Toxicogenomics (täk'-si-ko-jə-no'-miks)
The study of how genes respond to environmental stressors and toxicants.

Initiatives

The New Biology

"Now that we have a draft of the genome, the next big challenge is understanding how genes interact with the environment." NIEHS director Kenneth Olden thus explained the importance of the field of toxicogenomics at the symposium "Toxicogenomics: The 'New Biology' Revolution in Environmental Health Sciences," held 4–5 November 2002 in Washington, D.C. But with this "new biology" come new questions, including technical, regulatory, and ethical issues about using new biotechnologies derived from the Human Genome Project to inform public policy and promote human health. These were some of the questions addressed at the symposium, the first to be held by the newly convened National Academies Committee on Emerging Issues and Data on Environmental Contaminants. The National Academies convened the standing committee at Olden's request.

The field of toxicogenomics is quite new, dating from about 1996, when rapid genetic sequencing first became possible. It can be difficult for researchers to simply reproduce research results, noted committee chair David L. Eaton, an environmental health professor and associate dean for research in the School of Public Health at the University of Washington in Seattle: "There's a lot of uncertainty about some of the terminology and nomenclature used [in toxicogenomics], and we hope [the committee] might normalize that as it relates to using toxicology data and risk assessment."

One of the major technical successes that rocketed the field forward was the invention of the microarray chip. The chip allows the analysis of the expression of thousands of genes at one time, said David Craford, vice president of marketing at Affymetrix in Santa Clara, California, a major "gene chip" producer. Prior to the development of the chip, analyzing single genes took days. The chip is "the compact disc of the genomics industry," Craford said—it's a standardized and convenient way to make the same genetic content available to many different people.

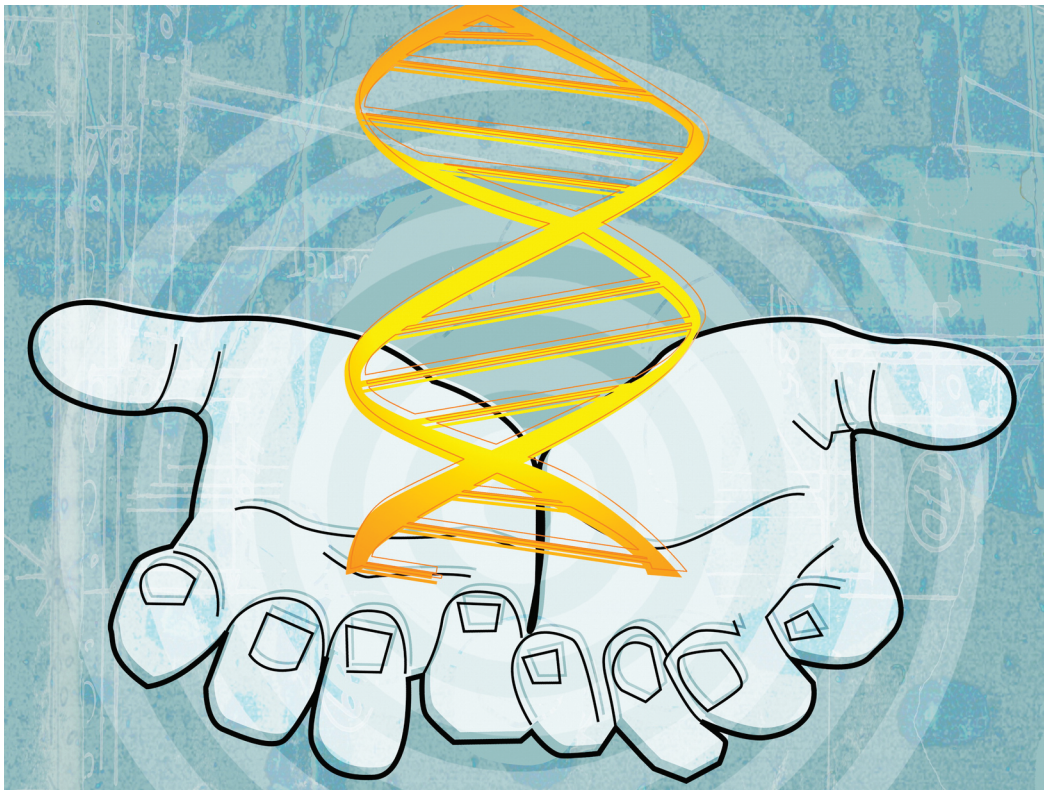
But the goal for researchers engaged in toxicogenomics is not just collecting data but figuring out how to deal effectively with the information, many conference presenters stated. "For example," said Eaton, "how do you know what level of gene expression changes are significant to public health or are toxicologically relevant? That's one of the biggest challenges in this whole area."

The importance of defining how and when to use toxicogenomic data looms large when considering its use in legal cases. "Lawyers are salivating to get their hands on genomic information," said Gary Marchant, an associate professor at Arizona State University College of Law in Tempe. Genomic information could reveal currently hard-to-detect truths such as whether a toxic agent was in fact responsible for a plaintiff's illness, or how much exposure a plaintiff actually received. Such revelations could benefit plaintiffs and defendants alike, Marchant predicted. It could also bring a flood of cases, he said, because everyone has been exposed to many chemicals, and genetic studies could reveal gene changes before illnesses have actually occurred.

In the environmental regulatory arena, "gene expression profiling has the potential to provide a fast, cheap initial screen of potential toxicants," Marchant said. But, he noted, the question again comes up: When do gene expression changes translate into adverse effects?

Olden sees toxicogenomics as enabling scientists to use exposure levels that are consistent with the levels humans actually experience when testing the health effects of chemicals. He also foresees use of human tissue instead of animals in toxicology, as well as studies of the interaction of multiple agents on human health. Samuel Wilson, deputy director of the NIEHS, predicted that in about 10 years, genomics technologies will bring us medications tailored to individuals. He expects enhanced efficiency in drug design and toxicity assessment in about 5 years.

Short-term goals for toxicogenomics researchers should include developing predictive assays that reveal signature patterns of gene



The whole world in our hands. With the power of toxicogenomics come challenges, questions, and concerns.

Artville

expression changes created by various classes of chemicals and biomarkers of adverse health effects, said Raymond Tennant, director of the National Center for Toxicogenomics at the NIEHS. These assays would form the basis of a "knowledge base" composed of elements including a gene expression database and analysis and query tools for applying the data.

The meeting provided a forum for government agency representatives to discuss the various approaches they are using and challenges they face in addressing and incorporating these new technologies into their plans and strategies. Several agencies see epidemiology, risk assessment, and prevention legislation as areas where toxicogenomics data could be used profitably. One top challenge is data quality assurance—ensuring that data are collected and analyzed in standardized, accepted, reproducible ways. Another is public perception—privacy concerns are an important consideration, as are fears about biotechnology, as evidenced by the controversy over genetically modified foods. "It was good to hear from various stakeholders, including regulatory agencies, on how they hope to use the new information provided by toxicogenomics," said Eaton.

Policies and recommendations on the use of toxicogenomics by government agencies are emerging as urgent needs at this stage of the field's development. These needs were tagged at an earlier workshop on the use of genomics in toxicology and epidemiology, held at the International Council of Chemical Associations meeting in March 2001, said Carol J. Henry, vice president for science and research at the American Chemistry Council. The full summary of that workshop appears in the October 2002 issue of *EHP* (110:1047–1050 [2002]). The U.S. Environmental Protection Agency recently released its "Interim Policy on Genomics," which states that "while genomics data may be considered in decision-making at this time, these data alone are insufficient as a basis for decisions." However, the policy continues, "EPA believes that genomics will ultimately improve the quality of information used in the risk assessment process."

The committee, which will next meet in February 2003, plans to form subcommittees to investigate topics including the impact of using toxicogenomics data in risk assessments. More information on the committee's activities is available online at **http://dels.nas.edu/emergingissues.**
–Tina Adler

Matt Turner/EHP

txgnet *EHP Toxicogenomics*

Toxicogenomics focuses on determining the role that genes play in biological responses to environmental toxicants and stressors. This new scientific discipline has sprung from the dramatic progress being made in numerous genome sequencing projects and the advances taking place in genomic technologies for expression profiling of mRNAs and proteins.

With this inaugural issue of the new quarterly *EHP Toxicogenomics* comes the launch of a complementary website, located at **http://ehp.niehs.nih.gov/txg/**, which brings together vital information being generated in this emerging field. In addition to housing the online version of *EHP Toxicogenomics*, the site also features additional scientific resources, such as data sets and supplementary materials, to provide the essential information needed to keep up to date in this fast-evolving field.

EHP Toxicogenomics includes the latest original peer-reviewed research from the related disciplines of toxicogenomics, pharmacogenomics, metabolomics, proteomics, and translational aspects of genomic research, as well as commentaries and news articles. The Call for Papers link on the homepage allows visitors to access *EHP*'s instructions for authors and provides an address for electronic submissions.

Readers can also retrieve articles relating to toxicogenomics published in the monthly edition of *EHP* through the Other *EHP* Articles on Toxicogenomics link. This link leads to a list of editorials and news articles published over the past two years, and will be updated as new articles are published.

EHP Toxicogenomics editor Kenneth S. Ramos, a molecular toxicologist at Texas A&M University, is introduced on the site, as are the seven associate editors, leading scientists in the fields of computational biology, informatics, genomics, molecular medicine, and proteomics. The site also introduces the 21-member editorial review board, which will oversee the journal's peer review process.

With its expertise in closely related areas such as toxicology, exposure assessment, and microarray technology, the NIEHS has been at the forefront of toxicogenomics. June 2000 saw the launch of the National Center for Toxicogenomics, which will oversee work at cooperating research institutions through a grants consortium program [see "National Center for Toxicogenomics: An Introduction," p. A18 this issue]. Links to the websites for both the center and the grants consortium are posted on the *EHP Toxicogenomics* homepage.

Visitors who wish to receive a complimentary inaugural year subscription to the print version of *EHP Toxicogenomics* can follow the Free Introductory Subscription link on the homepage.
–Erin E. Dooley

BIOINFORMATICS

HapMap: Building a Database with Blocks

The next time you encounter someone of a different race or sex, ponder this: you and that person are, genetically speaking, 99.9% identical. All the variation that defines you as an individual—including any inherited illnesses or heightened sensitivity to pollution—is found in just 0.1% of your DNA. The rest of your DNA is common to all humans and derives from a single ancestral population, probably from Africa, experts say. On 29 October 2002, an international consortium of 15 publicly and privately funded research groups launched a $100 million effort to study how that 0.1% of variation is distributed across the human genome.

Most of the variations are in the form of simple DNA mutations called single nucleotide polymorphisms (SNPs). Certain groups of SNPs are inherited together in blocks called haplotypes. The Haplotype Mapping (HapMap) Project, as the effort is known, will map the architecture of these blocks on DNA.

The project's fundamental premise is that haplotype blocks can be marked with a few identifying SNPs called tags. Scientists using the HapMap database to study a particular disease will rely on these tags to access all the haplotype variations in a genomic area of interest. In effect, the HapMap splits the genome into useful chunks, or "neighborhoods," of genetic variability. The tags are merely guideposts for the carefully elucidated variability that resides within each haplotype block. So a researcher who sees that a particular SNP is involved in a toxic mechanism will also know what other possibly relevant SNPs are in the vicinity. This shortcut obviates the need to screen more SNPs than necessary without sacrificing critical genomic information.

Previous research has confirmed that haplotype blocks from different ethnic groups are nearly identical, which suggests the HapMap will be broadly applicable to the entire human population, says Mark Daly, a computational biologist at the Whitehead Institute, a genomics research group based in Cambridge, Massachusetts. Daly is leading the bioinformatics component of the project.

To control for ethnic diversity, the map will be constructed using DNA from 200–400 native Africans, Asians, and Europeans, in addition to U.S. residents of European ancestry. Daly says the project will advance the understanding of the root cause of inherited diseases such as cancer and diabetes.

The HapMap will also provide a useful tool to study the effect of gene variations on toxicity susceptibility, Daly says. By comparing haplotypes among both sick and healthy people, scientists will pinpoint variations that increase susceptibility to environmental exposures. "In many cases, the environmental contribution is more important than genetics to the disease process," Daly says. "But until we get a handle on both the [genetic and environmental factors], we won't really understand disease. This project represents an effort to accelerate the genetic portion of that understanding."

The HapMap will be housed at Cold Spring Harbor Laboratory in New York. According to Daly, data that have been checked for quality control will be made freely available to the public throughout the mapping process. The entire HapMap is expected to be completed within three years.

–Charles W. Schmidt

Code of many colors. DNA from around the globe will help clarify how variation is distributed across the human genome.

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