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Risk Science & Application

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Overview: Gene-Environment Interactions

By Julie E. Goodman, Ph.D., DABT

Our risk of experiencing a particular health effect is the result of a complex interplay between genetic and environmental factors.

Nurture *vs.* nature? This question is often asked regarding the causes of specific health effects. In most cases, the answer is "both." That is, many diseases are caused by a combination of genetic (nature) and environmental (nurture) factors. This phenomenon is known as a gene-environment interaction.

Well over 99% of human genes are the same from one person to another, but the small fraction that differ can lead to differences in disease rates.

The genetic factors that affect disease include alterations in genes themselves and biological factors that influence the role genes or gene products play in normal biological processes. In the environment, one usually thinks of chemical, biological, and physical agents in water, air, or soil. While exposure to these agents may affect many diseases, the environment also includes other factors such as food, smoking, lifestyle, behavior, stress, and temperature. All of these environmental factors may play a role in disease processes, and their role can often depend on one's genetic makeup. For example, while one person can develop cancer from smoking cigarettes, another may smoke two packs a day for 60 years and remain cancer free. That is, two individuals can be exposed to the same environmental factors, but differences in their genetic makeup have the potential to either preclude or initiate the onset of a particular disease.

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I N S I D E

Letter to our Readers

September 2009

Dear Colleague,

In this issue, we examine the relationship between genes and the environment as a contributor to risk, and address the challenge of communicating the effects of this relationship on human health in an accurate and productive manner. We expect that applications of genetic factors to risk assessment will increase in the future. In this context, it's important to remember that although genetic susceptibility can be used to identify disease risk, it alone cannot determine causality.

Contributors to this issue include Dr. Julie E. Goodman, leader of Gradient's epidemiology practice, Dr. Robyn L. Prueitt, a health scientist at Gradient, and Dr. Lisa A. Bailey, a toxicologist at Gradient. Joining us with a guest editorial are Mr. E. Donald Elliott, J.D., Professor (adj) of Law at Yale University and a partner at Willkie Farr & Gallagher LLP in Washington, D.C., and Ms. Johanna Hickman, also at Willkie Farr & Gallagher LLP, who discuss the legal challenges that arise as our knowledge of the role of genes in chemical sensitivity grows.

We hope that this issue of *Trends* sheds light on both the potential advantages and difficulties associated with the growth of this budding industry.

Yours truly,

Teresa S. Bowers

Teresa S. Bowers, Ph.D.

Trends is a free publication of Gradient Corporation, a national leader in risk assessment and negotiation of risk-based remediation. If you have a colleague who would benefit from this publication, please contact Andrew Bisbas at (617) 395-5000 or email us at *trends@gradientcorp.com*.

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Overview: Gene-Environment Interactions

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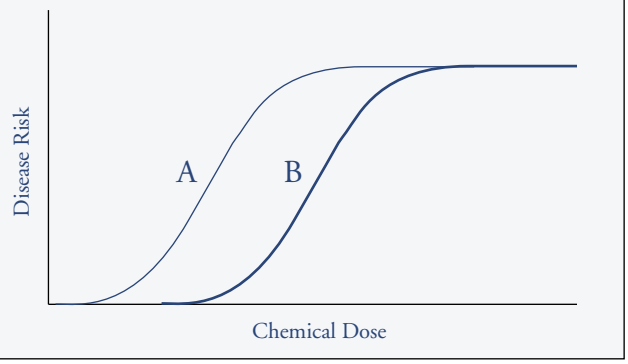
Well over 99% of human genes are the same from one person to another, but the small fraction that differ can lead to differences in disease rates. Sometimes, a genetic factor alone can cause a health effect: several variations in the huntingtin gene lead to Huntington's disease, and an extra chromosome 21 results in Down Syndrome. In many other instances, a genetic factor alone doesn't cause disease, but can make an individual more susceptible to an environmental factor (see figure). This is often the case, particularly with small changes in the DNA sequence, called single nucleotide polymorphisms, or SNPs. For example, alterations in *glutathione-S-transferase*, a gene that codes for a protein that enables chemicals to be excreted in urine, have been shown to increase cancer risk associated with exposure to many chemicals. In contrast, genetic alterations that lead to detoxification of a chemical would likely lead to lower disease risks from that chemical.

Disease Risk Based on Genetic Susceptibility



Each curve represents a group of people with the same genetic variant, or genotype. At low and high exposures, the disease risks for both groups are the same. At intermediate exposures, people with genotype A have a higher risk than those with genotype B.

Often the differences in risk from an environmental agent based on genetic makeup are quite small – so small that they can be considered negligible in any one person. But if one considers the number of people in a factory, a community, a city, or a country, these small differences in risk can actually lead to observable differences in disease rates in populations exposed to a specific environmental factor. Assume that a particular genetic variation increases the risk of cancer from a chemical exposure from 1 in 10,000 to 3 in 10,000. This increased risk is essentially inconsequential for an individual because the change in probability is negligible. In a city of one million people, however, chemical exposure could increase the number of people with cancer from 100 to 300. Two hundred additional cancer cases is a significant public health issue.

With the mapping of the human genome, scientists are able to study more genetic variants and their interactions with environmental factors. Yet the role of the vast majority of genes in general biological processes is not known, much less in disease processes. Many of the environmental risk factors for diseases have not been identified. For environmental factors that have been identified, the necessary dose for adverse effects and mode of action are not well known. It should also be noted that it is rarely the case that it is one gene and one environmental factor that cause disease. There are usually a number of other factors, both genetic and environmental, that increase or decrease disease risk.

Although the relationship between nature and nurture is hardly two-dimensional and varies considerably with circumstance, there is still much to gain from piecing together this complex puzzle. As scientists learn more about how genes and environmental factors work together to cause human diseases, there will be more opportunities for genetic information to be used in the development of strategies for the prevention and treatment of many illnesses, particularly for high risk individuals.

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By The Way...

The genetic testing market is expected to exceed $6.6 billion by 2015, while prenatal and newborn testing in the U.S. is currently estimated at $622 million.

Source: Bio-Medicine, October 30, 2008 (http://www.bio-medicine.org/biology-technology-1/Genetic-Testing-Market-to-Exceed--246-6-Billion-by-2015--According-to-New-Report-by-Global-Industry-Analysts--Inc--8728-1/).

Genetic Susceptibility and Risk Assessment

By Robyn Prueitt, Ph.D.

Advances in identifying genetic susceptibility have the potential to significantly improve risk assessment.

Risk assessment is the process of evaluating potential adverse health effects resulting from exposure to chemicals in the environment and defining the level at which these effects are unlikely to occur. The goal is to protect not only the general population, but also those who have some underlying sensitivity. Thus, it is important to identify individuals who may be at greater risk from exposure than the general population.

Public health agencies do not yet routinely consider information on gene-environment interactions in risk assessment.

Analysis of gene-environment interactions can be used in risk assessment to aid the identification of genetically-susceptible subgroups, as genetic variation can lead to different patterns of response to particular doses of chemicals. Traditionally, risk assessors have used a default uncertainty factor to account for differences in susceptibility among people when calculating risks. If information about genetic susceptibility to a chemical is known, this chemical-specific data could replace the default factor, reducing the uncertainty and leading to a better estimate of risk. Analysis of gene-environment interactions can also be used to provide insights into the mechanistic pathways of toxicity, which also reduce some of the uncertainties in the risk assessment process by improving our estimates of toxicity.

Data on genetic susceptibility may be useful in developing site-specific remediation goals. If a genetically susceptible population is at risk from exposure to a contaminated site, stricter remediation measures might be proposed. For example, clean-up goals for a nitrate-contaminated site may be lowered if the surrounding population includes a higher than normal fraction of individuals with glucose-6-phosphate dehydrogenase (GSPD) deficiency, a condition with increased susceptibility to the toxic effects of nitrates. In contrast, such data could limit the extent of remediation measures by more accurately predicting the potential for exposure of the sensitive population and better targeting regulatory resources.

Public health agencies do not yet routinely consider information on gene-environment interactions in risk assessment. Although the U.S. EPA anticipates that such information will be useful for the assessment of risks to specific human populations, the agency does not currently provide guidance for incorporating such data into risk assessments. However, the EPA has stated that such data may be used in risk assessments on a case-by-case basis (U.S. EPA, 2002).

The agency has incorporated gene-environment interaction data into risk assessments for certain herbicides and has recently developed a draft framework intended to move the agency toward evaluation and utilization of such data in risk assessment (U.S. EPA, 2009).

Before gene-environment interaction data can be used in human health risk assessment and public health decision-making, there are still many challenges that must be faced. The methods for identifying genetically susceptible populations, along with methods for quantifying the magnitude of sensitivity, must first be developed. As the use of these methods becomes widespread, the number of susceptible populations identified will likely grow, and regulatory agencies will need to use the most up-to-date information on susceptible populations each time they revisit a particular health standard. Much of the current research on genetic susceptibility emphasizes the identification of single-gene alterations associated with chemical metabolism. Studies of the joint effects of multiple polymorphisms also need to be conducted to better understand the continuum of genetic susceptibility to toxic agents. A further challenge is the need to achieve consistency across regulatory agencies in how they review, interpret, and communicate data related to gene-environment interactions. But, although challenges remain, the use of gene-environment interaction data can be an important tool to reduce uncertainties in human health risk assessment.

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Glossary

Gene – An inheritable portion of DNA that corresponds to a functional product in an organism.

Gene-environment interaction – An effect that is the result of interactions between an individual's genetic make-up and the environment.

Genome – The total complement of genes in an organism.

Genotype – The description of an individual's specific DNA sequence variant.

Polymorphism – An inheritable variation in DNA sequence that appears in at least 1% of a population.

Single nucleotide polymorphism – A small change in DNA sequence.

Communicating Genetic Susceptibility

By Lisa Bailey, Ph.D.

Advances in our understanding of genetic susceptibility will necessitate an increased emphasis on effective risk communication.

As knowledge about genetic susceptibility to environmental factors grows, more responsibility will increasingly be put on the individual to understand their own genetic predisposition and potential susceptibility. The rapid advancement in the science, and the associated regulation that will likely follow, needs to be paralleled with genetic counseling, outreach, and education for the individual, policy makers, doctors, and nurses who will often be in the forefront of communicating genetic susceptibility, and judges who will often be in the position of deciding whether certain environmental and genetic susceptibility information is admissible in toxic tort litigation.

The common saying that "a little knowledge is a dangerous thing" is a very real concern.

A key communication challenge will be with the inherent probabilistic nature of genetic susceptibility. That is, what is the probability (or risk) that an individual with a known genetic polymorphism that may confer susceptibility to a particular environmental toxin will actually experience adverse effects? If, for example, a genetic polymorphism has been shown to cause a two-fold increase in metabolism of a particular chemical, what does that mean in terms of risk for that chemical? Does it translate to a doubling of the risk? It may, or it may not; *i.e.,* doubling of the metabolism may not be significant at all if the baseline risk conveyed by the more common form of the gene is very low. This comparison requires some understanding of the involvement of that gene in the mode of action for the chemical of concern. The relative increase in risk also depends on the baseline risk specific to that individual, which is a consequence of many factors other than genetics. The probability of susceptibility that one might learn from genetic screening is based purely on genetic information and some understanding of the toxic mode of action for a certain chemical. This type of assessment does not take into account the extent to which the particular individual's environment or personal behavior will interact with their genetic information. That is, gene-environment interactions are not only gene-specific, but environment-specific, each of which is unique to the individual.

Similar to current aspects of risk communication, it will be critical to communicate that even for a genetically susceptible individual, there is some dose at or below which one can be exposed where adverse effects are very unlikely, and that above this dose there is only an increased risk and not a guarantee that adverse effects will occur. Furthermore, at a given chemical concentration, doses will differ for different people (even for those with the same genetic susceptibility) depending on body weight, exposure durations, and the types of activities that one is engaged in at the time of potential exposure (*e.g.*, inhalation rates or frequency of hand-to-mouth activity for incidental soil ingestion). The common saying that "a little knowledge is a dangerous thing" is a very real concern. Although the level of exposure required to cause an adverse effect may be lower for a genetically susceptible individual, it is very important that the individual understand that a certain level of exposure is still necessary for an effect to occur, and without that level of exposure adverse effects are not likely.

It is therefore essential that programs and educational strategies be developed to inform individuals who will be faced with trying to understand their own genetic makeup and potential environmental susceptibilities, and to provide the appropriate tools to groups who will often be responsible for communicating or making decisions based on this information. The EPA has begun a discussion on these issues in its "Interim Policy on Genomics," which can be found at http://www.epa.gov/osa/spc/pdfs/genomics.pdf.

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Genetic Susceptibility and Risk Assessment

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What's New at Gradient

Recent Awards and Appointments

Barbara D. Beck has become President of the Academy of Toxicological Sciences after serving as President-Elect for one year.

Marc A. Nascarella has been appointed an Adjunct Assistant Professor on the graduate school faculty of the Department of Public Health at the University of Massachusetts, Amherst.

Marc A. Nascarella was awarded a Society of Toxicology, Risk Assessment Specialty Section Presentation Award at the SOT annual Meeting in Baltimore, MD for his presentation entitled "The relationship between the IC_{50}, toxic threshold, and the magnitude of stimulatory response in biphasic (hormetic) dose-responses."

Barbara D. Beck was reappointed as Instructor in the Molecular and Integrative Physiological Sciences Program in the Department of Environmental Health at the Harvard School of Public Health.

Recent Publications

Barbara D. Beck's response to an April 3 editorial on the Consumer Product Safety Act, entitled "Toys R Congress," was published in the April 16 edition of *The Wall Street Journal.*

Glynn, S.A., B.J. Boersma, T.M. Howe, H. Edvardsen, S.B. Geisler, **J.E. Goodman,** L.A. Ridnour, P.E. Lonning, A.L. Borresen-Dale, B. Naume, V.N. Kristensen, S.J. Chanock, D.A. Wink, and S. Ambs. 2009. A Mitochondrial Target Sequence Polymorphism in MnSOD Predicts Inferior Survival in Breast Cancer Patients Treated with Cyclophosphamide. *Clinical Cancer Res.* 15(12):4165-4173.

Goodman, J.E., M.A. Nascarella, and **P.A. Valberg**. 2009. Ionizing Radiation: A Risk Factor for Malignant Mesothelioma. *Cancer Causes and Control.* (Epub ahead of print). DOI:10.1007/s10552-009-9357-4.

Goodman, J.E., R.L. Prueitt, D.G. Dodge, and **S. Thakali**. 2009. Carcinogenicity assessment of water-soluble nickel compounds. *Crit. Rev. in Toxicol.* 39(5):365-417.

Hamade, A.K. and C.G. Tankersley. 2009. Interstrain variation in cardiac and respiratory adaptation to repeated ozone and particulate matter exposures. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 296(4):R1202-15.

Nascarella, M.A. and E.J. Calabrese. 2009. The relationship between the IC_{50}, toxic threshold, and the magnitude of stimulatory response in biphasic (hormetic) dose-responses. *Reg. Tox. and Pharm.* (Epub ahead of Print). DOI:10.1016/j.yrtph.2009.04.005.

Nascarella, M.A, E.J. Stanek, G.R. Hoffmann, and E.J. Calabrese. 2009. Quantification of Hormesis in Anticancer-Agent Dose-Responses. *Dose-Response.* 7(2):160 -171.

Petito Boyce, C., A.S. Lewis, S.N. Sax, M. Eldan, S.M. Cohen, and **B.D. Beck**. 2008. Probabilistic analysis of human health risks associated with background concentrations of inorganic arsenic: Use of a margin of exposure approach. *Hum. and Ecol. Risk Assess.* 14(6):1159-1201. Won the journal's "Best Paper of the Year in Human Health Risk Assessment."

Prueitt, R.L., J.E. Goodman, and **P.A. Valberg**. 2009. Radionuclides in cigarettes may lead to carcinogenesis *via* p16INK4a inactivation. *J. of Environ. Radioactivity.* 100(2):157-161.

Upcoming Presentations

Amherst, MA. October 19-22, 2009. **Sagar Thakali,** Herbert Allen, and Dominic Di Toro. 25th Annual International Conference on Soils, Sediments, Water, and Energy: "Soil Metal Criteria Development Using the Terrestrial Biotic Ligand Model (TBLM) and Species Sensitivity Distributions."

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Guest Editorial: Are Polymorphisms Like Thin Skulls?

By E. Donald Elliott and Johanna Hickman

Advances in understanding individual genetic composition may have some interesting legal implications.

Automated sampling has already brought the cost of sequencing an individual human genome down to $50,000. Today, drugs are designed for people with a particular genetic composition, and the U.S. EPA's computational toxicology program aspires to understand how toxic chemicals affect biological pathways in particular human bodies. Someday sequencing an individual's genome may be as common as an x-ray.

Can a defendant in a toxic tort case defend on the grounds that the victim had an unusual susceptibility?

These developments may challenge our understanding of causation in toxic torts. "[T]he 'cause' of a disease," wrote then-professor, now judge, Guido Calabresi, "would depend on how, at any given time, it could most easily be controlled" (Calabresi, 1975). For example, before the discovery of the Koch bacillus, lack of fresh air could validly be consider the legal "cause" of tuberculosis.

Are we on the verge of a similar transformation in our understanding of how chemical exposures produce toxic effects? Will the discovery of genetic polymorphisms explain why some suffer toxic effects from chemical exposures, while others do not? For example, genetic variations can increase susceptibility to bladder cancer from arsenic exposure (Andrew *et al.*, 2009). Can a defendant in a toxic tort case defend on the grounds that the victim had an unusual susceptibility?

Traditionally, lawyers have assumed that the answer is "no." Under the "eggshell skull" rule, a wrongdoer whose actions are expected to cause only minor injuries is responsible for all injuries, even if the victim is unusually vulnerable (Wisconsin Supreme Court, 1891). In another precedent, the U.S. Supreme Court (1991) held that an employer may not exclude pregnant women to protect them against harmful materials.

On the other hand, courts have generally rejected defenses to criminal charges based on genetic predisposition to alcoholism, substance abuse or violence. Here courts generally argue that someone who knows (or should know) that she may be particularly susceptible is required to take precautionary actions to prevent injuring others (Farahany and Coleman, 2006). Similarly, society does not remove all gluten or peanuts from foods, even though some individuals are acutely allergic. We place the burden of avoiding allergens on particularly sensitive individuals.

None of these analogies is exact. But as our knowledge of genetic polymorphisms and chemical sensitivity grows, courts will struggle anew with whether a particularly sensitive person has any obligation to avoid exposures that might injure him but not others. How they come out will probably depend on the facts and interests involved in particular cases.

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Andrew, A.S., R.A. Mason, K.T. Kelsey, A.R. Schned, C.J. Marsit, H.H. Nelson, and M.R. Karagas. 2009. DNA repair genotype interacts with arsenic exposure to increase bladder cancer risk. *Toxicol. Lett.* 187(1):10-14.

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In the next issue:

Overview of Radiation Risk Assessment

Differences Between Ionizing and Non-Ionizing Radiation

Risks vs. Benefits of Medical Monitoring

Guest Editorial: Whence Nuclear Power?

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