MIT CEHS NEWSLETTER

Massachusetts Institute of Technology
CENTER FOR ENVIRONMENTAL HEALTH SCIENCES

Summer/Fall 2006

Gene Environment Interaction in the Age of Genome-Wide Association Studies—David J. Hunter

It has become commonplace to observe that for most "complex" diseases, both inherited genetic variation and environmental influences combine to influence disease risk. Over the past 50 years epidemiologists have discovered environmental factors that determine a substantial proportion of the risk of many chronic diseases. However, our statements that the highest proportion of risk of most chronic diseases is due to "environmental factors" have often led to confusion. Most epidemiologists use the word environment as an approximation to "everything that is not due to inherited genes" including all aspects of lifestyle such as diet, most physical activity, and even addictive behavior. Many members of the public may assume that we are talking about more general "Environmental Issues" such as air and water pollution, or synthetic chemicals in the "environment". By and large the evidence that these contribute substantially to the risk of major diseases, at least in the US, is limited.

There are two major arguments that an inherited genetic component interacts with environment or lifestyle factors in the "causation" of many diseases. First of course, is the observation that family history of a disease is often a risk factor for that disease, and when combined with more formal genetic epidemiology studies such as twin studies, the inherited component of many diseases can be calculated. The other observation is that many people who are exposed to adverse lifestyle factors do not develop the disease these factors cause, suggesting that there are susceptibility and resistance factors that mediate risk to environmental influences.

The completion of the human genome project (HGP) has revolutionized the way we study the inherited genetic contributions to disease. Prior to this, most genes known to influence disease risk conferred very high risk, which permitted the chromosomal localization of these genes through the study of families with a high burden of the disease of interest. The problem was that in many cases, the genes found to be associated with the familial forms of the disease have not been shown to be behind the more common non-familial cases. Most studies seeking the genes associated with the more common forms used the "candidate gene" approach in which variation in genes that were plausibly involved in the disease, or response to the environmental factors known to be associated with that disease, were examined. This approach had some limited successes, but was inevitably limited by our lack of understanding of all the biological processes that are relevant to environmental response, meaning that for most diseases we can only name as "candidates" a fraction of the genes that were truly relevant to the disease process. The human genome project, by giving us the sequence of the genome, in theory offers a way out of this problem. If it were possible to completely sequence the genome of a large series of cases of a disease and compare that with the sequence in a large series of controls, it is theoretically possible to identify all the inherited genetic differences between the two series. The problem with this approach is that obtaining a complete gene sequence in a human currently costs several million dollars making this "brute force" unaffordable. Fortunately, the nature of the way common genetic variants occur in the genome offers a short cut solution that has become affordable in the last year or two. Work at the Broad Institute and elsewhere demonstrated that most of the twelve million single nucleotide polymorphisms occur in linkage with other SNP's, such that many SNP's are strong surrogates of each other. Thus, a judiciously selected subset of SNP's can stand in for over eighty percent of all common SNP's. About 500,000 SNP's are thought to be needed to perform such a "whole genome SNP scan" in populations of Caucasian ancestry. At the same time as these discoveries were being made, technologies from Affymetrix and Illumina became available to conduct these large scale SNP assays at an affordable cost by running these "SNP chips" on one thousand or more cases of a disease and one thousand or more appropriately selected controls. Immediate successes have followed. Common genetic variants associated with diseases such as age-related macular degeneration and prostate cancer have been found. These discoveries have opened up a series of new opportunities to finally fulfill the promise of examining genes and environment jointly in epidemiologic studies in which both the gene variants and the environmental and lifestyle risk factors have been measured.

As part of our work through the Center, we have begun assessment of gene-environment interaction for a number of common diseases. A recent published example takes two SNP's associated with age-related macular degeneration and assesses whether the risk is greater for people simultaneously carriers of the risk allele for the genetic variant who have the known lifestyle risk factors. The figure from this recently published work by Debra Schaumberg of Harvard Medical School shows that this is indeed the case in men and women from the Health Professionals Follow-up Study and the Nurses Health Study. A SNP at the LOC#387715 locus predicts risk of AMD with relevant risk of about four in those that are homozygous for the variant compared with people who

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UPCOMING EVENTS

January 25, 2007
David Schwartz presents the Robert S. Harris Lecture

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January 26, 2007
CEHS Sponsored Gene-Environmental Interaction Symposium

See page 4 for details

Awards and Honors

Linda Griffith Wins Genius Award

Professor Linda Griffith has won a 2006 MacArthur Fellowship, more commonly known as a "genius" grant. Griffith was honored for "shaping the frontiers of tissue engineering and synthetic regenerative technologies," according to the John D. and Catherine T. MacArthur Foundation. This year, the foundation selected 25 MacArthur Fellows for their "creativity, originality and potential to make important contributions in the future," according to the MacArthur Foundation announcement. Fellows receive $500,000 in "no strings attached" support over five years. Candidates for the fellowship are nominated, evaluated and selected through a confidential process; no one may apply for the awards and interviews are not conducted.

Graham Walker Receives EMS Award

Graham C. Walker, received the EMS Award for outstanding dedication, leadership and pioneering research contributions in the field of DNA repair and mutagenesis. The Environmental Mutagen Society conferred awards at its annual meeting held in Vancouver , British Columbia, Sept 16-20, 2006

"The advance of genetic engineering makes it quite conceivable that we will begin to design our own evolutionary progress."
ISAAC ASIMOV, *The Beginning and the End*

James Sherley Wins 2006 Pioneer Award

Dr. James L. Sherley is among 13 scientists nationwide to receive 2006 Pioneer Awards from the National Institutes of Health for their "highly innovative research. Recipients will each receive $2.5 million over five years. Now in its third year, the Pioneer Award is a key component of the NIH Roadmap for Medical Research. The program supports exceptionally creative scientists who take highly innovative approaches to major challenges in biomedical research.

"The 2006 Pioneer Award recipients are a diverse group of forward-thinking scientists whose work could transform medical research," said Dr. Elias A. Zerhouni, director of the NIH. "The awards will give them the intellectual freedom to pursue exciting new research directions and opportunities in a range of scientific areas, from computational biology to immunology, stem cell biology, nanotechnology and drug development." Sherley, an associate professor of biological engineering is working "to develop routine methods for the production of human adult stem cells from liver, pancreas, hair follicles and bone marrow."

Leona Samson Receives ACS Research Professorship Award

Professor Leona Samson received a competitive continuation of her ACS Research Professorship Award. This award provides $60,000 per year for five years for the purpose of furthering research on DNA Alkylation and Repair.

Genomics and Bioinformatics Facilities Core

The Genomics and Bioinformatics Core led by Dr. Rebecca Fry has made significant contributions to studies of environmental health sciences in 2006. Working with CEHS investigators, the Core has:

*established specific genomic responses to single and double-strand breaks in DNA

*identified DNA repair independent and dependent responses to treatment with toxic agents

*identified strain specific responses to infection with *C. rodentium* in mouse models

*identified age specific responses to toxicity induced by aflatoxin B1

*established models of gene expression responses in various liver culture environments

The Core provides analytical and technical services to CEHS investigators for genomics and bioinformatics applications related to environmental health research. Analytical services provided by the G&B Group include Experimental Design Consultation and Data Analysis/ Advanced Analytical Processing. Also provided are technical services that include RNA quality validation, Microarray labeling, and Microarray/Genome hybridization scanning. In addition, the Core also provides access to two real time PCR machines for validation of experimental results.

The Core has recently launched competitive genomic hybridization through the Agilent platform. This technology is available for yeast, human and mouse genomes.

CEHS investigators are encouraged to contact Dr. Fry at rfry@mit.edu to discuss their research project and the ways in which these valuable services and tools can enhance their scientific investigations.

CEHS HAPPENINGS

CEHS 2006 POSTER SESSION

The CEHS Poster Session, a tradition started in 2004 continues to draw interest from a wide range of CEHS affiliated member labs. This year the poster session was held in May and there were approximately 60 posters presented from several different disciplines. It is the goal of the Center to bring together CEHS members/affiliates labs to highlight their ongoing research projects as well as providing an opportunity for interaction with others and possibly leading to future collaborative, multidisciplinary approaches to research in the area of environmental health science.

This year the Center offered prizes to poster participants. Our secret panel of judges included Drs. Bevin Engelward, John Essigmann, and Pete Wishnok. CEHS 2006 Poster Session Prize winners are:

1st Place: Graduate Student – Daniel Jarosz from the Walker Lab; Postdoc – Dharini Shah from the Samson Lab * *Prize - $500 travel award to one of the following meetings (SOT, ACS-DCT, AACR, EMS)* **2nd Place:** Graduate Student – Diana Borenshtein from the Schauer Lab; Postdoc – Jim Delaney from the Essignman Lab * *Prize - $100 gift certificate to the MIT Book Store)* **3rd Place**: Graduate Student – Leah Blasiak from the Drennan Lab; Postdocs (we had a tie!!!!) Bo Pang from the Dedon Lab and Michelle Williams from the Tannenbaum Lab * *Prize: - CEHS T-Shirt and Coffee Mug*

COVER ART!

Rao VP, Poutahidis T, Ge Z, Nambiar PR, Boussahmain C, Horwitz BH, **FoxJG, Erdman SE.** Innate immune inflammatory response against enteric bacterial pathogen *Helicobacter hepaticus* triggers mammary adenocarcinoma in mice. Can Res 66: 7395-7400, 2006.

CEHS Pilot Projects Awarded

CEHS allocates a significant portion of its NIEHS ES002109 funding to support pilot projects that: provide initial support for investigators to establish new lines of research in environmental health; allow exploration of innovative new directions representing a significant departure from ongoing research for established investigators in environmental health sciences; and stimulate investigators from other fields to apply their expertise to environmental health research. Current award recipients and their projects are:

- Jeffrey Coderre, Associate Professor, Nuclear Science and Engineering, to study the role of vascular endothelial cell damage in tissue response to low-dose radiation
- Patrick Doyle, Assistant Professor, Department of Chemical Engineering. "Technologies to Rapidly Scan Single Genomic DNA Molecules"
- Catherine Drennan - Associate Professor, Department of Chemistry. "Structural Studies of the AlkB Family of Proteins"
- John Essigmann, Professor, Division of Biological Engineering, to study transcriptional networks affected by agents that suppress toxicity and carcinogens by aflatoxin B1
- Kimberly Hamad-Schifferli, Assistant Professor, Department of Mechanical Engineering and Division of Biological Engineering. "Antisense gene regulation with nanoparticle-DNA conjugates"
- Arlin Rogers, Chief, Comparative Pathology Laboratory, Division of Comparative Medicine. "Molecular determinants of liver tumorigensis following combined exposure to aflatoxin B1 and infectious hepatocarcinogens in a mouse model"
- Roman Stocker, Assistant Professor of Civil and Environmental engineering, for microfluidic investigation of motility of environmental pathogens
- Steven Tannenbaum, Professor, Division of Biological Engineering, to develop a strategy for interrogating the metabolic state of hepatocyte cultures
- Michael Yaffe, Associate Professor, Division of Biological Engineering, to study a high-throughput automated microscopy-based RNAi screen for modifiers of the DNA damage response
- Jacquelyn Yanch, Professor, Nuclear Science and Engineering, for the design and construction of a long-term, low-dose-rate mammalian cell irradiator.
- Krystyn Van Vliet, Assistant Professor, Department of Materials Science and Engineering. "In vitro platforms to assess mechanically modulated environmental exposure"
- Kathleen Vandiver, Director of Community Outreach and Education programs at the Center for Environmental Health Sciences, and Beryl Rosenthal, director of exhibitions and public programs at the MIT Museum, for an exhibit called "The Cell is a Molecular Machine"

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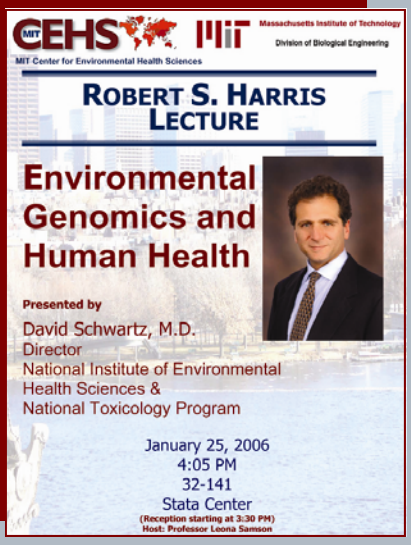
CEHS HAPPENINGS (CONTINUED)



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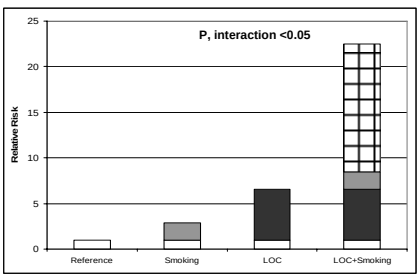
are homozygous for the wild type sequence. The risk for variant homozygotes is increased to over 20 if they are also current cigarette smokers. The risk is estimated to be approximately 50-fold increased if people are simultaneous carriers of this allele and another risk allele at the CSH locus.

What are the implications of data like these? Although we can do nothing about our inherited genetic risk directly, findings such as these suggest that in people who inherit risk it may be more important than ever to limit exposure to modifiable lifestyle factors, as in this case, cigarette smoking. In one sense, as smoking is a risk factor for non-carriers of this allele as well, the public health message does not change - not smoking reduces risk of AMD (and of course many other diseases). On the other hand, knowledge of the gene variant does permit us to identify individuals at an especially high risk if they smoke. This knowledge might provide extra motivation to quit smoking for those who have continued to smoke despite our broad public health message.

Interaction of (LOC387715) HTRA1 and Smoking in AMD: NHS/HPFS – 430 cases.



Schaumberg et al, Archives of Opthalmology 2007

These transformative gene mapping technologies are likely to permit the discovery of most of the common risk alleles for the common diseases for which sample sets exist, literally in the next two-five years. There is perhaps a danger that the flourishing of discoveries of susceptibility and resistance genotypes may reinforce old notions about genetic determinism. As Environment Health Scientists however, these data will give us hitherto unavailable information on what the true underlying genetic risk factors are. With this information we can for the first time explore gene-environment interactions for many diseases with the genes in hand, as opposed to using weak surrogates such as family history of the disease. Some of the genetic risk alleles will prove to be modified by environmental and lifestyle factors in ways that have meaning for prevention of these diseases. For other genes we may find that they are not modified by the environment. Whatever the outcomes, we are guaranteed of some exciting times ahead as these technologies are applied to epidemiologic studies.

The ultimate social utility of the information remains to be defined. Knowledge of gene-environment interaction should better define biologic mechanisms, providing targets for laboratory studies to further refine mechanisms. This knowledge may be used to design chemoprevention agents, in regulatory decisions on safe exposures, in providing more accurate information on health lifestyles, and to inform other disease prevention-oriented approaches. Centers for Environmental Health have much to offer as one of the few loci of multidisciplinary expertise to conduct the translational research necessary to capitalize on the common burst of research findings that will flow from genome-wide associations studies.

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