The Role of Genetic Polymorphisms in Environmental Health

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Interest is increasing in the role of variations in the human genome (polymorphisms) in modifying the effect of exposures to environmental health hazards (often referred to as gene–environment interaction), which render some individuals or groups in the population more or less likely to develop disease after exposure. This review is intended for an audience of environmental health practitioners and students and is designed to raise awareness about this rapidly growing field of research by presenting established and novel examples of gene–environment interaction that illustrate the major theme of effect modification. Current data gaps are identified and discussed to illustrate limitations of past research and the need for the application of more robust methods in future research projects. Two primary benefits of incorporating genetics into the existing environmental health research framework are illustrated: *a*) the ability to detect different levels of risk within the population, and *b*) greater understanding of etiologic mechanisms. Both offer opportunities for developing new methods of disease prevention. Finally, we describe a basic framework for researchers interested in pursuing health effects research that incorporates genetic polymorphisms. *Key words:* disease susceptibility, environmental health, genetics, polymorphism. *Environ Health Perspect* 111:1055–1064 (2003). doi:10.1289/ehp.6065 available via *http://dx.doi.org/* [Online 24 April 2003]

With the initial completion of the first draft of the human genome sequence (Lander et al. 2001; Venter et al. 2001), interest has dramatically increased in the role of genetics as a determinant of health. Progress in incorporating genetics into public health research has been steady over the last several years, relying mainly on the tools of genetic and molecular epidemiology. Research exploring the role of genetics in determining susceptibility to environmentally induced disease has also grown. The recent abundance of epidemiologic research examining associations between polymorphic genes that code for enzymes involved in xenobiotic biotransformation and disease has on occasion generated interesting findings. However, the approach used in these studies differs substantially from that of traditional environmental health science research. Whereas traditional environmental health sciences seek to understand the effect of exposure of a homogeneous population to some agent, many of the recent genetic and molecular epidemiologic studies have been structured to analyze gene–disease associations, regardless of exposure. In addition, many of the findings have not been replicated in subsequent studies, casting doubt on their validity and leaving the environmental health community with uncertain results with which to proceed.

In this review, we present a general introduction of this evolving area of research on gene–environment interactions for environmental health practitioners and students. We begin by assessing the integration of genetics into environmental health research using the same exposure → disease paradigm traditionally used by environmental health scientists, adding genetics to the existing paradigm as a potential modifier of dose or effect of the initial exposure. Then we discuss selected examples of gene–environment interaction from the literature, classifying them into one of three categories on the basis of evidence from laboratory and epidemiologic data. Finally, we describe the benefits of applying this model to future research efforts, and we offer a basic framework for investigators wishing to pursue this type of endeavor.

Environmental Exposures and Human Genetic Variation

Much of the impetus for this area of research has come from pharmacogenetics, which is concerned primarily with the study of genetic variation in drug efficacy and toxicity. It has been recognized for many decades that individual differences in response to pharmacologic treatment, exhibited as drug toxicity or a lack of therapeutic effect, are often caused by genetic differences that result in altered rates of biotransformation (metabolism). Notable examples include nerve damage among individuals homozygous for some variants of the *N*-acetyltransferase 2 gene ("slow acetylators") given isoniazid as an antituberculosis therapy, hemolytic anemia among glucose 6-phosphate dehydrogenase–deficient patients given aminoquinoline antimalarial drugs, and varied rates of biotransformation of debrisoquine, an antihypertensive drug, due to genetic variation at the *CYP2D6* locus (Weber 1997).

The process of biotransformation—the enzymatic alteration of foreign or xenobiotic compounds—is conventionally divided into two phases. Phase I enzymes introduce new (or modify existing) functional groups (e.g., –OH, –SH, $–NH_3$) to xenobiotics and are catalyzed primarily by the cytochrome P450 enzymes (CYPs), although numerous other oxidases, reductases, and dehydrogenases may also participate. These intermediates are then conjugated with endogenous ligands during phase II, increasing the hydrophilic nature of the compound, facilitating excretion. Enzymes involved in phase II include the *N*-acetyltransferases (NATs), glutathione *S*-transferases (GSTs), UDP glucuronosyltransferases, epoxide hydrolases, and methyltransferases. Phase I and II reactions are catalyzed by enzymes collectively known as xenobiotic metabolism enzymes (XMEs). XMEs are most abundant in the liver, although most tissues have some XME activity. A balance between phase I and II enzymes is generally necessary to promote the efficient detoxification and elimination of xenobiotics, thereby protecting the body from injury caused by exposure (Parkinson 1997). More recently, the role of drug transporters (e.g., P-glycoprotein) in influencing xenobiotic disposition has been highlighted. These transporters facilitate the excretion of xenobiotics into bile or blood (Silverman 2000), and thus form what has been called phase III biotransformation.

Sequence variations (in the past often referred to as mutations) in the genes encoding these enzymes and other proteins result from stochastic genetic processes and may accumulate in the population, depending on selective pressures. If the frequency of a specific sequence variant reaches 1% or more in the population, it is referred to as a polymorphism, and a frequency of 10% or more is typically thought of as common. Alternate versions of genes containing different sequence variants are known as alleles (Harris 1980). The resulting patterns of variation in a

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gene or chromosome form what is known as a haplotype, and a proposal for a nomenclature system to aid in the designation of haplotypes has recently been given (Nebert 2002).

A polymorphism may have no effect (i.e., is "silent"), or it may be considered functional if it results in altered catalytic function, stability, and/or level of expression of the resulting protein. Functional polymorphisms in XMEs include *a*) point mutations in coding regions of genes resulting in amino acid substitutions, which may alter catalytic activity, enzyme stability, and/or substrate specificity; *b*) duplicated or multiduplicated genes, resulting in higher enzyme levels; *c*) completely or partially deleted genes, resulting in no gene product; and *d*) splice site variants that result in truncated or alternatively spliced protein products (Ingelman-Sundberg et al. 1999). Polymorphisms in the regulatory regions of genes may affect the amount of protein expression as well, and mutations in other noncoding regions may affect mRNA stability or mRNA splicing. Most research in genetics in environmental health has focused on these types of functional variants.

About 90% of all DNA sequence variations occur as single nucleotide polymorphisms (SNPs)—that is, single-base-pair substitutions (the first type of functional variant, point mutations) (Brookes 1999). As of March 2002, more than 1,255,000 SNPs have been identified and catalogued as a result of multiple research efforts (SNPs Consortium 2002). There are estimated to be three or four SNPs in the average gene and roughly 120,000 common coding-region SNPs, of which approximately 40% are expected to be functional (Cargill et al. 1999). These estimates do not include variants outside the coding region of genes, and therefore the total number of SNPs affecting protein function can be expected to be greater.

Functional polymorphisms in XMEs can affect the balance of metabolic intermediates produced during biotransformation, and some of these intermediates can bind and induce structural changes in DNA or binding other critical macromolecules, such as sulfhydryl-containing proteins. Similarly, polymorphisms in DNA repair enzymes can affect an individual's ability to repair DNA damage induced by some exposures, such as ultraviolet radiation. The interindividual differences in these and other components of the human genome that relate to environmental exposures have therefore been predicted to modify environmental disease risk (Perera 1997). In addition to polymorphisms, age, sex, hormones, and behavioral factors such as cigarette smoking, alcohol consumption, and nutritional status can influence the expression of phase I and II biotransformation genes (Levy 2000) and thus are also important in understanding environmental disease risk.

One can contrast the role of polymorphisms in XMEs and other components of the environmental response system with variants that are highly penetrant (i.e., that almost invariably lead to disease) but have low population frequency. The interest and focus here are on the role of common sequence variants that alter the effect of exposures that may lead to disease states, or their precursors, and hence are of lower penetrance. Although the individual risk associated with these polymorphisms is often low, they potentially have greater public health relevance (i.e., population-attributable risk) because of their high population frequency (Caporaso and Goldstein 1995).

A comprehensive effort to identify polymorphisms in genes involved in environmentally induced disease, known as the Environmental Genome Project (EGP), was initiated by the National Institute of Environmental Health Sciences (NIEHS) in 1998 (Olden and Wilson 2000). In addition to the identification of polymorphisms, the EGP aims to characterize the function of these polymorphisms and supports epidemiologic studies of gene–environment interactions as well. Like the Human Genome Project, the EGP has devoted substantial resources to the ethical, legal, and social issues related to this project.

Examples of Genetic Effect Modifiers

The working hypothesis typically employed is that for most polymorphisms that alter responses to chemical hazards, the genetic difference does not produce a qualitatively different response, but rather induces a shift in the dose–response relationship. Thus, for example, a polymorphism in an XME that decreases the catalytic efficiency of an enzyme that detoxifies a particular drug might make the standard dose of that drug toxic. This concept extends not only to the acute effects of drugs, but also potentially to chronic response to nondrug chemicals found in the workplace and general environment. Below we describe several examples of gene–environment interaction that illustrate the potential public health implications, as well as difficulties in interpretation, of this type of research.

The relationship between aromatic amine exposure, *N*-acetyltransferase 2 polymorphism (*NAT2*), and bladder cancer is a classic illustration of the principle of dose–effect modification of an environmental exposure by polymorphisms. An initial study by Lower et al. (1979) suggested that the effect of exposure to aromatic amines (bladder cancer), by occupation (e.g., dye industry) or smoking, differed by *NAT2* phenotype. A preponderance of slow acetylators existed among exposed persons, and subsequent studies have confirmed these results (Cartwright et al. 1982; Hanke and Krajewska 1990).

Recently, Marcus and colleagues conducted a meta-analysis of acetylation status and bladder cancer risk case–control studies (Marcus et al. 2000a) and a case–series meta-analysis of 16 studies of the *NAT2*x smoking interaction in bladder cancer (Marcus et al. 2000b). Across all studies, they calculated an odds ratio (OR) of 1.3 [95% confidence interval (CI), 1.0–1.6] for smokers who are slow acetylators compared with smokers who are rapid acetylators, verifying that smokers who are slow acetylators have a modestly increased risk (Marcus et al. 2000b). Limiting the study selection to European studies with large sample sizes (number of cases ≥ 150), the OR was 1.7 (95% CI, 1.2–2.3). Different patterns of tobacco use and tobacco type may account for some of these differences. In addition, using estimates of the prevalence of smoking and *NAT2* genotype, Marcus et al. (2000b) predicted bladder cancer risk for smokers and nonsmokers by acetylator status, designating never-smoker rapid acetylators as the reference category. Nonsmoking slow acetylators were predicted to have no increase in risk (OR = 1.10), ever-smoking rapid acetylators have about two times the risk (OR = 1.95), and ever-smokers who are slow acetylators have about 3-fold higher risk (OR = 3.21). Marcus et al. (2000b) also estimated that the population-attributable risk of the gene–environment interaction was 35% for slow acetylators who had ever smoked and 13% for rapid acetylators who had ever smoked.

In the laboratory setting, complementary experiments can be designed to gain understanding of the biologic basis of the observed effect. This ultimately contributes to the argument of causality. Primary human cell lines, transient and stable transfection assays in cell lines, and transgenic animal models have frequently been used to investigate these questions. With respect to aromatic amines, *NAT2*, and bladder cancer, *in vitro* and *in vivo* studies have demonstrated that polymorphic *N*-acetylation of some aromatic amines can bioactivate these procarcinogens in the bladder (Hein et al. 1993; Mattano et al. 1989; Trinidad et al. 1990). After *N*-oxidation of aromatic amines such as 4-aminobiphenyl or 2-naphthylamine by CYP1A2 in the liver, *O*-acetylation of the resulting hydroxylamine by NAT2 can produce unstable acetoxy esters that decompose to form highly electrophilic aryl nitrenium ion species. In addition, the formation of the acetoxy ester, a proximate carcinogen, can proceed through *N*-acetylation and *N*-oxidation reactions that yield *N*-hydroxy-*N*-acetyl aromatic amines, which then form the acetoxy ester through *N*,*O*-acetyltransferase catalyzed by NAT2. In slow acetylators, initial acetylation in the liver is less efficient, and hence biotransformation of the aromatic amine is more likely to proceed through the CYP1A2 route. Subsequently, the

hydroxylated aromatic amine can be further bioactivated in the bladder, either enzymatically or nonenzymatically, potentially leading to DNA binding and point mutations. This is considered a likely mechanism of initiation of bladder carcinogenesis (Autrup 2000; Colvin et al. 1998; Williams 2001). Thus, after the early findings by Lower et al. (1979), the concerted efforts of epidemiologic and toxicologic studies have quantitatively evaluated this gene–environment interaction and elucidated a probable mechanism.

Recent research exploring genetic modifiers of other common exposures with significant public health importance have begun to yield interesting findings. In addition to gene–environment interactions that link exposures, polymorphisms, and disease states, associations of particular exposures with biomarkers of exposure or effect and polymorphic variants have been evaluated. To broadly describe the status of this research, we compiled a nonexhaustive list of these exposures and biomarkers or diseases with their potential genetic effect modifiers, shown in Table 1, by searching the published literature (see Appendix 1 for additional information about the genes). As an exercise to identify gaps in knowledge about the exposure–disease association and effect modification that merit further investigation, we then classified the evidence for these relationships according to the following system: 3, associations proposed from basic scientific laboratory reports; 2, associations with laboratory evidence and suggestive epidemiologic data; 1, associations with laboratory evidence and supporting epidemiologic data.

Table 1 shows several different types of exposures, including exposures to industrially produced compounds and by-products (e.g., butadiene and dioxin), substances in the diet (e.g., alcohol and aflatoxin B_1), and both voluntary and involuntary examples of exposure (e.g., tobacco smoke and environmental tobacco smoke). As would be expected, some genes appear to be associated with several different exposures. This can be attributed partially to the relatively nonspecific roles of their gene products in biotransformation of exogenous substrates. It is also likely that once genotyping methods for a particular gene have been developed and streamlined, its role in several pathways will be explored. In total, based on our review of the published literature, we gave few examples in Table 1 a classification of 1, which indicates that evidence clearly demonstrating effect modification by polymorphisms is quite limited.

An example of the evolving knowledge of effect modification by polymorphisms is that of exposure to aflatoxin B_1, a mycotoxin found in some foodstuffs, and an established risk for hepatocellular carcinoma (HCC), especially when combined with hepatitis virus exposure (Ross et al. 1992). The biotransformation of aflatoxin B_1 proceeds through a CYP450-mediated oxidation and then through reactions catalyzed by GST, epoxide hydrolase, and/or glucuronosyltransferase to yield excretable metabolites (Eaton and Groopman 1994). For exposed persons, having *GSTM1* and *EPHX1* (epoxide hydrolase 1) genotypes conferring a lack of enzyme and less active enzyme, respectively, was shown to result in increased HCC risk (London et al. 1995; McGlynn et al. 1995). Similarly, functional variants in CYP1A2 and CYP3A4, both of which catalyze the phase I metabolism (epoxidation) of aflatoxin B_1, would also be expected to modify HCC risk in exposed persons, although epidemiologic data for this have not yet been gathered. Biomarker studies of urinary aflatoxin metabolites and aflatoxin–albumin adducts in peripheral blood have validated their use as indicators of HCC risk at the group level, and polymorphisms in *GSTM1* and *EPHX1* yielded higher levels of adducts (Wild and Turner 2001). Thus, in the case of aflatoxin, exposure-specific, validated biomarkers can be used in lieu of clinical disease measures to estimate the effect modification by specific variants. Even for this example, however, only a few studies exist, and they have limited statistical power; hence, the magnitude of the modifying effect of polymorphisms remains highly uncertain. Future efforts to determine the predictive value of biomarkers of other exposures will facilitate the analysis of the effects of polymorphisms in modifying the effects of those exposures.

Contradictory findings are often found in the literature. Similar issues have been encountered in pharmacogenetic studies. Evans and Relling (1999) have commented that the use of different end points in assessing response to drugs, the heterogeneous nature of diseases studied, and the polygenic nature of many drug effects all contribute to the study-to-study variation often observed. These same factors will also be important in types of studies discussed here. Additionally, there is controversy regarding the issue of population stratification, or bias in estimate of association between a polymorphism and disease because of confounding of a true risk factor with ethnicity (Thomas and Witte 2002; Wacholder et al. 2002), as it relates to study-to-study variation. Wacholder et al. (2000) have shown that well-designed case–control and cohort studies of cancer are free of significant bias due to population stratification. The debate, however, remains contentious.

The examples of gene–environment interaction presented thus far have been fairly simple. More realistically, chronic disease risk is a function of multiple genes interacting with each other and with multiple environmental factors over a lifetime. Taylor et al. (1998) provided evidence for a three-way interaction between *NAT2*, *NAT1*, and smoking that modifies bladder cancer risk such that individuals who smoke and have *NAT2* slow acetylator alleles in combination with the high-activity *NAT1*10* allele (homozygotes or heterozygotes) have heightened bladder cancer risk. Contrasting findings, however, have been reported more recently (Cascorbi et al. 2001).

Advantages of Incorporating Polymorphisms into Health Effects Studies

The addition of polymorphisms affords several noteworthy opportunities for health effects studies of exposures to environmental toxicants and toxins. Stratification of a studied health outcome or biomarker by relevant genotype (or phenotype) may allow for detection of different levels of risk among subgroups of exposed persons (Rothman et al. 2001). Collectively, the studies on aromatic amine exposure, *NAT2* genotype, and bladder cancer demonstrate this point. Investigations that assess bladder cancer risk associated with exposure to aromatic amines alone would observe a magnitude of effect that represents the average risk for rapid and slow acetylators combined. This estimate would not suggest that aromatic amines are as etiologically significant, that is, are potent carcinogens, for particular subpopulations, as a stratified analysis would indicate. This has been referred to as effect dilution (Khoury et al. 1993). Effect dilution may be especially important for common exposures—to dietary constituents or air pollution, for example—whose association to a disease outcome is often weak.

Second, evidence of effect modification by genotype yields insights into the potential biologic processes of toxicity or carcinogenicity, as substrates or targets of candidate gene products are identified as potential causative agents (Rothman et al. 2001). The effect of lipopolysaccharide (LPS; also known as endotoxin), a component of particulate matter in rural areas, on lung function parameters may turn out to be a modern example of this. Arbour et al. (2000) have shown that response to LPS, measured by decrease in forced expiratory volume in the first second (FEV_1), differed by *TLR4* genotype. *TLR4* codes for the toll-like receptor that binds LPS and initiates a signal transduction pathway that leads to inflammation of the lung. Their data suggest that individuals with the variant *TLR4* genotype may be resistant to LPS-induced lung inflammation but may be more susceptible to a systemic inflammatory response. These findings may aid in answering the difficult question of what component(s) of particulate matter is responsible for the range of health effects observed, particularly in rural areas where LPS levels are appreciable.

Finally, enhanced understanding of pathologic mechanism gained by the concerted

Table 1. Proposed genetic effect modifiers of common exposures.

Exposure	Outcome	Gene	Rating[a]	Reference
Arsenic	Arsenic metabolites in urine	*GSTM1*	3	Chiou et al. 1997; Vahter 2000
		GSTT1	3	
		Methyltransferase	3	
Beryllium	Chronic beryllium disease	*HLA-DP* β_1	1	Richeldi et al. 1993; Richeldi et al. 1997; Saltini et al. 1998
Lead	Blood lead level	*ALAD*	1	Kelada et al. 2001; Schwartz et al. 1995; Wetmur 1994
	Bone lead level	*ALAD*	1	Fleming et al. 1998; Schwartz et al. 1997
		VDR	2	Schwartz et al. 2000a, 2000b
Mercury	Atypical porphyrin profiles	*CPOX*	3	Grandchamp et al. 1995; Rosipal et al. 1999
		UROD	3	Mendez et al. 1998; Moran-Jimenez et al. 1996
Alcohol	Esophageal cancer	*ALDH2*	1	Chao et al. 2000; Hori et al. 1997; Tanabe et al. 1999; Yokoyama et al. 1996, 1999
Aflatoxin B_1	Aflatoxin–albumin adducts	*CYP1A2*	3	Eaton et al. 1995
		CYP3A4	3	Gallagher et al. 1996
	HCC	*GSTM1*	2	London et al. 1995; McGlynn et al. 1995
		EPHX1	2	
Heterocyclic amines	Colon cancer	*NAT2*	2	Brockton et al. 2000; Gil and Lechner 1998; Hein et al. 2000; Lang et al. 1986
	Breast cancer	*NAT2*	2	Deitz et al. 2000
		SULT1A1	2	Zheng et al. 2001
Aromatic amines (dye industry)	Bladder cancer	*NAT2*	1	Cartwright et al. 1982; Hanke and Krajewska 1990
Halomethanes	Metabolite levels in blood	*GSTT1*	3	Landi S et al. 1999; Pegram et al. 1997
Benzene	Hematotoxicity	*CYP2E1*	2	Ross et al. 1996; Rothman et al. 1997
		NQO1	2	
	Sister chromatid exchange in lymphocytes	*GSTT1*	2	Xu et al. 1998
Halogenated solvents (e.g., TCE)	Renal cell carcinoma	*GSTT1*	2	Bruning et al. 1997; Sweeney et al. 2000
Organochlorine compounds (e.g., PCBs, TCDD)	Immunotoxicity	*CYP1A1*	3	Nebert et al. 1996
		CYP1A2	3	Landi MT et al. 1999; Stresser and Kupfer 1998
		AHR	3	Nebert et al. 1996
Organophosphate pesticides	Chromosomal aberrations	*PON1*	2	Au et al. 1999
		GSTM1	2	
		GSTT1	2	
		CYP3A4	3	Eaton 2000; Sams et al. 2000
Butadiene	Sister chromatid exchange in lymphocytes	*GSTT1*	2	Kelsey et al. 1995; Norppa et al. 1995; Wiencke et al. 1995
Lipopolysaccharide (endotoxin)	FEV_1	*TLR4*	2	Arbour et al. 2000
Hay dust	TNF-α production in hypersensitivity pneumonitis	*TNF*α	2	Schaaf et al. 2001
Ozone	Influx of inflammatory cells in the lung	*TLR4*	3	Kleeberger et al. 2000
Airborne PAHs	PAH metabolites in urine, DNA adducts, or measures of genotoxicity	*CYP1A1*	2	Binkova et al. 1996; Knudsen et al. 1999;
		GSTM1	2	Merlo et al. 1998; Motykiewicz et al. 1998;
		NAT2	2	Nielsen et al. 1996; Viezzer et al. 1999;
		GSTP1	2	Whyatt et al. 2000; Wu et al. 1998
		EPHX1	2	
	Lung cancer	*GSTM1*	2	Lan et al. 2000
Nitro-PAHs	Genotoxic effects in respiratory tract	*NAT2*	3	Adamiak et al. 1999; Watanabe et al. 1997
Ultraviolet light	Basal cell carcinoma	*XPD*	2	Dybdahl et al. 1999
Ionizing radiation	DNA damage in lymphocytes	*XPD*	3	Duell et al. 2000; Fan et al. 1999; Lunn et al. 2000
		XPF	3	
		XRCC1	3	
	Prolonged cell cycle delay	*APE1*	2	Hu et al. 2001
Tobacco smoke	Lung cancer	*CYP1A1*	2	Bartsch et al. 2000; Houlston 2000; Xu et al. 1996
		GSTM1	2	Bartsch et al. 2000; Houlston 1999; McWilliams et al. 1995
		NAT1	2	Hein et al. 2000
		NAT2	2	Bouchardy et al. 1998
		EPHX1	2	Benhamou et al. 1998
		XRCC1	2	Ratnasinghe et al. 2001
	Bladder cancer	*CYP1A2*	3	Nebert et al. 1996
		NAT2	1	Marcus et al. 2000a, 2000b
		GSTM1	2	Engel et al. 2002
	Bronchogenic carcinoma	*AHR*	3	Nebert et al. 1996
	Emphysema and chronic obstructive pulmonary disease	*EPHX1*	2	Koyama and Geddes 1998
		GSTM1	2	
Environmental tobacco smoke	Lung cancer	*GSTM1*	2	Bennett et al. 1999

Abbreviations: TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCE, tetrachloroethylene; PAHs, polycyclic aromatic hydrocarbons; PCB, polychlorinated biphenyls; TNF, tumor necrosis factor.
[a]Rating system: 1, associations with laboratory evidence and supportive epidemiologic data; 2, associations with laboratory evidence and suggestive epidemiologic data; 3, associations proposed from basic scientific laboratory reports.

efforts of epidemiologic and toxicologic studies may allow for the development of drugs or dietary interventions that prevent disease onset or progression. As an example, oltipraz [OPZ; 5-(2-pyrazinyl)-4-methyl-1,2-dithiole-3-thione] is a drug that induces phase II XMEs, notably the GSTs (Carr and Franklin 1998). Early evidence showed that OPZ can protect against the hepatocarcinogenic effects of aflatoxin B_1 in rats, and subsequent efforts have demonstrated that administration of OPZ to humans significantly enhanced excretion of a phase II product, aflatoxin–mercapturic acid (Kensler et al. 2000). Interestingly, there is also evidence that OPZ may act by competitively inhibiting CYP1A2, thereby preventing the activation of aflatoxin (Langouet et al. 1995). In total, the understanding of aflatoxin biotransformation pathways from animal models and *in vitro* human tissue studies led to the hypothesis-based epidemiologic studies and ultimately contributed to the development of a chemoprevention strategy for aflatoxin-induced HCC.

Additionally, studies on the health effects of exposure to regulated environmental contaminants that incorporate genetic susceptibilities will enlarge the body of knowledge pertaining to the range of human variability in response to these contaminants. For example, the *National Report on Human Exposure to Environmental Chemicals* (CDC 2001) reports body burden among National Health and Nutrition Examination Study (NHANES) subjects for 27 chemicals. Studies developed to look at the effect of these chemicals should include genes that might confer susceptibility. In this way, the risk assessment process may be improved by using refined estimates of human variability instead of the default assumptions conventionally used (i.e., uncertainty factor of 10), potentially improving public health protection and the regulation of industry through redefinition of acceptable exposure levels. This advantage has been touted for some time, but no clear example yet exists of how this can be done, especially in the face of numerous ethical, legal, and social issues surrounding the use of genetic information. Still, the promise holds, and the potential continues to grow as more functional variants are discovered and their roles in effect modification are deduced.

In the environmental health community, discussion of the issue of focusing disease prevention efforts on genetically susceptible individuals has begun, with an emphasis on the inherently complex ethical, legal, and social issues. Researchers at the University of Washington's Center for Ecogenetics and Environmental Health (Burke W. Personal communication) and at the University of Cincinnati Center for Environmental Genetics (Vandale and Bingham 2000) are devoting considerable efforts to exploring these issues using case studies. In addition, the University of Washington Institute for Public Health Genetics and the University of Michigan Public Health Genetics Interdepartmental Concentration offer public health students the opportunity to learn about these issues.

Recommendations

For environmental health scientists interested in pursuing health effects research that incorporates genetic effect modifiers, we describe a framework for an investigation that includes polymorphisms. This framework assumes that the investigator(s) already has chosen the study design. Case–control and cohort studies are used most often to evaluate gene–environment interaction, and their benefits and drawbacks have been compared and contrasted (Caporaso et al. 1999; Langholz et al. 1999).

Exposure assessment. Exposure assessment is of paramount importance in studies of gene–environment interaction. Typically, efforts aim to characterize the type, duration, intensity, and timing of exposure. Exposure misclassification is a major concern, because it can bias the estimate of the effect of exposures as well as the estimate of the joint genotype–exposure effect (Rothman et al. 1999). New methods such as biomonitoring approaches (Rothman et al. 1995) and geographic information systems (Kulldorff et al. 1997; Rushton and Lolonis 1996; Ward et al. 2000) can be used to achieve more precise exposure assessments.

Candidate gene selection. The selection of candidate genes is one of the first methodologic issues encountered. Generally, one can investigate the role of a gene whose product is hypothesized to be involved in the biotransformation, cell signal transduction, repair, or disease process relevant to a specific exposure. Sources of toxicologic or other biomedical data that can be used to identify candidate genes include previously published literature (PubMed), the Agency for Toxic Substances and Disease Registry's Toxicological Profiles, the National Library of Medicine's ToxNet, the National Institute for Occupational Safety and Health's Registry of Toxic Effects of Chemical Substances, the National Toxicology Program Report on Carcinogens, On-line Mendelian Inheritance in Man (OMIM), and the Human Genome Epidemiology (HuGE) Net database (see Appendix 2 for website addresses).

Once candidate genes have been selected, sources of genetic information can be used to identify important polymorphisms in candidate gene(s). These sources include websites for specific gene families (e.g., CYPs, NATs), OMIM, the NIEHS's EGP Database, the National Cancer Institute's Cancer Genome Anatomy Project, and polymorphism databases (e.g., the SNPs consortium and the National Center for Biotechnology Information's dbSNPs database) (see Appendix 2 for a listing of relevant URLs). Focusing on polymorphisms with known functional effects is, of course, advantageous.

Efforts to study complex gene–environment interactions are tempered by the difficulty in obtaining adequate sample size (Rothman et al. 2001). Two primary factors to consider are the prevalence of the polymorphism in the population and the magnitude of effect modification. As Caporaso (1999) has pointed out, there is a trade-off between the prevalence of a polymorphism and the magnitude of effect that may be detected. On one hand, common polymorphic variants are less likely to exhibit a strong effect; on the other hand, there is more statistical power in studying these variants because they are more common. Furthermore, the population-attributable risk of common variants will be greater, even if the penetrance is modest.

More recently, investigators have expanded their study design to include analysis of haplotypes. Haplotype analysis is advantageous in that more information about variation in a gene is captured by this approach relative to single polymorphisms, and thus studies using haplotypes should aid in elucidating the role of genetic variation in complex disease (Nebert 2002). Inferring haplotypes from genotype data requires using specific algorithms (e.g., Terwilliger and Ott 1994), and methods are evolving to include adjustment for covariates in the analysis (Schaid et al. 2002).

Selection of a method to obtain samples for genotyping. Collection of DNA samples from the study population is an area of technologic evolution. Besides venous blood samples, from which DNA can be extracted, buccal cell collection brushes (Walker et al. 1999) or mouth washes (Garcia-Closas et al. 2001; Heath et al. 2001) have been employed and offer increased convenience to the study participant, but DNA yield can be substantially lower.

Informed consent. Informed consent for genetic testing is also an important consideration. Beskow et al. (2001) recently described the major issues to consider in obtaining informed consent and developed a general template for researchers to use (see also CDC 2002). In addition, the Department of Health and Human Services (DHHS) provides information about human subjects protection, and templates for informed consent protocols can be accessed at the DHHS website (Appendix 2).

Selection of a genotyping method. Many different methods can be used to genotype subjects. Choosing an appropriate method and using quality control procedures are critical because even minor genotype misclassification can substantially bias study results (Garcia-Closas et al. 1999; Rothman et al. 1999). The choice of method depends on both the type of polymorphism to be analyzed and the type of sample

obtained. DNA sequence analysis is considered the gold standard, but it is time-consuming and expensive. Restriction fragment length polymorphism analysis can be used if the polymorphism of interest is known to result in the addition or deletion of a restriction site. More recent, high-throughput approaches include 5′-nuclease–based fluorescence assays (Taqman), matrix-assisted laser desorption/ionization–time-of-flight (MALDI-TOF) mass spectrometry analysis, and DNA microarrays (Shi 2001).

Data analysis. Botto and Khoury (2001) have advocated that, in the context of a case–control study where exposure and genotype are dichotomized, the conventional 2 × 2 table analysis of exposure and disease be expanded to include genotype, yielding a 2 × 4 table. In this manner, the raw exposure and genotype data are displayed in such a way that relative risk estimates for each factor alone and their joint effect can be easily generated. Attributable fractions also can be computed from these data. Regression models of interactions can also be employed (Breslow and Day 1980; Neter et al. 1996). Although not discussed here, issues regarding multiple comparisons and false-positive findings are also important to consider, and readers are referred to De Roos et al. (In press) for guidance.

Conclusions

The role of polymorphisms as determinants of health is being explored in many areas of public health research. In environmental health, recently gathered epidemiologic and toxicologic data suggest that the health effects of many different types of exposures can be modified by polymorphisms, although the effect modification may be weak and the power of many studies is inadequate to demonstrate an effect. Current and future efforts to identify new polymorphisms in genes involved in environmental response will broaden the scope of potential genetic effect modifiers. Determining the effect of these polymorphisms (phenotype) will then be of paramount importance.

Although the individual risk associated with a polymorphism may be relatively low, the population-attributable risk may be large, and thus this area of research merits investigation. As newly identified and previously known polymorphisms are incorporated into epidemiologic research, gene–environment interactions can be detected and quantified. Through toxicologic studies, the mechanisms of these interactions can be elucidated. Correlations between biomarkers of exposure and effect with disease outcomes will facilitate the process of identification of variants that act as effect modifiers. As with any scientific endeavor, intriguing results in this area of research need to be replicated in different studies and populations to confirm the role of a variant as an effect modifier.

Although many gene–environment interaction studies on human populations have been

Appendix 1. Genes and Polymorphisms with Relevance to Environmental Health

Gene	Gene product	Polymorphism	Effect of polymorphism	References
CYP1A1	Aryl hydrocarbon hydroxylase	T3801C (m1) A2455G (m2)	Unknown None	Spurr et al. 1987 Persson et al. 1997
CYP1A2	Arylamine hydroxylase	C-164A	Decreased inducibility	Chida et al. 1999; Sachse et al. 1999
CYP2E1	Ethanol-inducible P450	5′ flanking repeat region	Increased activity after ethanol exposure	Hayashi et al. 1991; Marchand et al. 1999
CYP3A4	Steroid-inducible P450	5′ promoter A→G mutation	Unknown, perhaps expression levels	Rebbeck et al. 1998; Walker et al. 1998
AHR	Aryl hydrocarbon receptor	G1721A	CYP1A1 inducibility?	Smart and Daly 2000
EPHX1	Epoxide hydrolase	Tyr113His His139Arg	Altered protein stability?	Hassett et al. 1994
NQO1	NAD(P)H: quinone oxido-reductase 1	C609T	Altered enzyme induction	Moran et al. 1999; Ross et al.1996
NAT1	*N*-Acetyltransferase 1	Many alleles	Rapid vs. slow acetylation	Hein et al. 2000
NAT2	*N*-Acetyltransferase 2	Many alleles	Rapid vs. slow acetylation	Hein et al. 2000
SULT1A1	Sulfotransferase	Arg213His	Low activity and low thermal stability	Raftogianis et al. 1997
GSTM1	Glutathione *S*-transferase-μ	Deleted (null) allele(s)	No enzyme produced	Seidegard et al. 1988
GSTP1	Glutathione *S*-transferase-π	Ile104Val Ala113Val	Altered activity and substrate affinity	Ali-Osman et al. 1997
GSTT1	Glutathione *S*-transferase-θ	Deleted (null) allele(s)	No enzyme produced	Pemble et al. 1994; Wiebel et al. 1999
PON1	Paraoxonase	Arg192Gln Met55Leu Promoter point mutations	Change in activity and substrate specificity Change in enzyme expression levels	Furlong et al. 2002; Humbert et al. 1993
VDR	Vitamin D receptor	RFLP in 3′ UTR Multiple SNPs	Unknown Known for some SNPs	Cooper and Umbach 1996
HLA-DP β_1	Antigen recognition protein	Lys69Glu	Change in $CD4^+$ recognition	Richeldi et al. 1993
XPD (*ERCC2*)	Nucleotide excision repair (NER) enzyme system	Lys751Gln	Improved function	Dybdahl et al. 1999
XPF	NER	multiple SNPs	Unknown	Fan et al. 1999
XRCC1	Base excision repair	Arg399Gln	Unknown	Shen et al. 1998
APE1	Apurinic/apyrimidinic endonuclease 1	Asp148Glu	Reduced endonuclease activity	Hadi et al. 2000
ALAD	δ-Aminolevulinic acid dehydratase	G177C	Alleles 1 and 2, 2 allele yields a more electronegative protein	Wetmur 1994
TLR4	Type I transmembrane protein	A896G D299G	Unknown Altered cell signal transduction after LPS exposure	Arbour et al. 2000
TNF-α	Cytokine	G-308A	Altered transcriptional regulation?	Abraham and Kroeger 1999

Abbreviations: RFLP, restriction-fragment-length polynorphism; UTR, untranslated region.

completed in the past decade, the number of examples demonstrating important and consistent positive relationships is remarkably small. It now appears that the "one gene, one risk factor" approach to understanding the etiology of environmentally related chronic diseases is not likely to yield high rewards. Nevertheless, it remains clear that most chronic diseases of public health importance arise from a complex and often poorly understood combination of genetic and environmental factors. New tools for high throughput genotyping of hundreds or thousands of sequence variants in a sample, coupled with very large-scale population-based studies that use sensitive biomarkers and comprehensive exposure assessment strategies are likely to be needed to begin to unravel the complex multiple gene–environment interactions responsible for most chronic diseases of public health importance. This will require new paradigms for interdisciplinary collaborative research that involve very large-scale studies as well as new bioinformatics tools to help scientists make sense of the dizzying array of complex data that will come from such studies. Finally, increasing interest and discussion have been generated about the development of an integrated database that links new findings on exposures, etiologic pathways, relevant genes, polymorphisms in these genes, and their function (De Roos. In press). This database would guide the design of new studies as well as data analysis and interpretation of results (De Roos. In press).

In summary, the ability to detect different levels of risk within the population and greater understanding of etiologic mechanisms are the primary benefits of incorporating genetics into the existing environmental health research framework. The insights gained by employing this framework should ultimately allow for the development of new disease prevention strategies. The use of this information in risk assessments may also be a viable area of development. Finally, whether the use of this information in disease prevention efforts targeted to genetically susceptible individuals is acceptable is an ethical question that is beginning to be addressed and necessitates considerable attention in the future.

Appendix 2. Websites

Environmental health websites

Agency for Toxic Substances and Disease Registry's Toxicological Profiles
http://www.atsdr.cdc.gov/toxpro2.html
National Library of Medicine's ToxNet
http://toxnet.nlm.nih.gov/
PubMed
http://www4.ncbi.nlm.nih.gov/PubMed/
National Institute of Environmental Health Sciences Environmental Genome Project
http://www.niehs.nih.gov/envgenom/home.htm
National Toxicology Program Report on Carcinogens
http://ntp-server.niehs.nih.gov/NewHomeRoc/AboutRoC.html
National Institute for Occupational Safety and Health (NIOSH), Registry of Toxic Effects of Chemical Substances (RTECS)
http://www.cdc.gov/niosh/rtecs.html

Gene families

Cytochrome P450s
http://www.imm.ki.se/CYPalleles/
N-Acetyltransferases
http://www.louisville.edu/medschool/pharmacology/NAT.html

Genetic information websites

On-line Mendelian Inheritance in Man (OMIM)
http://www.ncbi.nlm.nih.gov/Omim
Human Genome Epidemiology (HuGE) Net
http://www.cdc.gov/genomics/hugenet/
Cancer Genome Anatomy Project (CGAP)
http://cgap.nci.nih.gov/
PubMed
http://www4.ncbi.nlm.nih.gov/PubMed/
SNPs Consortium
http://snp.cshl.org/
The Pharmacogenetics and Pharmacogenomics Knowledge Database
http://www.pharmgkb.org/do/serve?id = home.welcome
National Center for Biotechnology Information (NCBI) dbSNPs
http://www.ncbi.nlm.nih.gov/SNP/

Informed consent

Centers for Disease Control and Prevention (CDC)
http://www.cdc.gov/genomics/info/reports/policy/consentarticle.htm
http://www.cdc.gov/genomics/info/perspectives/infmcnst.htm
Department of Health and Human Services (DHHS)
http://ohrp.osophs.dhhs.gov/polasur.htm#INF

Academic centers

University of Washington Center for Ecogenetics and Environmental Health
http://depts.washington.edu/ceeh/
University of Cincinnati Center for Environmental Genetics
http://www.eh.uc.edu/ceg/
University of Washington Institute for Public Health Genetics
http://depts.washington.edu/phgen/
University of Michigan Public Health Genetics Interdepartmental Concentration
http://www.sph.umich.edu/genetics/

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