Issue Number 15

INTERFACE: GENES AND THE ENVIRONMENT

CENTER FOR ENVIRONMENTAL GENETICS UNIVERSITY OF CINCINNATI FALL 1998

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Genetic Information in the Workplace—Boon to Health, or Pretext for Discrimination?

There is no doubt that recent advances in the science of genetics hold promise for improving human health. Clinical genetic tests now identify many hidden hereditary problems. These tests provide information that can serve as the basis for early treatment and life-style changes that can prevent or favorably alter the course of disease. Clinical genetic testing is now being performed frequently in a number of contexts. At the present time, there are about 50 tests for disease-linked genes. This article deals with several important issues regarding the expansion of genetic information in our society.

Genetic information

Some of the ***variant*** (unusual) ***genes*** identified through testing will not produce any problems for the individuals in question. These persons are referred to as "carriers" of an abnormal gene. They are not at greater risk of disease. The potential problem with genetic carriers lies in the fact that these genes are likely to be passed on to other generations. One example is a female carrier of the color-blindness gene; this gene is on the X chromosome. Although she is not affected, she has one in two chances of giving birth to a son with color blindness. A more serious example is cystic fibrosis; although both the mother and father might have one defective copy (***allele***) of the cystic fibrosis *CFTR* gene, neither is affected but they have a one-in-four chance of having a child with cystic fibrosis (child receiving the defective allele from both the mother and the father). At this time, the major use of genetic tests is by couples who wish to identify potential disease-causing genes that could be inherited by their children.

Among those adults who decide to take a genetic test, a small fraction will be informed that they have a version of a gene that is linked to a disease. This does not mean that the person will inevitably develop the disease. It simply means that they have a higher risk than average of developing a particular disease. Depending on the gene and on its penetrance (strength in determining physiological outcomes), the increased risk can be small or large. For example, the risk of breast cancer—in the 5% or less of individuals worldwide carrying only one "good" copy of the *BRCA1* gene—is about 37% by age 40, 66% by age 55, and 82% over a lifetime. In the case of diseases caused by a single ***dominant*** gene, the risk is estimated to be nearly 100%; luckily, those diseases are very rare.

It has been estimated that each of us has between 6 and 14 variant alleles of genes that increase our risk of some type of disease or another, and this estimate might be very conservative. Most of us will never be tested and remain unaware of those genes. For those who are tested, knowledge of their hereditary data can be very significant. If both the individuals tested and their physicians have this information,

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often times preventive health care programs can lower the risk of disease or its severity if the disease is already developed. On the other hand, when this same kind of information becomes evident to outside parties, the individuals involved may face unexpected social pressures—including problems related to employment and insurance coverage. Genetic information—which ideally should be a boon to human health—may thus become a great social peril with regard to questions of privacy and justice.

Genetic testing in the workplace

Workplaces are required by law to maintain health and safety standards. This means that employers must always be looking for potential health hazards in the workplace. This also means that employers must monitor hazardous exposures. Biochemical testing of the blood and urine of employees (***biological monitoring***) is sometimes used to determine if exposure standards are being maintained. Sometimes these tests show that workers have become overexposed to a particular hazardous substance. If standards are not being met, clean-up measures are required to be undertaken. In any case, rest or reassignment of the overexposed employees is a necessary step. These preventive measures on behalf of workers create administrative difficulties for employers, and such mandatory preventive measures imply costs.

Recently, there has been genetic testing of employees in certain industries. Proponents of testing in the workplace contend that this information is for ***prevention***. The proponents point out that some people have ***gene variants*** that lead to unusual physiological reactions when in contact with certain environmental agents. Such people are, in fact, at greater risk ("hypersensitive") to this type of contact, even when current exposure level standards are met. Common sense would indicate that, whenever possible, these workers should be aware of their situation. Steps should be taken to protect them from potentially endangering exposures. On the other hand, some employers might use this information for other purposes. With these data the employers could refuse to hire job applicants who have disease-linked traits. The employers might even fire current employees with similar characteristics—should this knowledge become available to the employers.

Opponents to genetic testing in the workplace point out that this information often leads to ***genetic discrimination***, claiming that the hiring and firing on the basis of particular gene variants is a way of shifting the economic burden of working with hazardous substances from the employer to the employee. In keeping with a long legal tradition, it has been the duty of the employer to maintain accepted standards of industrial hygiene. Opponents contend that all workers should have the right to seek work and to maintain it, as long as they are judged to be capable—by usual (non-genetic) employment standards.

Information about disease-linked genes could also be used to exclude persons from non-industrial work sites. If it became known that a person's genetic status put him or her in a higher health risk classification, then many kinds of employers, including those in nonhazardous areas, might be capable of discriminatory actions. Obviously, companies would be very interested in using this information, if they could. Such information would save companies a lot of extra costs involved in payments for health insurance on workers who might be classified as less healthy than "the average."

There is no doubt that tests for many new disease-linked genes will be available in the next few years. These will include tests for more common diseases such as late-onset diabetes, heart disease, early-onset Alzheimer disease, and different types of cancer. These diseases represent ***multiplex phenotypes***, *i.e.* at least two and probably five or more variant genes play a role in causing these diseases. A little knowledge could therefore become dangerous. If unchecked, employers could soon exert enormous pressure on employees to obtain the genetic information about employees. Access to this information would be enormously damaging to workers' rights to seek and maintain employment freely. Access to this information would also seriously affect workers' insurance status.

The current legal situation

Only a few States have laws prohibiting companies from acquiring and using genetic information. Beyond that, there are some federal and State laws, prohibiting job-related discrimination on the basis of physical disabilities. Court cases will determine the relevance of these laws to non-manifested genetic-related disorders, in the form of "hypersensitivity" or "genetic predisposition." The following table summarizes the current legal status of legislation that potentially might ban genetic discrimination in the workplace.

Legal Basis for Bans on Genetic Discrimination in the Workplace

Rehabilitation Act (Federal law, 1973)
Deals with protection against disability discrimination in the workplace

Americans with Disabilities Act (ADA, Federal law, 1990)
States that all symptomatic disabilities are protected against discrimination in the workplace

14 States have laws related to genetic discrimination
Most of these deal with specific types of genes or disorders, and only a few mention protection against compulsory testing or misuse of genetic information

Several different branches of the government have joined in the debate on the use and misuse of genetic information. The National Institutes of Health (NIH) and the Department of Energy (DOE) are both involved in the Human Genome Project (HGP). The HGP is a huge international undertaking, aimed at classifying and mapping the roughly 100,000 human genes. Both NIH and DOE use 3% of their HGP funds to study the ethical, legal and social issues (ELSI) of emerging genetic science and technology. NIH and DOE are particularly concerned with preventing genetic discrimination in employment and insurance.

The executive branch of government has also gotten involved. Vice President Al Gore, for example, spoke out at a press release held at the National Academy of Sciences, 20 January 1998. He announced that the current administration supports legislation to ban the use of genetic information in the workplace. Mr. Gore's recommendations included:

> "Employers should not require or request that employees or potential employees take a genetic test or provide genetic information as a condition of employment or benefits."
>
> "Employers should not use genetic information to discriminate against, limit, segregate, or classify employees in a way that would deprive them of employment opportunities."
>
> "Employers should not obtain or disclose genetic information about employees or potential employees under most circumstances."
>
> "The use of genetic information and genetic testing should be permitted in some situations to ensure workplace safety and health and to preserve research opportunities, if the employee has provided consent and if the information is maintained in medical files that are kept separate from personnel files..."

Who else should be concerned?

The issues discussed here point out why genetic information has tremendous potential for both good and bad, depending on how society uses it. The

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public needs to know about how genetic technologies, in general, and genetic testing, in particular, affect their lives. To do this, the public needs opportunities to review essential aspects of genetic science and to ***feel comfortable with genetic terminology***. In order to feel comfortable, we need to have continuing education for everyone, concerning this rapidly moving field of human genetics. The public also needs to know what important health-related benefits would result from testing. While, ideally, there may be many advantages, there must be carefully thought out plans for making genetic information useful for prevention.

Beyond that, there should be opportunities for public discussions concerning the uses of genetic information and how these have an impact on our lives. Public service and community organizations can be helpful—looking for opportunities to formulate their own programs for exhibits, studies, and discussions around these questions. Science educators and health professionals should also be involved by teaching courses and taking part in discussions.

The CEG has taken this responsibility very seriously. The Center now comprises a community outreach project, called "Learning Exchange for Genetic and Environmental Disease Solutions" (LEGENDS). The project promotes awareness of environmental and genetic factors in disease, and discussion concerning the social, legal, and public policy implications of genetic technologies. The Center invites groups in the Cincinnati area to participate. LEGENDS includes workshops, focus group discussions, exhibits, and a Web Site (which can be reached through the CEG home page). The contact person is Susan Vandale, telephone 513-558-8999, or email ***vandale@email.uc.edu***.

——Contributed by Susan Vandale and Eula Bingham (CEG Community Outreach and Education Program)

Thomas Jefferson's Y Chromosome

In a somewhat politically controversial report [***Nature* 396**: 27, 1998], the team of Tyler-Smith (University of Oxford, England) studied the Y chromosome of descendants of President Jefferson and Sally Hemings, one of Jefferson's slaves but also a half-sister of Jefferson's wife who died in 1782. DNA analysis of the Y chromosome can reveal male-line relatives, because—apart from occasional mutations—most of the Y chromosome is passed unchanged from father to son. A present-day descendant of the last son of Sally Hemings (born in 1808, when Sally was 35 years old, and Thomas Jefferson was 65 years old and had been a widower for 26 years) was found to have a "Jefferson-like" ***haplotype*** (linkage analysis pattern on the Y chromosome). In other words, chances are at least 100 times more likely that Jefferson was the father of Sally's last son than if someone unrelated was the father.

Genomes Are Dynamic

Lewis Thomas—Harvard-trained physician, father of modern immunology and experimental pathology, and poet-philosopher of medical science [***Interface***, issue #2]—once wrote: "The capacity to blunder slightly is the real marvel of DNA. Without this special attribute, we would still be anaerobic and there would be no music." As more and more genomes are being completely sequenced, we are beginning to appreciate what Thomas was thinking and what Barbara McClintock (1983 Nobel Laureate) had professed for decades—that cells are constantly in a state of flux, engineering their own genomes to take advantage of changes in the environment. Enzymes that copy and maintain the DNA are continually introducing changes in some parts of the genome and not others, creating hotspots of mutation that increase the efficiency of evolution. In times of stress, for a cell to initiate its own restructuring and renovation is indeed remarkable [***Science* 281:** 1131, 1998]. An insect becoming resistant over generations to an insecticide, or a child's bacterial otitis media becoming resistant to a particular antibiotic, are examples of this phenomenon. In fact, tumor cells that change from "being sensitive" to becoming "resistant" to a particular chemotherapeutic drug—are undoubtedly tampering with their genome, to the benefit of the tumor's progression but not to the benefit of the host.

You are What You Eat

Eubacteria and ***Archaebacteria*** have been regarded as different kingdoms**;** archaebacteria often grow well at temperatures close to that of boiling water and are termed ***hyperthermophiles***. As more and more prokaryotic genomes have been completely sequenced, analysis of the evolution of these kingdoms becomes a little bit easier. Comparing three genomes of extreme thermophilic archaebacteria with the genome of *Aquifex aeolicus*, a eubacterial hyperthermophile, Koonin and coworkers show [***Trends Genet* 14:** 442, 1998] strong evidence for massive gene exchange. Their data are consistent with the suggestion that bacterial hyperthermophily evolved secondarily within moderately thermophilic bacteria by the continuous acquisition of thermotolerance genes from pre-adapted hyperthermophiles, namely the archaebacteria.

This is one of the best examples yet of "***horizontal transfer***," *i.e.* genes from an organism in one kingdom or phylum being taken up by an organism in another kingdom or phylum! In fact, a "gene-transfer ratchet" mechanism for explaining horizontal transfer across phyla was just recently proposed [***Trends Genet* 14:** 307, 1998].

'Terminator' Technology

Monsanto, a large company involved in plant engineering, has developed a controversial "germination control" technique in which crops are genetically modified to destroy their own seeds. One of the reasons for developing germination control was the ability of Monsanto to protect the intellectual property rights of those developing the seed. Needless to say, the proposed technology has invoked anger—especially amongst farmers in developing countries—who would not be able to save new seeds for replanting if they chose to use such germination control crops [***Nature* 396:** 503, 1998].

Obviously, a hypothetical "germination control gene that got out of control" would make a great science-fiction story! But critics are worried ("What if an entire species of plants became unable to make seed?") and are campaigning fiercely for a worldwide ban. Some effects are already being felt. At the October 1998 meeting of the World Bank's agricultural research agency, the Consultative Group on International Agricultural Research, they decided to ban germination control seeds.

Plants As Sentinel for Radioactivity

Following the explosion of a nuclear reactor at Chernobyl in April of 1986, 30 lives were lost and thousands of survivors were exposed to extreme levels of radiation contamination. More than 600 square kilometers of the Ukraine continue to contain radionuclides at levels greater than 40 Curies per square kilometer, and both habitation and agriculture are strictly prohibited. How can we develop a rapid and reliable estimation of the genetic hazards of nuclear pollution in animals and plants of such a heavily contaminated area?

An exciting possible solution involves the tiny plant *Arabidopsis thaliana*, frequently studied because of its tiny genome. Kovalchuk and coworkers [***Nature Biotechnol* 16:** 1054,1998)] have designed a nonfunctional β-glucuronidase as a bio-indicator for detecting DNA rearrangements due to radiation damage. Using a plant as a sentinel might also serve as ethically more acceptable than using animal systems!

HGP, Fast Forward!

J. Craig Venter, with the Perkin-Elmer Corp (Norwalk Connecticut), has proposed to sequence the entire human genome, or at least all the coding regions (genes), within 3 years and at 1/10th the cost of the federally-funded project (described in the ***Interface*** spring '98 issue). Francis Collins, Head of the National Human Genome Research Institute (Bethesda, Maryland), produced a new 5-year plan that includes producing a "working draft" by 2001 and a gold-standard version of the entire genome by 2003, two years ahead of the old schedule. When asked if this plan was in response to Venter's dramatic proposal, Collins answered that "This is not a reaction. It is action." There are two recent, very informative articles on the successes of the first decade [***Nature Genet* 20:** 333, 1998] and the new goals of the HGP [***Science* 282:** 6822, 1998].

In addition to progress with the human genome, several other exciting genomes have been completed since the last ***Interface*** issue: *Treponema pallidum* (the bacterium that causes syphilis); *Chlamydia trachomatis* (the major cause of blindness in Asia and Africa); *Rickettsia prowazekii* (the cause of typhus); and the nematode *Caenorhabditis elegans*!! Sequencing the *C. elegans* genome is the most incredible advance yet—because this tiny worm is considerably more complex than *Saccharomyces cerevisiae* (baker's yeast), previously the most complex eukaryote to have its genome completed. Barely visible to the naked eye, *C. elegans* develops with 1,090 cells during which 131 die from apoptosis (programmed cell death), leading to 959 in the adult worm. Every cell has been named and its differentiation thoroughly studied, via microscopy and laser techniques for knocking out specific cells. Now we know that this tiny worm—with a mouth, heart, and respiratory, digestive and reproductive systems—lives effectively with **19,099** protein-coding genes [***Science* 282:** 2012, 1998]. With a genome of 97 million bases, about one-thirtieth that of the human, *C. elegans* has about one-fifth as many genes as the human. Genetic studies in this nematode have always been a goldmine, but you ain't see nothin' yet!

LETTERS TO THE EDITOR

RESPONSES/COMMENTS TO VARIOUS QUESTIONS

COMMENT **Concerning our NewsLetter's issue #1 hypothesis that "individual differences in soldiers (who have identical exposures to nerve gas) developing the Gulf War Syndrome might be associated with the paraoxonase (*PON1*) polymorphism," this autumn the laboratory of Bert La Du (University of Michigan, Ann Arbor) has developed a phenotyping assay that measures the ratio of two enzyme activities—paraoxonase activity-to-arylesterase activity with phenylacetate as substrate. Although they have studied so far only two groups of 20 controls each, plus 25 soldiers diagnosed with the Gulf War Syndrome, one particular (AB) phenotype was found to be statistically significantly associated with this syndrome. Of course, larger numbers of patients and controls now need to be studied to corroborate this preliminary finding.**

COMMENT **Just when several panels had decided that electromagnetic fields (EMFs) were not important as a risk factor in causing childhood malignancy, as discussed in several earlier issues of *Interface*, an advisory panel to the National Institutes of Health (NIH) chaired by Michael Gallo (Robert Wood Johnson Medical School, Piscataway NJ) concluded last summer that "EMFs are a potential human carcinogen." The 30-member panel used a more liberal standard, which allows a substance to be labeled a carcinogen based "only on an association in a population, even in the absence of evidence linking a substance to tumors in lab animals."**

COMMENT **Issue #6 of the *Interface* described asthma as a polygenic multifactorial trait (meaning two or more genes cause the disease). In the 18 Dec 98 issue of *Science*, two independent laboratories have now provided very convincing evidence that an immune system messenger called interleukin-13 (IL-13) plays a central role in asthma. Previously it had been difficult to distinguish between the effects of IL-13 and IL-4 because both cytokines dock on similar receptor complexes on the surface of immune cells. With the development of a specific IL-13 blocker, and giving this drug to mice already primed for an asthma attack, these two labs showed the attack to be almost completely aborted.**

COMMENT **Issue #13 of the *Interface* discussed the likelihood that a human polymorphism for arsenic metabolism will be found. A study by a Swedish research group on Northern Argentina children exposed to about 200 µg/liter in drinking water [*Environ Health Perspect* 106: 355, 1998] now suggests that there might be a polymorphism for the arsenic methyltransferase (AsMT) and that arsenic methylation might be inducible with increasing exposure. As indicated in the issue #13 article, arsenic can be both toxic and therapeutic. Arsenic trioxide was shown [*N Engl J Med* 339: 1341, 1998] consistently to produce complete remissions in patients who have relapses of acute promyelocytic leukemia (APL) that are resistant to all-*trans*-retinoic acid and chemotherapy—implying an alternative mode of action. As(III) can cause oxidative stress and apoptosis (as illustrated in Figure 2 of issue #13). Apoptosis (programmed cell death) of APL cells is likely to be this other mode of action [*N Engl J Med* 339: 1389, 1998].**

COMMENT **In several of our previous issues, the importance or lack of relevance of environmental endocrine disruptors has been discussed. Steven Safe had written [*Environ Health Perspect* 103: 346, 1995] that a woman taking a birth control pill ingests about 16,675 gram-equivalents per day and postmenopausal estrogen therapy 3,350 gram-equivalents per day, whereas eating estrogenic flavonoids in food is 102 and environmental organochlorine estrogens is 0.0000025 gram-equivalents per day. Safe has been criticized and challenged for his calculations. Helmut Greim [summer 98 issue of *IUTOX NewsLetter*] writes that even if Safe is wrong "by a factor of 1,000, the potency of estrogen-/antiestrogen-like xenobiotics exposure is at least 10,000 times lower than that of natural flavonoids in human food." "... Many authors have neglected the most basic toxicological principle: the dose makes the poison."**

Q **Some mice were cloned this summer in Hawaii. What's the big deal? How does this differ from cloning that sheep, Dolly?**

A *Several groups had challenged the Spring '97 results of the Scottish researchers' claim of having cloned Dolly from an adult cell. Yanagimachi and coworkers at the University of Hawaii* [***Nature* 394**: 369, 1998] *have now confirmed that cloning from adult cells is not only possible but repeatable with a reasonably high efficiency—using slight modifications of the technique reported by Ian Wilmut (Roslin Institute, Scotland). The basic principle is to inject nuclei from adult cells into eggs whose own nuclei have been removed, and then to "activate" the egg with its new nucleus. In Scotland, the same electrical pulse that fused the nucleus with the egg also prompted the egg's activation. In Hawaii, the nucleus was microinjected into the egg with a very fine needle, the cells were given 6 hours to "give the egg time*

to alter the donated DNA so that its developmental genes can be expressed again," and then strontium added to the culture medium stimulates the release of calcium—the same signal that tells fertilized eggs that it is time to start dividing. The Yanagimachi paper reported a yield of more than 50 cloned mice using this technique!

An explosion of further advances since last summer has ensued. Transplanting cryopreserved (frozen) ovarian tissue from elephants into mice, researchers showed that the elephant tissue was able to undergo normal development in immune-deficient mice [***Animal Reprod Sci* 53***:* 265, 1998]*; this technique has far-reaching implications for the preservation of endangered species. In Madison, Wisconsin, transgenic cattle were produced by reverse-transcribed gene transfer in oocytes* [***Proc Natl Acad Sci USA* 95**: 14028, 1998]. *Human embryonic stem (ES) cells, which have the potential to differentiate into every adult tissue just as mouse ES cells do, were shown to grow in cell lines capable of developing into any tissue type* [***Science* 282**: 1014, 1998]*, which led to congressional hearings on Capitol Hill a week later. In Nara, Japan, eight calves were cloned from oviduct epithelial cells of a single adult cow* [***Science* 282**: 2095, 1998]. *Using the Hawaiian technique of nuclei from granulosa cells injected into enucleated oocytes, as described above, a South Korean research team announced (Dec 98, without a scientific publication) that they had "cloned a human embryo" to the 4-cell stage, then destroyed it without implanting it into a human body. As the technology becomes easier to clone a human, of course, the ethical issues loom larger! Stay tuned!*

Q I am taking fluoxetine and my physician mentioned to stay away from grapefruit juice. Why?

A *Prozac (R) (fluoxetine) is a widely prescribed antidepressant in the U.S. Fluoxetine is a member of the "CYP2D6 panel" (leading article,* ***Interface*** *issue #11, Spring '97). Grapefruit juice contains an inhibitor of the CYP2D6 enzyme which normally breaks down fluoxetine. Drinking large amounts of grapefruit juice will block 2D6 action, meaning that your recommended prescribed dosage of fluoxetine might then be "too high," leading to side-effects (of which there are many!) from what the body perceives as an excessive dose of this drug.*

Q *Interface* is a GREAT NewsLetter! Is the title of Dr. Talaska's talk (issue #14) correct? It strikes me as funny...

A *Perhaps the title of his presentation, "The impact of N-acetyltransferase on human genotoxic response to prevent discrimination and maintain privacy and confidentiality," tried to cover too much! "N-acetyltransferase" refers to the human* ***NAT2*** *N-acetylation polymorphism. Slow acetylators who work with chemical dyes and smoke cigarettes have an increased risk of urinary bladder cancer; slow acetylator cigarette smokers and chemical dye workers do exhibit more DNA damage (genotoxicity) than nonsmokers and people who are not chemical dye workers. As covered in the leading article of this issue, if an employer finds out the* ***NAT2*** *status of an employee and wants to prevent disease in the work place, this could be interpreted as a loss of privacy and confidentiality and could lead to discrimination in the work place!*

Observations by a Biologist

Good Mom, Bad Mom

There has been increasing attention given to the development of "behavioral phenotyping" tests of mice that are genetically different, and especially of transgenic and "gene-knockout" mice. In addition to testing for "anxiety," "learning" and "memory," scientists have been studying maternal behavior by quantitating the behavior of "pup retrieval." In other words, if a scientist scatters all the pups in a newborn litter to the far corners of the mouse cage, a wild-type mother will dutifully, instinctively dash around the cage—quickly picking up all her babies and returning them to her nest for further breast-feeding. This is called "robust maternal behavior."

Studies in mice who have had a disruption of any of several genes suggest that these genes are somehow related to being "good mouse mothers." The heterozygous deletion (one allele disrupted) of the paternally imprinted gene *Mest*, leading to decreased expression of this gene product (whatever it is!) in the hypothalamus and amygdala of adult females, eliminates retrieval behavior [***Nature Genet* 20:** 163, 1998]. Other genes that diminish good maternal behavior include the proto-oncogene *FosB*, dopamine β-hydroxylase (*Dbh*), and the prolactin receptor (*Prlr*) [***Nature Genet* 20:** 108, 1998]. Can different alleles in humans—or drugs or other environmental agents that might inhibit the enzymes/proteins of the above-mentioned genes—cause important effects on maternal behavior?

Latest on the *BRCA1* and *BRCA2* Genes

Identification and characterization of two genes, *BRCA1* and *BRCA2*, which play a role in perhaps 5% of breast and/or ovarian cancer and some portion of prostate cancers, have been discussed in several earlier issues of the ***Interface***. As an example of "reverse genetics," these genes were isolated by epidemiological studies and their chromosomal location (phenotype associated with genotype, issue #12) - rather than "forward genetics" (cloning a gene and determining its function first, before looking for associations with disease). As is common with reverse genetics, the true "functions" of *BRCA1* and *BRCA2* are not yet certain.

The BRCA1 and BRCA2 proteins have now been found to participate together in a repair pathway of double-stranded DNA breaks, as well as homologous recombination [***Molec Cell* 2:** 317, 1998]. Consistent with this finding, BRCA1 was shown to be required for transcription-coupled repair of oxidative DNA damage [***Science* 281:** 1009, 1998] and associated with the centrosome during mitosis [***Proc Natl Acad Sci USA* 95:** 12983, 1998]. BRCA2 appears to act in maintaining genomic stability by participating with the cell-cycle proteins p53 and RAD51 [***Proc Natl Acad Sci USA* 95:** 13869, 1998].

Disruption in a tumor suppressor gene, the adenomatous polyposis coli (*APC*) gene, leads to an increased risk of colorectal cancer. The ***I1307K*** (change of isoleucine to lysine at position 1307 in the enzyme) variant of the *APC* gene was found in four of eight Ashkenazi Jewish pedigrees that have an increased risk of breast cancer [***Nature Genet* 17:** 79, 1997]. Redston and his team clarified this association [***Nature Genet* 20:** 13, 1998], however, by showing that the effect of the *APC* I1307K allele on breast cancer risk is largely, or entirely, limited to those with *BRCA1* "***founder mutations***" (similar DNA change inherited among descendants in a family pedigree). Thus, testing for the *APC* I1307K allele, as an important breast cancer susceptibility allele, is not justified.

SCIENCE LITE

The following are actual excerpts from classified sections of city newspapers :

- Illiterate? Write today for free help.
- Auto Repair Service. Free pick-up and delivery. Try us once, you'll never go anywhere again.
- Our experienced Mom will care for your child. Fenced yard, meals, and smacks included.
- Dog for sale: eats anything and is fond of children.
- Man wanted to work in dynamite factory. Must be willing to travel.
- Stock up and save. Limit: one per customer.
- Get rid of aunts. Zap does the job in 24 hours.
- 3-year-old teacher needed for preschool. Experience preferred.
- Mixing bowl set—designed to please a cook with round bottom for efficient beating.
- Girl wanted to assist magician in cutting-off-head illusion. Blue Cross benefits and salary.
- Dinner Special -- Turkey $4.75; Chicken or Beef $4.25; Children $2.00
- For sale: antique desk—suitable for lady with thick legs and large drawers.
- Now is your chance to have your ears pierced and get extra pair to take home, too.
- We do not tear your clothing with machinery. We do it carefully by hand.
- For sale. Three canaries of undermined sex.
- Great Dames for sale.
- Have several very old dresses from grandmother in beautiful condition.
- Vacation Special: have your home exterminated.
- Semi-Annual after-Christmas Sale.
- For Rent: 2-bedroom hated apartment.
- Man, honest. Will take anything.
- Used Cars: Why go elsewhere to be cheated. Come here first.
- Christmas tag-sale. Handmade gifts for the hard-to-find person.
- Wanted: Hair cutter. Excellent growth potential.
- Wanted. Man to take care of cow that does not smoke or drink.
- Our bikinis are exciting. They are simply the tops.
- Wanted. Widower with school-age children requires person to assume general housekeeping duties. Must be capable of contributing to growth of family.
- And now, the Superstore-unequaled in size, unmatched in variety, unrivaled inconvenience.
- We will oil your sewing machine and adjust tension in your home for $3.00

CEG Members in the News

Eula Bingham, received the Henry Smythe, Jr. Toxicologist Award at a meeting of American Academy of Industrial Hygiene held in Seattle, Washington. She also presented two papers. The first, ***"A (former) regulator looks at animal testing"*** was presented at the Arkansas Toxicology Symposium (November 1998, Little Rock), the second, ***"Occupational health and safety heritage: discussion from those who have shaped our history"*** was given at the 126th Meeting of the American Public Health Association (November 1998, Washington DC).

Ranjan Deka organized a symposium on "Molecular Anthropology in the 21st Century" at the 14th International Congress of Anthropological and Ethnological Sciences, held at the College of William and Mary (August 1998, Williamsburg, Virginia). He delivered a talk entitled ***"Dynamic mutations and evolution of trinucleotide repeats."***

Nira Ben-Jonathan was invited to participate in an international seminar series on "Plastics in the environment" at the Institute of Toxicology of the University of Zürich, giving a talk entitled ***"Xenoestrogens: in vivo and in vitro effects of bisphenol A on reproductive functions"*** (January 1999, Switzerland).

Tom Doetschman was invited to give a seminar at the Institute of Molecular and Cell Biology entitled ***"Cardiovascular functions of FGF2"*** (September 1998, Singapore). At the Medical University of South Carolina, to the Division of Cardiovascular Development, Department of Cell Biology, he delivered a seminar on ***"Just what does FGF2 do, anyway?"*** (November 1998, Charleston). He was also an invited Speaker at the meeting of the National American Association of Laboratory Animal Science delivering the Wallace P. Rowe Memorial Lecture entitled ***"Genetic engineering in the mouse"*** (October 1998, Cincinnati, Ohio). And at the 9th International Conference of Inflammation Research Association he was invited to speak on ***"TGFβ1 in inflammation"*** (November 1998, Hershey, Pennsylvania).

Tatiana Foroud delivered two talks at the recent Psychiatric Genetics meeting (Bonn, Germany) entitled "***Linkage of an alcohol-related severity phenotype to chromosome 16"*** and ***"Genomewide scan of affected relative pairs using the NIMH genetics initiative bipolar affective disorder pedigrees."***

George Leikauf was a featured speaker at the American Association for Aerosol Research and delivered a talk on ***"Pathogenetics of particulate matter"*** (June 1998, Cincinnati, Ohio). He also lectured on ***"Oxidant-induced lung injury: genetic determinants and transgenic models"*** at the University of Alabama (August 1998, Birmingham).

Grace Lemasters was appointed to the US EPA Science Advisory Board's Environmental Health Committee, October 1, 1998 to September 30, 2000.

Jun Ma gave a seminar at the University of Nebraska on ***"Understanding how transcriptional activation works in living cells"*** (September 1998, Lincoln).

Dan Nebert was an invited speaker and chairman of the session on "Stress Response Mechanisms," 5th international Meeting of the International Society for the Study of Xenobiotics (ISSX) in Cairns, Australia (October 1998). He was also invited to speak and participate in the Workshop on "Genetic Susceptibility to Environmental Exposure," at the Institute for Science, Law, and Technology, Illinois Institute of Technology (November 1998, Chicago). In addition, he was an invited speaker and member of the Conference Organizing Committee for the 12th Annual International Barton Creek Conference on Carcinogenesis and Risk Assessment, "Gene-Environment Interactions: Emerging Issues, Technologies and Biological Paradigms" (December 1998, Barton Creek, Texas).

Alvaro Puga was a kenote speaker at the 16th Annual Meeting of the New England Membrane Enzyme Group (October 1998, Ascoutney Mountain Resort, Vermont). He also gave a talk at the 12th International Conference on Carcinogenesis and Risk Assessment (December 1998, Barton Creek, Texas).

Nancy Steinberg-Warren received an award for outstanding achievement and leadership for 1998 which was presented on behalf of the National Society of Genetic Counselors. She has a new appointment as Assistant Professor and Director of the Genetic Counseling Graduate Program, College of Allied Health Sciences, University of Cincinnati. She presented three papers at the National Society of Genetic Counselors "Annual Education Meeting" on ***"Start Healthy: A comprehensive community approach to preconceptional health," "Siblings of children with Down syndrome: the relationship between knowledge about Down syndrome and self-concept,"*** *and* ***"Current genetic screening practices of IVF Centers that participate in oocyte donation"*** (October 1998, Denver, Colorado).

Rakesh Shukla has become the Director of the Center for Biostatistical Services, which provides assistance in formulating, phrasing and devising appropriate study designs, for defining appropriate outcome, predictor and confounding variables, and for calculation of sample size and power. These services are also available to CEG investigators through the Genetic Epidemiology and Biostatistics Facilities and Services Core of the CEG.

Glenn Talaska gave an invited Plenary Lecture entitled ***"Biomarkers for carcinogen exposure and effect"*** at the 4th International Symposium on Biological Monitoring in Occupational and Environmental Health. (September 1998, Seoul, Korea). This Symposium was sponsored by the World Health Organization.

Interface is supported by NIH grant # ES06096 from the National Institute of Environmental Health Sciences, and is published by the University of Cincinnati Center for Environmental Genetics, **Marshall Anderson, PhD, Director**

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CONGRATULATIONS Three CEG members, **Joseph Broderick, MD,** Professor of Neurology, **Gregory Grabowski, MD,** Professor of Pediatrics, and **Jeffrey Whitsett, MD,** Professor of Pediatrics, were among 112 faculty members at UC listed as the best physicians in the United States. ***"The Best Doctors in America: 1999 Edition"*** published by Woodward/White Inc. (Aiken, South Carolina), chose them from a survey of more than 30,000 US doctors (December 1998).

Welcome

The CEG has a new member:
James Stringer, PhD
Associate Professor of Molecular Genetics, Biochemistry and Microbiology, College of Medicine, University of Cincinnati
james.stringer@uc.edu
http://www.molgen.uc.edu/cv/Stringer/Stringer.html
His research has focused recently on investigating the function of the Bloom Syndrome (BS) gene in maintaining genome stability. This work is in collaboration with another CEG member, Joanna Groden. He produced two cell lines: FSH1, which detects homologous recombination events, and G11, which detects mutations caused by loss of a base from a mononucleotide run.

CEG - SPONSORED SPEAKERS

Ann Schwartz, PhD, MPH
Department of Human Genetics
MCP Hahnemann School of Medicine
Allegheny Singer Research Inst., Pittsburg, Pennsylvania
21 May 1998 ***"Genetic epidemiology of lung cancer"***

Bert La Du, MD, PhD
Emeritis Professor, Acting Director of Research
University of Michigan, Ann Arbor, Michigan
10 December 1998 ***"Quantitative analysis of specific isozymes to discover their pharmacogenetic and toxicogenetic functions."***
11 December 1998 ***"Protective roles of paraoxonase (PON1) against organophosphates and oxidative damage to cells."***

Best Bumper Sticker: "The gene pool could use a little chlorine"