Winter 2004

HEALTH EFFECTS REVIEW

Gene-Environment Interactions

Introduction

Before the human genome was sequenced, one apparent promise was that deeper knowledge about our genetic make-up could help solve persistent mysteries of morbidity and mortality. While genetics has brought insights into the biological basis of some single-gene disorders, it has not identified the causes of common chronic diseases. What we have learned, however, is that unlike single-gene disorders, most chronic conditions, including heart disease, cancer, and psychiatric illnesses, do not have a simple genetic basis. Instead, they result from the complex interactions of multiple genes with environmental and so-called lifestyle factors, including behavior [1, 2].

Because of subtle differences in our genetic make-up, individuals within a population can respond very differently to specific environmental exposures. These genetic variations modify the effect of the exposure, and they can affect a range of biological processes. The gene-environment interactions mean that while some individuals face a lower risk of developing a disease as a consequence of an exposure, others are more susceptible. This report looks at the biological significance of gene-environment interactions and their implications for society and public health.

Toxicity and Susceptibility

Research into genetic variation and environmental exposures grew out of the study of how genetic variation influences individuals' responses to drugs. Because of genetic differences, a standard dose that may be effective in one person may be ineffective or even toxic in another. Individuals similarly exhibit a wide variation in how they respond to environmental exposures. Susceptibility can also be related to environmental and lifestyle factors, including nutrition, gender, age, and a person's history of infections and exposures [3].

When variations in the human genome-single base changes, insertions, or deletions-occur in 1 percent or more of the population, they are called polymorphisms. Polymorphisms have been found in most of the genes that can influence the outcome of an exposure to a xenobiotic, or foreign substance. The biological processes that can be affected by genetic variation include the uptake, biotransformation (metabolism), and excretion of xenobiotics; cell cycle control; cell signaling; DNA repair; and cell division and cell death [2]. Polymorphisms can play important roles in modifying the effects of environmental exposures-that is, in gene-environment interactions. Because they are inherited and persist within a population, the impact of polymorphisms at the population level can be considerable.

Biotransformation can serve to either activate or detoxify xenobiotics, and it is described as occurring in two phases. During Phase I, enzymes add functional groups such as -OH and -SH to foreign substances that have been absorbed by the body. These reactions are catalyzed mainly by the Cytochrome P450 enzymes, although other oxidases, reductases, and dehydrogenases can also be involved. During Phase II, enzymes including glutathione S-transferase and N-acetyltransferase detoxify the reactive intermediates, making them more water soluble and thereby facilitating their elimination from the body. The enzymes that catalyze Phase I and Phase II reactions, while found mainly in the liver, are also contained in most tissues in the body. Drug transporters such as P-glycoprotein also play important roles, sometimes described as Phase III biotransformation, in facilitating the excretion of foreign substances into the bile or blood [3].

Polymorphisms in Phase I and Phase II enzymes can have a range of effects on the enzymes' ability to metabolize foreign substances. The mutations may cause duplications of genes, bringing higher levels of enzymes; deletions or partial deletions of genes, which would eliminate their proteins; and splice site variants, which result in proteins that have been truncated or otherwise altered. However, about 90 percent of all mutations, called single nucleotide polymorphisms (SNPs), involve a change to a single base pair that causes a substitution in the amino acids that are produced [3]. In 1997, the U.S. National Institute of Environmental Health Sciences launched the Environmental Genome Project, a national effort to identify polymorphisms in the human genome and study their health effects [2, 4]. By 2003, nearly 1.8 million SNPs had been identified [5]. By 2004, more than 20,000 SNPs had been discovered in 217 genes involved in cell cycle control and DNA repair [2].

For environmental exposures, researchers believe that polymorphisms alter the dose-response relationship [3]. While some individuals metabolize compounds slowly, others metabolize them more quickly. Either situation can mean greater susceptibili-

ty to an exposure, as is the case with the biotransformation of isoniazid, an anti-tubercular drug. In addition, during biotransformation, Phase I and Phase II enzymes need to be balanced so that xenobiotics can be efficiently detoxified and eliminated. An imbalance between the speed of Phase I and Phase II can result in high levels of partially metabolized, harmful substances [3].

William W. Au and colleagues have studied the roles played by environmental factors and polymorphisms in chemical metabolizing genes in the development of cervical cancer [6]. Cervical cancer involves a series of stages in which benign lesions may progress to malignant carcinoma. A major risk factor for cervical cancer is high-risk human papilloma virus (HPV), which is found in more than 90 percent of cervical cancers. However, the majority of women with HPV do not develop cervical cancer [7]. Environmental exposures including cigarette smoke are also implicated in the development of cervical cancer.

In comparing populations in Venezuela and the United States, the researchers found that environmental and genetic susceptibility factors contributed to cervical cancer in significantly different ways. HPV was associated with cervical cancer in both countries, although less so in Venezuela, where multiple sex partners and early sexual activities were significant risk factors. In the United States exposure to cigarette smoke was a significant risk factor, and researchers found that an inherited polymorphism in a chemical metabolizing gene, GSTM1, for the deletion mutation and absence of the enzyme, was significantly associated with cervical cancer (OR = 3.4, 95% CI = 1.0-11.8). In HPV-infected cells, the expression of viral E6 and E7 proteins causes specific degradation of the cellular p53 and Rb proteins, which are involved in tumor suppression. Smokers who had inherited susceptibility through their metabolizing genes were likely to have increased DNA damage and chromosome aberrations. The researchers hypothesized that in HPV-infected individuals with this polymorphism, cells would continue to accumulate chromosome aberrations, which could favor the progression of benign lesions to malignancy [6].

Genetic Variation and Lead

The characterization of a polymorphism believed to make individuals more susceptible to lead exposure gives an example of how research into the gene-environment interaction can be useful for understanding the effects of environmental exposures. Compared with adults, children face an increased risk of environmental exposures, and because their brain and central nervous system are still developing, they are particularly susceptible to the neurologic effects of lead. Children's blood lead levels vary by race, income, environmental exposure, and other factors. Biologic differences that are not yet well understood also may account for some of the variation. Lead absorption, for example, varies with nutritional deficiencies and genetic factors that influence mineral metabolism [8].

A polymorphism of ALAD, a protein that is the second enzyme on the biosynthesis pathways of heme, has been suggested as a modifier of the toxicity of lead. Studies have shown that environmentally exposed children and also workers with occupational lead exposures who have either the ALAD 1-2 or ALAD 2-2 genotype had significantly higher blood lead levels than individuals with the wild-type ALAD 1-1 [9, 10]. The ALAD-2 genotype is found in 11 to 20 percent of the U.S. white population [9]. The implication is that ALAD-2 binds lead more effectively than ALAD-1. Individuals with ALAD1-2 and ALAD 2-2 might have higher concentrations of blood lead and total body burden of lead, and therefore they might exhibit signs of low-level exposure [9].

Others studies have evaluated the association between blood lead and a vitamin D receptor (VDR) gene [8]. Lead competes for absorption and protein-binding sites with minerals such as calcium, and when calcium levels in children are reduced, cellular lead uptake and therefore blood levels increase. Calcium metabolism is partly regulated by the vitamin D endocrine system and the VDR. Studies suggest that a VDR-Fok1 polymorphism appears to be associated with increased bone mineral density and an increased in calcium absorption in children.

In a study of 275 two-year-old children in New York State, Haynes et al looked at the relationship between levels of lead in the dust on the floors of the children's homes and a polymorphism in the VDR gene, which appears to modify blood lead concentrations. Children who are two and under are most susceptible to lead absorption and also to lead exposure, and floor dust is the major source of exposure for that age group [8].

The researchers hypothesized that, after they adjusted for differences in lead exposure, children who were homozygous for the F allele-which is a marker for increased calcium absorption-would have higher blood lead levels than children who were either heterozygous for the F allele or homozygous for the f allele. The study results suggest that during the first two years of life VDR-Fok1 may modify the relationship of lead exposure and blood lead levels. As the levels of floor dust lead increased, children homozygous for the F allele had a greater blood lead level increase, presumably from increased absorption and retention of lead. The VDR-Fok1 polymorphism was associated with increased blood lead levels in this study and it appears to be an effect modifier of the relationship of floor dust lead and concentrations of lead in the blood [8].

Implications

The application of genetic technologies to toxicology and epidemiology and the focus on gene-environment interactions raises a number of questions about how the information will be used [11, 12].

The identification of susceptible individuals and groups within a society could lead in several different directions. Understanding the levels of exposure that pose health risks could improve regulation of environmental exposures by, for example, protecting susceptible individuals. Currently, some regulations are based on such inadequate information that they are either unnecessary or not protective enough. Information about environmental behavioral risk factors could also be useful in developing specific public health interventions. The study of cervical cancer in Venezuela and the United States showed that the two populations face different risk factors and therefore would benefit from different interventions for reducing cervical cancer [6].

However, past experience with genetic information shows that its misuse can lead to discrimination by, for example, employers and insurance companies. The identification of susceptible individuals and groups could also mean discrimination against them and their exclusion from workplaces where they might face exposures to which they are sensitive [2, 13].

In general, the use of DNA samples taken from study subjects and patients raises a number of concerns about how the samples will be used and who will have access to their genetic information. Roche and Annas [11] argue for "genetic exceptionalism," on the basis that genetic information is "uniquely private and sensitive" and deserves to be treated differently than other medical information. Their claim is that DNA contains information about not just individuals' medical history and their current health status, but also about the future health risks they may face. It contains information about their relatives as well. Although genetic information is not deterministic-in part because of gene-environment interactions, in fact-it still is uniquely private. It typically is taken more seriously than other medical information, such as blood pressure and cholesterol levels, that also could predict future risks. Access to this information can also have greater emotional and psychological consequences for individuals [11].

Roche and Annas further argue that current medical confidentiality laws offer insufficient protection for genetic information, and that we need separate rules to regulate the collection, analysis, storage, and release of DNA samples [11]. "[I]n the absence of authorization no one should know more about an individual's genetic make-up than that individuals chooses to know themselves, and that an individual should also know who else knows (or will know) about their private genetic information" [11].

References cited:

1. Chakravarti A and Little P. 2003. Nature, nurture and human disease. Nature 421: 412-414.

2 Olden K. 2004. Genomics in environmental health research-opportunities and challenges. Toxicology 198: 19-24.

3. Kelada SN, Eaton DL, Wang SS, Rothman NR, Khoury MJ. 2003 The role of genetic polymorphisms in environmental health. Environ. Health Perspect. 111: 1055-1064.

4. Pesch B, Bruning T, Frentzel-Beyme R, Johnen G, Harth V, Hoffman W, Ko Y, Ranft U, Traugott UG, Thier R, Taeger D, Bolt HM. 2004. Challenges to environmental toxicology and epidemiology: where do we stand and which way do we go? Toxicology Letters 151: 255-265.

5. SNPs Consortium Ltd. 2003. Single Nucleotide Polymorphisms for Biomedical Research. Available: http://snp.cshl.org Accessed 1 June 2005.

6. Au W. 2004. Life style, environmental and genetic susceptibility to cervical cancer. Toxicology 198: 117-120.

7. Au W, Sierra-Torres CH, Tyring SK. 2003. Acquired and genetic susceptibility to cervical cancer. Mutation Research 544: 361-364.

8. Haynes EN, Kalkwarf, HJ, Hornung R, Wenstrup R, Dietrich K, Lanphear BP. 2003. Vitamin D receptor FOK1 polymorphism and blood lead concentration in children. Environmental Health Perspectives 111: 1665-1669.

9. Suk W and Collman GW. Genes and the Environment: their impact on children's health. 1998. Environmental Health Perspectives 106 (Suppl 3): 817-820.

10. Wu M-T, Kelsey K, Schwartz J, Sparrow D, Weiss S, Hu H. 2003. A -Aminolevulinic acid dehydratase (ALAD) polymorphism may modify the relationship of low-level lead exposure to uricemia and renal function: the normative aging study. Environmental Health Perspectives 111: 335-350.

11. Roche PA and Annas GJ. 2001. Protecting genetic privacy. Nature Reviews/Genetics. 2: 392-396.

12. Shostak S. 2003. Locating gene-environment interaction: at the intersections of genetics and public health. Social Science and Medicine 56: 2327-2342.

13. Perera FP. 1997. Environment and cancer: who are susceptible? Science 278: 1068-1073.

Prepared by the Department of Environmental Health, Boston Univeristy School of Public Health under the direction of the International Joint Commission's Health Professionals Task Force. The Health Effects Review is a quarterly publication that summarizes the latest scientific literature on human health effects and environmental pollutants. This does not represent the official position of the International Joint Commission.

Review Coordinator: Verónica Maria Vieira, M.S.
Senior Science Advisor: Dr. David M. Ozonoff

For further information please contact Jim Houston, Secretary, Health Professionals Task Force
E-mail: houstonj@ottawa.ijc.org