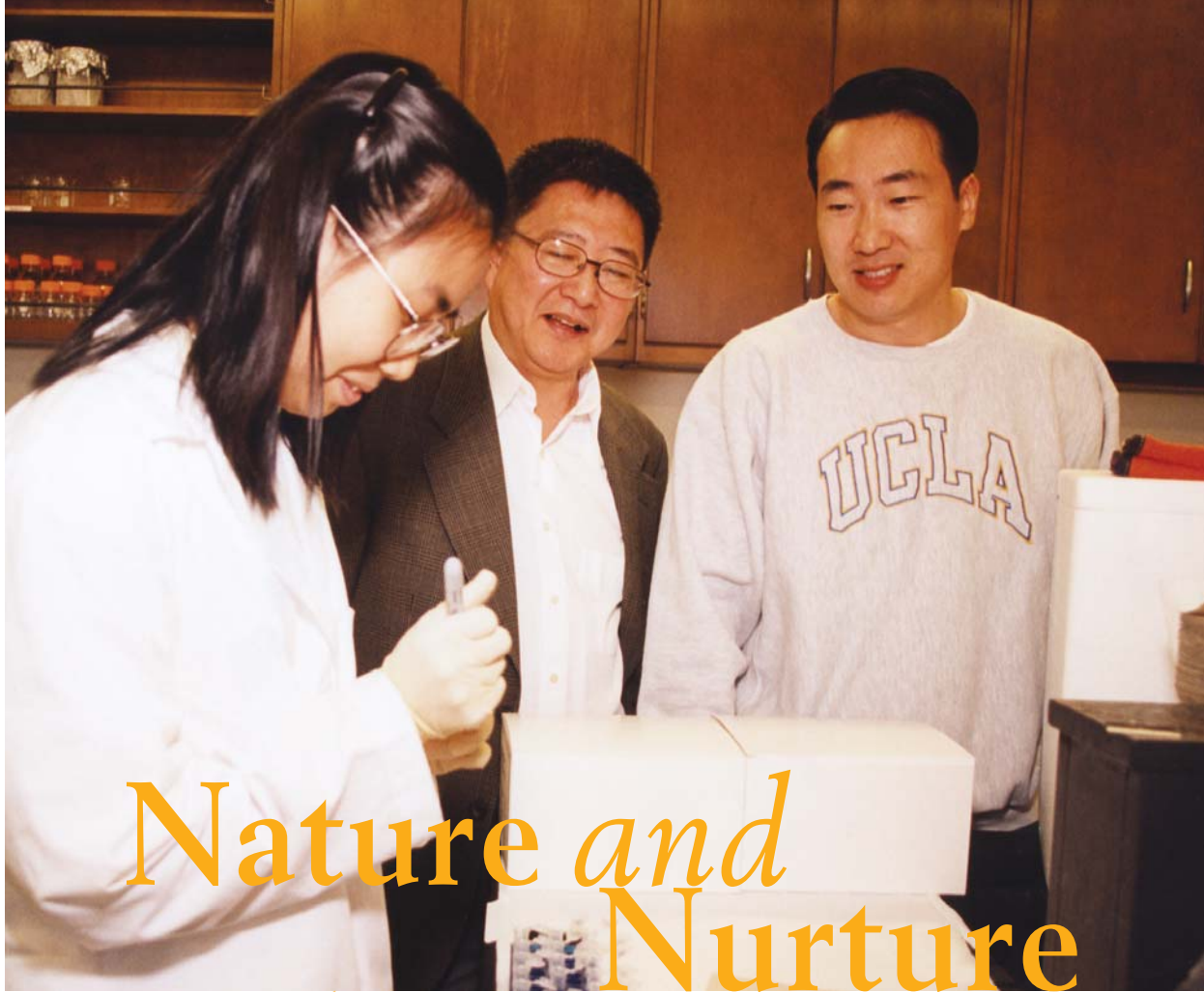


RESEARCHERS
IN THE EMER-
GING FIELD OF
ENVIRONMENTAL
GENOMICS ARE
IDENTIFYING
WHO'S AT RISK
AND WHAT
THEY CAN DO
ABOUT IT.



Nature and Nurture

In Disease, the Gene-Environment Interaction Matters Most

Dr. Zuo-Feng Zhang (center), a molecular epidemiologist who studies cancer, is co-director of the new Center for Environmental Genomics, based in the School of Public Health and Jonsson Cancer Center.

Discoveries of inherited genes that make individuals dramatically more likely to develop certain types of cancer, cardiovascular disease or neurodegenerative disorders have received much fanfare in recent years. But often overshadowed in the coverage of these findings is the important fact that the implicated genes are extremely rare.

“We’ve seen big headlines when molecular geneticists have been able to clone single genes and show that a certain inherited mutation is responsible for a disease,” says Dr. Beate Ritz, associate professor of epidemiology at the UCLA School of Public Health. “When this is reported, a lot of people think we’ve found ‘the breast cancer gene,’ or ‘the heart disease gene,’ not realizing that these are highly unusual cases. In the vast majority of the population, genes play a much more minor role in these diseases.”

Disease was once thought to have one of two causes: environmental or genetic. The scientific revolution fueled by modern molecular biology and the sequencing of the human genome has taught us that it’s rarely that simple; much more typically, it’s an interaction between the two. This has spawned a new scientific field, environmental genomics, of considerable public health importance. Earlier this year the UCLA Center for Environmental Genomics

was established within the School of Public Health in collaboration with the Jonsson Cancer Center, with the goal of bringing together leading experts from a variety of fields – cancer, environmental health, epidemiology, biostatistics, human genetics, pathology and pharmacology, to name a few – to investigate the molecular mechanisms by which environmental agents such as air pollutants and radiation interact with genetic predisposing factors to cause disease. A better understanding of these processes would pave the way not only for targeted drug therapies, but also for targeted public health efforts to reduce environmental exposures in high-risk populations.

“There are high-risk genes in which, for people with a certain mutation, the lifetime chance of getting a particular disease is 80 or 90 percent,” says Dr. Zuo-Feng Zhang, professor of epidemiology and co-director of the new center. But, Zhang notes, these types of genes – perhaps the most high-profile of which are BRCA-1 and BRCA-2 for inherited breast cancer – have a low prevalence in the general population, usually affecting less than 1 percent.

By contrast, Zhang explains, when there are mutations in “low-risk genes,” such as those that detoxify carcinogens and activate DNA repair mechanisms, the relative risk increases on a much smaller scale – but the prevalence of these genes in the population is often quite high, and they are much more highly dependent on interactions with environmental exposures for disease to result. For example, GSTM-1, a gene that can detoxify the tobacco-related carcinogen, is dysfunctional in close to half of the U.S. white population. “If you’re a smoker and you don’t have the function of this gene, your cancer risk is much higher,” says Zhang, a molecular epidemiologist who studies cancer.

“What genetics has done for the last 100 years is identify the single gene for an inherited disease, where one change is usually sufficient,” says Ritz. “These are usually young-onset and extremely rare diseases – not the ones that public health has focused on. And because they are so rare, genetics alone has worked – you could analyze families, then with the molecular tools that came along you could find the one gene that this family had.”

The far more common low-risk genes increase one’s propensity to develop a certain disease, but only in conjunction with other genes and with particular environmental factors – from air pollutants or occupational exposures to tobacco smoke, alcohol, or a certain diet. “These are the complex dis-

eases, which are much more widespread, much more of a public health concern,” Ritz says. “And I am certain we’ll never find the ‘one gene’ for those.”

The challenge facing researchers in environmental genomics is to determine why people with a gene variant that increases their likelihood for getting a certain disease wind up with the disease, while others with the same mutation do not. Are the different outcomes related to other genes, or are environmental factors at play? Toxins are being introduced into the environment that have never been encountered in 100,000 years of human genetic development – to what effect? Which genetic make-ups are able to detoxify these potential carcinogens, and which are not?



Such complex questions could never have been answered prior to the advent of the Human Genome Project, the ambitious, recently completed effort to determine the DNA sequence of the more than 30,000 human genes; and technologies subsequently developed to simultaneously view the expression of large numbers of genes or proteins – the workhorses of cells. The experiments facilitated by these technologies can be illuminating. For example, researchers can view how all genes are expressed in a normal state, then see how the cells they produce respond to a particular environmental exposure as a way to understand differential genetic responses. “What we’re doing with these methods

Dr. Robert Schiestl, director of the Center for Environmental Genomics, notes that a molecular understanding of gene-environment interactions can facilitate studies attempting to prevent interactions that lead to disease.

is going back to descriptive biology,” says Dr. Robert H. Schiestl, professor of pathology, environmental health sciences and radiation oncology and director of the UCLA Center for Environmental Genomics. “In the early days of biology, organisms were described; now, we describe the molecular mechanisms of organisms after exposure to environmental agents. Once we know those mechanisms, we can do studies to try to interfere with the negative effects through nutritional interventions or chemopreventive therapies.” (For more on Schiestl’s work, see page 8.)

Researchers at Schiestl’s center use a variety of approaches and bring different types of expertise to the problems the center is tackling. The Southern California Particle Center and Supersite, also based in the School of Public Health, is involved in studies to identify factors that make certain people more vulnerable to the biological effects of air pollutants. Pesticides, another issue of particular importance in agriculture-rich California, have been catalogued and are now being investigated by researchers, including Ritz, for their potential role in neurological disorders such as Parkinson’s disease. Ritz is working with 50 “candidate” genes that have been described for Parkinson’s, and is examining the impact of pesticides, air pollution, diet and smoking on these genes in residents of California’s Central Valley. Zhang is involved in identifying molecular genetic susceptibility markers that might interact

with environmental exposures such as air pollution to increase the risk of diseases such as lung, oral, and esophageal cancers; and in intervention studies weighing the effects of targeted chemotherapies on such markers. Other center researchers are studying the interaction between genes and occupational exposures, including beryllium and radiation, to which certain people appear to be more sensitive than others.

There is no shortage of questions to pursue; indeed, one of the major challenges in the field is knowing where to start. “The Human Genome Project is complete,” says Zhang, “but we know only a very few disease-related genes. With more than 30,000 genes, we have a long way to go to identify their function and role in the disease-development process.” There are two main approaches researchers take, Ritz notes. Some investigate hypotheses about specific “candidate genes,” while others use statistical tools in an effort to find genetic differences, or polymorphisms, that correlate with increased disease risk. Those methods remain crude, but researchers hope experts in the emerging field of bioinformatics will help to develop new techniques that will make such an approach less of a needle-in-a-haystack search.

When studies find that some in the population have genes that make them susceptible to particular environmental influences, what then? There are

Leadership Gift Establishes Ann Fitzpatrick Alper Program to Conduct Further Research on Environmental Causes of Cancer

A leadership gift by Art Alper in memory of his wife, Ann Fitzpatrick Alper, has helped to establish a \$1 million research effort at UCLA’s School of Public Health and Jonsson Cancer Center to investigate the environmental causes of cancer.

The Ann Fitzpatrick Alper Program in Environmental Genomics, part of the Center for Environmental Genomics, is headed by Dr. Robert H. Schiestl, professor of pathology, environmental health sciences and radiation oncology and the center’s director. The program is exploring such issues as the risk of lung cancer in non-smokers, the effects of air pollution particles on human cells, prostate cancer and pesticide exposure, a possible link between boron and prostate cancer, and hypersensitivity to radiation.

The gift, which is being augmented with a donation from the Kenneth Jonsson Family Foundation and UCLA’s Jonsson Cancer Center Foundation, was made in memory of Ann Fitzpatrick Alper, who died last year from complications of lung cancer. Art Alper met his wife at UCLA, where both were students, and they married in 1955. A former teacher turned author and marriage and family counselor – and an environmental activist who drove a hybrid car – Ann Fitzpatrick Alper developed the disease despite not having smoked since she was a college student in the early 1950s, making smoking alone an unlikely cause of her cancer.

social, economic and ethical concerns that are still being debated surrounding the issue of genetic testing and how to deal with the results. “Much of the science is still in its infancy, and in most cases it’s premature to make recommendations,” says Ritz. On the other hand, drug companies are rightfully moving in the direction of screening patients to determine which ones might be prone to suffering adverse effects from a particular compound.

As the environmental genomics field advances, few doubt that there will be revolutionary effects on both medicine and public health. “It now costs about \$500,000 to have your entire genome sequenced,” says Schiestl. “In 10 years, it might be down to \$1,000, because of the advancing technology. That means that many people will have a complete profile of their genetic factors. It means medicine can be individualized – we’ll know which drugs are better for which patients, for example. But it also has strong public health implications. People can be brought up to avoid certain exposures that would be particularly harmful to them.”

“The knowledge we get from molecular genetic research will enable us to conduct risk assessments in the general population of people without disease,” agrees Zhang. “This is very important in public health, because if people know they are at risk of getting a certain cancer, for instance, they might be more eager to take preventive measures.” Moreover, he adds, this knowledge can be used to make public health interventions more cost-effective. Smoking cessation programs could target smokers with genomes that make them particularly susceptible to tobacco-related diseases. The identification of genetic changes foreshadowing the onset of disease will reduce the cost of chemoprevention studies by providing earlier results. “These are all public health impacts,” says Zhang. “Environmental genomics will help us to prevent diseases rather than waiting until they occur.”



Dr. Beate Ritz is studying the impact of pesticides, air pollution, diet and smoking on 50 previously described Parkinson's disease “candidate” genes in residents of California's Central Valley.

Researchers in the program are looking for subtle variations in DNA that predispose some individuals to developing cancer after contact with environmental pollutants, and to shed new light on how pollutants interact with genetics to cause a variety of cancers. About 95 percent of the nearly 2.5 million Americans who will be diagnosed with cancer this year have no known genetic predisposition to the disease. It's believed that these people develop malignancies due to complex interactions between their genes and their environment. The goal for scientists looking to prevent cancer is to discover what specific combination of an individual's genetics and factors such as diet, air pollution, exposure to tobacco, and sensitivity to sunlight result in disease.

“The key to the future is to understand why certain people develop certain cancers,” says Dr. Linda Rosenstock, dean of the UCLA School of Public Health. “Through this kind of research, merging environmental factors and molecular genetics, we may be able to find the answers.”

“This program promises to be a unique effort that we hope will unravel many of the mysteries surrounding the interaction of genes and the environment in the development of cancer,” adds Dr. Judith C. Gasson, director of UCLA's Jonsson Cancer Center. “This work will reflect Ann's passion for a safer environment along with her hope that future generations will not suffer the devastation of cancer.”

Additional gifts for the Ann Fitzpatrick Alper Program in Environmental Genomics may be sent to UCLA's Jonsson Cancer Center Foundation at 8-950 Factor Building, Box 951780, Los Angeles, CA, 90095-1780.

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