Genes and the Environment: Their Impact on Children's Health

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Because the human population is biologically diverse and genetically heterogeneous, it is not surprising that differences in susceptibility to disease among individuals with or without exposure to environmental agents exist. Individuals vary greatly in their susceptibility to disease. This is true of adults and children. The etiologies of many diseases of childhood are due to a combination of factors, including genetic susceptibility and environmental exposures during vulnerable periods of development. Genes regulate cellular growth and development, DNA replication and repair, the metabolism of endogenous agents in the body, and the metabolism and excretion of exogenous agents that the body comes in contact with in the environment. This regulation varies over the life span, contributing to the cellular consequences of the environmental exposures. This paper summarizes the contributions of genetics in understanding the etiology of environmentally induced diseases in children. The use of biomarkers of genetic susceptibility in the study of these diseases will be discussed. Future research needs for expanding our knowledge of the interactions between genetic and environmental components of childhood diseases will be presented. — *Environ Health Perspect* 106(Suppl 3):817–820 (1998). *http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-3/817-820suk/abstract.html*

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Introduction

The probability or risk of developing childhood diseases is influenced not only by genetic parameters, but by time, aging, and one's exposure to environmental agents.

Exposures to environmental agents at various stages of a child's life from gestation through young adulthood can confer differing opportunities for damage (Figure 1) (*1*). Depending on the stage of life, some processes are more active or better controlled than others. During fetal development there is active cellular growth and development, which vary by trimester of gestation. Brain development and certain organ system development are very rapid in the first trimester but slow down in the final trimester. Certain enzyme systems are developed and others are not. Opportunities for mistakes in DNA replication are plentiful and DNA repair mechanisms in certain cells may not be mature. The fetus is exquisitely sensitive to exposures of estrogens and other hormones that are needed for growth and differentiation, but environmental sources of endocrine-disrupting chemicals may overload the system and cause damage to the developing organism (*2*). These effects may not be apparent until adulthood.

After birth, the developing child may be exposed to environmental agents in the home, at day care, or in other environments that may impact on their development (*3*). Although not as vulnerable as the fetus, young children are also at risk from adverse effects of high doses of toxicants in their environment. For example, children may be sensitive to the effects of environmental tobacco smoke, air pollution, or allergens in the home, manifested in pulmonary hyperreactivity and asthma in susceptible subpopulations (*4*). Children are very susceptible to the neurologic effects of lead exposure. The brain and central nervous system of the child continue to develop for many years, and deficits in cognitive development and learning-related behaviors have been seen in children as old as 11 to 14 years who have been exposed to lead and polychlorinated biphenyls (*5,6*).

Puberty, with its concomitant changes in hormone production, growth and development of the sexual organs, and physical growth, is a critical window of vulnerability in adolescence. The mammary gland may be especially susceptible to the effects of cigarette smoke, alcohol, or organochlorine chemicals during this period, conveying future risk of breast cancer in adulthood (*7*). Receptor-mediated cellular processes may be especially vulnerable to changes during this period of development. Vulnerability has direct consequences for the risk of diseases of childhood as well as future risk of cancer or other chronic diseases in adulthood.

Defining Genetic Susceptibility

Because the human population is biologically diverse and genetically heterogeneous, it is not surprising that differences in susceptibility to disease among individuals with or without exposure to

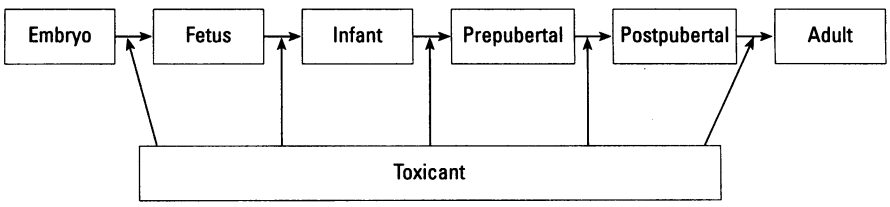

Figure 1. Exposures to environmental agents can occur at various stages of a child's life. Exposure during critical periods of vulnerability can affect a child's risk of disease.

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Abbreviations used: ALAD, delta-aminolevulinate dehydratase; A-T, ataxia telangiectasia; FEP, free erythrocyte protoporphyrin; XP, xeroderma pigmentosum.

environmental carcinogens should exist. Individuals vary greatly in their susceptibility to disease. Studies at the molecular level in humans suggest that there is wide interindividual variability in genetic parameters, consistent with this differing susceptibility to disease.

Recent discovery of the cystic fibrosis gene, the gene for Duchenne's muscular dystrophy, and a gene involved in the development of juvenile onset diabetes opens the door to new research on the etiology and possible prevention of these diseases in future generations. Other not so well-known syndromes apparent in childhood, such as Waardenberg syndrome, which causes severe hearing loss in children, or fragile X syndrome, which produces a cascade of developmental delays and deficits in children, have also been linked to distinct genes on somatic or sex-linked chromosomes. These discoveries are critical to our understanding of genetic susceptibility of disease in children. Selected diseases of childhood with known genetic links are listed in Table 1.

To maintain the integrity of the genetic material, cells have evolved complex mechanisms for repairing DNA damage. DNA repair enzymes correct DNA damage caused by carcinogens, including the removal of DNA adducts. Without correct repair of DNA damage resulting from endogenous and exogenous sources, the function of the DNA to replicate and maintain cellular function accurately would be compromised. As such, continued introductions of mutations into DNA can lead to increased risks for developing cancer over time. By studying individuals with multiple tumors, hereditary conditions resulting in defective DNA repair or chromosomal instability have been identified that lead to increased cancer risk. For example, xeroderma pigmentosum (XP) is an inherited condition that involves defects in excision repair. Individuals with this syndrome have extreme photosensitivity and are at increased risk for developing skin cancers (*8*). Children with XP are kept out of the light to reduce their risk of developing skin lesions. Another genetic disease that may increase one's susceptibility of future cancers is ataxia telangiectasia (A-T). A-T is a rare hereditary neurologic disorder that affects children. A gene has been identified for this disorder; it has also been determined that the function of the normal protein is probably in the regulation of cell division and also in apoptosis. However, in addition to the neurologic effects of this disease, patients with A-T and A-T carriers have increased risks for developing cancers and are more sensitive to the effects of ionizing radiation (*9,10*).

Table 1. Genes and inherited childhood diseases.

Description	Gene	Chromosome
Ataxia telangiectasia	*ATM*	11
Cystic fibrosis	*CFTR*	–7
Duchenne's muscular dystrophy	*DMD*	X
Juvenile onset diabetes	*IDDM1*	6
Phenylketonuria	*PAH*	12
Waardenberg syndrome	*PAX3*	2

Perhaps the greatest advances in the use of molecular tools to unravel gene-environment interactions have developed from the associations between exposure, polymorphisms in carcinogen-metabolizing genes, and cancer risk. The enzymes involved in carcinogen metabolism fall into two broad categories: Phase I enzymes, which almost exclusively involve the cytochrome P450 gene superfamily but also include *N*-acetyltransferase, are involved in metabolic activation; and phase II enzymes such as glutathione *S*-transferases, which are involved in detoxification reactions, are considered protective pathways. Recent advances in molecular DNA techniques have allowed for the identification of polymorphisms at the genetic level for several enzymes important in carcinogen metabolism. The induction of these enzyme systems varies over one's lifetime.

The use of molecular DNA techniques, including the development of polymerase chain reaction-based methods, coupled with our knowledge of some of the genes in the multistage process of chemical carcinogenesis, has aided in our ability to study the genetic basis for the interindividual differences observed in populations. It is the development of these techniques and the search for critical target genes that has guided epidemiologists in their quest to explore gene–environment interactions in human populations. Until now these studies have been useful in furthering our knowledge of carcinogenesis mainly in adults. These techniques can be applied to noncancer end points in populations of children to understand the components of genetic susceptibility and vulnerability to environmental toxicants in diseases that affect children. Biomarkers of exposure, effect, and susceptibility have been validated in adult studies. They are beginning to be applied in studies, such as one recently conducted in Poland (*11*), where genotypes of mother–infant pairs of individuals exposed to air pollution carcinogen were determined. These studies showed a relationship between biomarkers measuring pollutant exposure and susceptibility and health end points such as birth weight and head circumference in the infants (*11*). These biomarkers will allow the study of the interrelationship between exposures and genetic factors at the molecular and cellular level. The time is right to apply these exciting advances toward quantifying the biologic dose of environmentally relevant exposures and to study these effects in susceptible subgroups of the children.

Gene–Environment Interaction: An Example

The study of gene–environment interaction is critical to fully understanding all of the causal factors of disease in children. Characterization of genetic polymorphism of important genes involved in the metabolism of environmental toxicants is also necessary. A specific example of research that is applying these principles to the study of an exposure with enormous public health importance to children follows. The characterization of a genetic polymorphism of a commonly occurring gene now allows population scientists to begin to understand the relationship between lead exposure levels and cognitive impairment in susceptible subpopulations of children.

The second enzyme of the heme biosynthesis pathway, delta-aminolevulinate dehydratase (ALAD), is a protein that is encoded by a gene on the 9q34 chromosome. It is polymorphic in the population, with two common alleles, ALAD-1 and ALAD-2. This structure results in three distinct genotypes, ALAD 1-1, 1-2, and 2-2, which are distributed in the population. The alleles differ by a single base pair change, a guanine to cytosine transversion of coding nucleotide 177, which predicts the substitution of an asparagine for a lysine in the enzyme (*12*). The activity of this enzyme has long been used in the clinical diagnosis of lead poisoning, and now the distribution in the population of the gene that controls this enzyme can be used to understand individual susceptibility to effects from exposure. It is hypothesized that individuals with the ALAD-2 allele could be more susceptible to lead exposure if the ALAD-2 subunit binds lead more tightly than the ALAD-1 subunit (*13*). Individuals with the ALAD 1-2 and 2-2 allele might have higher blood lead concentrations as well as higher total

body burden, making them more likely to show clinical and subclinical manifestations of low-level exposure. The ALAD-2 allele is typically found in 11 to 20% of the white population (*12,14*), but it was not detected in an African population (*15*).

Work on this hypothesis began in a population of male lead workers in a German factory (*16*). Those workers who were heterozygous and homozygous for the ALAD-2 phenotype had higher average lead levels that those workers who were homozygous for ALAD-1 (*17*). There was a difference in the median blood lead level of 11 µg/dl between the workers with ALAD-2 and ALAD-1 genotypes. In a group of environmentally exposed children with blood lead levels lower than the working population, the same relationship was found (*17*). There was a difference in the median blood lead level of 9 µg/dl found between the two groups of children.

In another study of occupationally exposed carpenters, no difference was found in blood lead levels with ALAD subtype (*18*). These carpenters had much lower exposures to lead than the other worker studies. In the study conducted by Wetmur et al. (*17*), enrollment of the children in the study was based on clinical screening of free erythrocyte protoporphyrin (FEP) levels. This screening may introduce a serious selection bias into the study if there was reduced sensitivity lead-induced FEP elevation within the ALAD-2 subgroup. This bias would lead to a spurious association with genetic trait because higher lead levels would be required to be identified for enrollment into the study. A recent study in Korea indicates that ALAD-2 was overrepresented among individuals with blood lead levels > 40 µg/dl (*19*).

In another study, where a group of adolescents with low-level lead exposure were tested using a battery of neuropsychologic tests, inconclusive results were obtained because only 5 of the 79 subjects had the ALAD-2 genotype. In this study ALAD status was inversely related to lead levels in deciduous teeth. Performance on the neurobehavioral tests was slightly better in ALAD-2 individuals (*20*).

This example provides some evidence for heterogeneity in lead exposure levels associated with genetic traits. One could hypothesize that health effects would follow the same relationship by genetic status. There are no studies currently available with the power to detect these important effects. Continued research in the field of lead is taking into account the discovery of this parameter of genetic susceptibility when studying the health effects in adults and children. Genetic susceptibility becomes increasingly important when low levels of exposure are involved and the health consequences may be subclinical. Prevention and intervention programs could be developed to target the susceptible subpopulations. Evaluation of markers of genetic susceptibility may help make these programs more effective.

Concluding Remarks

Opportunities exist for us to broaden our understanding of the combined role of genetics and the environment in the etiology of childhood diseases. It is necessary to apply what we have learned by studying genetic susceptibility of cancer and issues of gene–environment interactions in the etiology of cancer to the study of childhood public health concerns. It is also necessary to expand our knowledge of the adult consequences of exposures to important environmental toxicants during the vulnerable periods of childhood. As new human disease genes are cloned and advances are made in the understanding of gene regulation of critical cellular and molecular processes, new opportunities will open up for the study of noncancer disease end points.

Future research needs have been identified, including the following:

- Identify genetic markers of diseases of children, i.e., asthma, learning and behavior, birth defects
- Increase our understanding of the developmental process of cellular and molecular processes during critical periods of vulnerability from the fetal period through young adulthood, i.e., gene expression, enzyme regulation, DNA repair
- Look for evidence of gene–environment interaction in studies of childhood diseases, i.e., lead and ALAD
- Develop and utilize noninvasive techniques to gather tissue for biomarkers in children, i.e., buccal samples, cord blood, placenta
- Develop a repository of biologic samples and exposure data from ongoing studies of children to be followed up as adults
- Expand our knowledge base of the effects of exposure to environmental exposures during childhood on the risk of adult diseases, i.e., effects of prenatal exposures to endocrine disruptors on adult reproductive function, effects of adolescent smoking on cancer risk

The biotechnologic revolution has brought with it a myriad of advances in understanding the human genome. Continued pursuit in understanding how the environment influences the risks of human disease proscribed by our genetic blueprints will bring us closer to understanding the etiology of many important public health concerns of children, our most susceptible subpopulation.

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