# Genes and Environment: A SNPshot

Have you ever heard someone try to dispel concern about their smoking by describing elderly relatives who were lifelong smokers? This gambit usually fails, but there actually is something to the excuse. Increasingly, researchers are uncovering the extent to which genes control susceptibility and vulnerability to environmental health hazards, including cigarette smoke, toxic chemicals, alcohol, and more.

To understand why individuals react differently to the same chemicals requires analysis of differences in their genetic makeup. Single-nucleotide polymorphisms (SNPs), which are common one-letter variations in the DNA sequence occurring in at least 1% of the population (anything rarer is a mutation), are the simplest differences to examine on the wide scale, agreed participants at "Genetic Variation and Gene–Environment Interaction in Human Health and Disease," a seminar held 16 April 2003 at the NIH campus in Bethesda, Maryland. The NIEHS, the National Human Genome Research Institute, and the National Institute on Alcohol Abuse and Alcoholism sponsored the seminar, which was part of an NIH conference marking the 50th anniversary of the discovery of the chemical structure of DNA and the recently completed sequencing of the human genome.

## The Search for SNPs

Studying cancer-causing agents in the environment is difficult due to challenges such as the near-impossibility of determining a person's diet or occupational exposures over many years. SNPs, on the other hand, are abundant and traceable, said seminar participant Martyn Smith, a toxicologist at the University of California, Berkeley, School of Public Health and director of the university's NIEHS-sponsored Environmental Health Sciences Center. Functional SNPs are an intriguing topic of study, Smith said, because they are common and are likely to explain the majority of people's susceptibility.

A typical gene of 30,000 base pairs has 150 SNPs in it, noted Deborah Nickerson, a geneticist at the University of Washington in Seattle. Most SNPs are "silent," and thus have little or no effect on human health. But some greatly influence disease risk. SNPs near one another in the genome can be related, forming blocks in a gene and potentially making it easier to trace susceptibilities in the general population. The *BRCA1* breast cancer gene has just such blocks, Nickerson discovered only days prior to the seminar. Discovering such blocks will make it easier for researchers to understand the role of *BRCA1* in breast cancer development in women who don't have rare inherited mutations in this gene, she said.

Smith and collaborators in Leeds, England, are looking for SNPs that make humans more susceptible to leukemia. Most cases of leukemia can't be explained by environmental exposures or heredity alone, and instead arise from gene–environment interactions, he told seminar participants.

In the early 1990s, scientists discovered that a SNP on the *NQO1* gene reduces the activity of the enzyme it regulates and increases the risk of benzene-induced leukemia. This finding led Smith and colleagues to propose that chemicals that cause oxidative stress and that are detoxified by *NQO1*, such as benzene and flavonoids in high doses, may increase the risk of myeloid leukemia. They have also suggested that low folate intake increases the risk of lymphocytic leukemia in both adults and children, whereas certain SNPs in folate-metabolizing genes decrease the risk. Smith and his colleagues are also looking at SNPs in genes involved in apoptosis and DNA repair in relation to leukemia risk, and are further expanding their research to the study of lymphoma.

Clement Furlong, a geneticist at the University of Washington in Seattle, reported that some people are more sensitive to insecticides and possibly nerve agents because of genetic variability in the gene that regulates production of the enzyme paraoxonase (PON1). PON1 oxidizes lipids, metabolizes organophosphates, and activates or inactivates medications including statins, glucocorticoids, and antibiotics.

Although children have attained their life-time level of the enzyme by about 15 months of age, PON1 levels and efficiency vary considerably from person to person, Furlong said. He cited research published in the 15 June 1999 issue of *Toxicology and Applied Pharmacology* showing that veterans who suffered from Gulf War syndrome had low PON1 levels. However, studies have shown that injecting purified PON1 into mice without the *PON1* gene protects them against chemical assault. Furlong is confident that injections of engineered recombinant PON1 will someday be similarly used to detoxify humans who have been exposed to organophosphates.

## Major Advances in the Field

The hunt for genetic susceptibility to many chemicals and diseases has been made possible by major advances in molecular methods that enable researchers to rapidly sequence whole genomes and associate SNPs with specific diseases. "We spent many, many years uncovering about a dozen polymorphisms in the [*PON1*] gene," Furlong said at a press conference following the seminar. But thanks to revolutionary new technologies, in just the last couple of months, Nickerson and her group have identified more than 150 additional *PON1* polymorphisms. In a matter of days, she sequenced the entire *PON1* gene from four individuals suspected of having sequence variations and then identified those variations, Furlong said, revealing one coding-region SNP that affects the efficiency of detoxication of some chemicals and other noncoding-region SNPs that affect PON1 plasma levels.

Nickerson's group in Seattle is part of the NIEHS Environmental Genome Project (**http://www.niehs.nih.gov/envgenom/home.htm**), a national effort to identify genetic variations among individuals that make them more vulnerable to environmental agents. The Seattle researchers are resequencing 554 environmentally responsive genes taken from 450 individuals and creating a database of SNPs in those genes. As of April 2003, they had resequenced 214 of the genes.

At the postseminar press conference, NIEHS director Kenneth Olden announced

the completion of the first phase of the Environmental Genome Project. Research in this phase focused on finding common sequence variations in human genes involved in DNA repair and cell cycle pathways. Future goals involve studying apoptosis, homeostasis, and drug-metabolizing genes, all of which are thought to play a role in vulnerability to environmental exposure. **–Tina Adler**

# 100th *Research Brief* Published

The NIEHS/U.S. Environmental Protection Agency Superfund Basic Research Program (SBRP) reached an important milestone in April 2003 with the release of its 100th *Research Brief*. Since their inception in 1997, these publications have been a key component of the SBRP's efforts to disseminate its latest findings and demonstrate how environmental health science and remediation research contribute to reducing human health risk and improving decision making for hazardous site cleanups.

Each *Research Brief* summarizes significant peer-reviewed findings from SBRP-funded research, translating the science into language appropriate for diverse audiences. The 100th issue provides an historical overview of the briefs and categorizes the first 99 issues by research area.

The briefs are distributed via e-mail on the first Wednesday of each month to more than 2,600 scientists in 27 countries. Subscribers include federal and state government employees, academicians, remediation and engineering professionals, and advocacy groups.

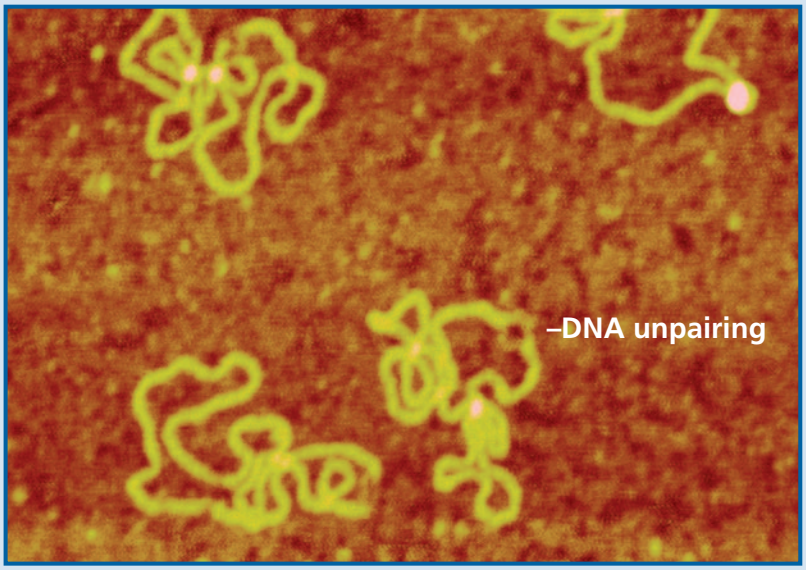
Throughout the year, SBRP staff review materials submitted by the program's 19 grantee universities to select topics for inclusion in the *Research Briefs*. The staff also regularly search the scientific literature to identify late-breaking advances of interest to the briefs' readership. SBRP staff envision using the *Research Briefs* as a model for other communication efforts, possibly developing briefs in a format specifically for lay audiences.

The *Research Briefs* as well as subscription information are available at **http://www-apps.niehs.nih.gov/sbrp/RB2000/RB.cfm**. Up-to-date listings by research area are located at **http://www-apps.niehs.nih.gov/sbrp/RB2000/rbcategories.htm**. **–Erin E. Dooley**

Left to right: SBRP; Richard R. Sinden, Yuri Lyubchenko

## Headliners | Genetics

NIEHS-Supported Research



–DNA unpairing

### A New Target of DNA Instability: Repeat Expansions

Potaman VN, Bissler JJ, Hashem VI, Oussatcheva EA, Lu L, Shlyakhtenko LS, et al. 2003. Unpaired structures in SCA10 $(ATTCT)_n$•$(AGAAT)_n$ repeats. J Mol Biol 326:1095–1111.

Genes in normal individuals contain short lengths of trinucleotide repeats in which a combination of nucleotides, the building blocks of DNA, are repeated several times. Such "repeats" usually repeat themselves fewer than 30 times, but research has identified 18 human genetic diseases associated with expansion of the number of these repeats, sometimes into the thousands. Fragile X syndrome, myotonic dystrophy, and Huntington disease are a few of these devastating diseases, which become increasingly severe and have earlier onsets in successive generations, a process known as anticipation. Scientists have theorized that if the cause of the repeat expansion can be discovered, there is hope for preventing it from occurring.

NIEHS grantee Richard R. Sinden and colleagues at Texas A&M University recently discovered a unique repeat associated with spinocerebellar ataxia type 10 (SCA10), a disease characterized by seizures and lack of muscle control. The repeat is made up of 10 nucleotides in the sequence $(ATTCT)_n$•$(AGAAT)_n$. Normally this sequence repeats 10–22 times. People with SCA10 may have as many as 4,500 copies of this sequence.

The researchers studied the structural properties of this repeat cloned in circular plasmids. The $(ATTCT)_n$•$(AGAAT)_n$ sequence is unique among expanding repeat sequences in that it has a very high content of A+T base pairs. The high A+T content is a feature of DNA sequences that form unpaired structures known as DNA unwinding elements, or base unpairing regions. The Texas researchers demonstrated that the $(ATTCT)_n$•$(AGAAT)_n$ repeat does indeed unpair, leaving the DNA strands accessible for interaction with other molecules and thereby acting as a false site of DNA replication. The researchers hypothesize that if $(ATTCT)_n$•$(AGAAT)_n$ and other DNA repeats act as strong origins of replication, "then anomalous and fractious replication may lead to amplification and expansion."

Although it remains to be seen if repeats associated with other expansion-related diseases support incorrect DNA replication initiation, this finding gives researchers a new target on which to focus, and may lead to further discoveries on how to prevent and treat genetic disease. **–Jerry Phelps**