-American control subjects — children and adults. Those samples provided important data to the collaboration among numerous researchers from dozens of institutions, led by Dr. David Reich from Harvard University and Dr. Simon Myers of Oxford University in the U.K. The new biological atlas is expected to help scientists better understand the genetic origins of inherited conditions that occur at higher rates in African-Americans, as well as assisting the discovery of disease-causing mutations in all human populations.

Hakon Hakonarson, M.D., Ph.D., director of CHOP’s Center for Applied Genomics, and a co-author of the paper, titled “The landscape of recombination in African Americans,” says “The DNA samples from our biobank played a crucial role in enabling the genetic map, setting the stage for important scientific discoveries in the future.”

NIH Extramural LRP Application Cycle - September 1 Through November 15

The National Institutes of Health (NIH) extramural loan repayment program (LRP) cycle will be open from September 1 through November 15, 2011.

If you are or will be conducting qualified research at a domestic nonprofit institution outside the NIH, you may be eligible for one of the five extramural LRP’s:

- Clinical Research
- Pediatric Research
- Health Disparities Research
- Contraception and Infertility Research
- Clinical Research for Individuals From Disadvantaged Backgrounds

You may submit only one LRP application to NIH in any fiscal year, even though your research may be appropriate for more than one of the programs.

First Time Applicants

If you are a first time applicant, the following information will help you prepare your LRP application:

- NOT-OD-09-107 - NIH Extramural Loan Repayment Programs - The official notice about the LRP’s in the NIH Guide for Grants and Contracts
- LRP Application Guide - A step-by-step overview to preparing your application

Current LRP Participants

If you are already an LRP participant whose current LRP contract will be ending in the next year and you still have qualified educational debt to be repaid, learn about submitting a renewal application.

You should apply for a renewal during the application cycle for the fiscal year in which your current contract will end. For example, if your current LRP contract ends in June 2012, you should apply during the application cycle that begins on September 1, 2011.

If you have questions, please contact CHOP’s institutional contact, Kaila Gammon at gammonk@email.chop.edu.

CHOP Trainee Profile System Now Open to Postdoctoral Fellows

In an effort to improve data collection at Children’s Hospital and to assist in the preparation of institutional National Research Service Award Training Grant applications, the Office of Postdoctoral Affairs is pleased to announce the official roll out of the CHOP Trainee Profile System.

This online, intranet-housed database enables postdoctoral fellows to sign in and update their “Trainee Profiles” with information related to their CHOP fellowships. Fellows will be asked to populate their profiles with general contact information, CHOP training information, past education and training information, and CHOP publication data. Completing and annually updating trainee profiles will be required as part of the annual postdoc evaluation process.

Only postdoctoral fellows currently have access to this system. Expanding the scope of the database to other trainee groups will be evaluated in the near future.

All postdoctoral fellows who update their profile by the end of September will be automatically entered to win a current generation iPod Nano during National Postdoc Appreciation Week, September 19 to 23, 2011.

For more information, view the CHOP Trainee Profile System page on the intranet.

Dr. Hakonarson, who was also involved in the initial design of the study, added that since African-American populations have an average of 80 percent West African ancestral genes and 20 percent European ancestral genes, they provide valuable resources in helping scientists discern patterns in human genetic variation.

The shuffling of genes from both parents that occurs during conception is called recombination, and some sites along chromosomes are more likely to recombine than other sites. The current study identified 2,500 “hotspots” for recombination that tend to be much more common and involve smaller stretches of DNA in people of West African ancestry, such as African-Americans, than in Europeans. Because errors in recombination may result in disease-causing mutations, these recombination hotspots are more likely to contain mutations responsible for diseases with higher rates among African-Americans. A previous scientific study recently showed that the majority of genome research has occurred in people of European ancestry, so this new map provides a contrasting population, with broader opportunities to investigate genetic origins of diseases.
The Center for Pediatric Clinical Effectiveness (CPCE) offers awards twice each year through its Pilot Grant Program. The purpose of this program is to promote and support CHOP investigators conducting clinical effectiveness pilot research studies that will attract external support for large-scale studies.

Clinical effectiveness research is research designed to produce evidence of what works best for treating, diagnosing, and preventing disease. A pilot study is a small study, conducted in preparation for the larger research study, in which study feasibility is tested and preliminary data are collected.

Award Eligibility

Investigators from all CHOP departments and divisions, including fellows in their final year of fellowship transitioning to a faculty position at CHOP, are encouraged to apply. Selected proposals will be supported for up to a maximum of $10,000 for one year. Projects should be able to be completed within one year.

Please note that studies already in progress or partially funded are not eligible for the program. Also, re-submissions are by invitation only. You will be notified if your proposal qualifies to be resubmitted for a future funding cycle.

Proposal Submission and Review

Submission Deadline: Monday, October 3, 2011
Notification of Award: Monday, November 7, 2011

All proposals should be in NIH format; additional details regarding the application, submission, and scoring process are available on the CPCE Web site.

The review process will consist of two rounds. Round one will determine if a proposal meets the definitions of clinical effectiveness pilot study and is of sufficient quality for further review. Only proposals that qualify for the second round will be critiqued and scored.

The second round will be scored using the NIH Study Section Criteria: Significance of Study, Approach, Likelihood of Impact on Clinical Effectiveness, Appropriateness of Budget, Likelihood of Future Research, and Innovation. The above criteria will be scored on a scale from 1 (high impact) to 9 (low impact).

Although projects may be funded up to a maximum of $10,000, priority will be given to projects that include a prudent spending plan. CPCE will attempt to fund all requested budgets in full, but may elect to partially fund certain protocols in order to increase the number of funded proposals.

Please submit the proposal as a single Microsoft Word document via email to Linda Scott, sponsored projects officer, at scottl@email.chop.edu no later than 4:00 p.m. on Monday, October 3, 2011.

Summer 2011 Issue of Discovery to Innovation Now Online

The Summer 2011 issue of Discovery to Innovation is now available online. The issue features research revealing factors that contribute to disease, findings that may one day lead to new therapies, funding that will make continued investigations possible, and much more.

Visit www.research.chop.edu/discovery_to_innovation/ to read the issue or explore the archives.

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/.