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Genetic Clues to Radiation Sensitivity

Howard Hughes Medical Institute researchers have identified a group of genes that influence a person's sensitivity to radiation. The findings are a step toward a long-term goal of developing new tests that would help physicians determine the optimal dosage of radiation for cancer treatment based on a person's genetic profile.

"This study identifies a set of genetic variants that influence how a cell responds to radiation-induced damage," said Vivian G. Cheung, senior author of a report published on April 6, 2009, in the journal *Nature*.

"Now that we know these genetic variations, we hope to build predictors that tell us who is more sensitive to radiation, so that we can decrease doses of radiation therapy to avoid damaging normal tissue," said Cheung, an HHMI investigator at the Children's Hospital of Pennsylvania and the University of Pennsylvania.

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Doctors who use radiation therapy for the treatment of blood cancers and certain brain tumors have long known that it can also put children at high risk for developing a secondary cancer. By understanding the genes and proteins that cells use to respond to radiation, researchers could identify new ways to make tumor cells more sensitive to radiation therapy. Manipulating those proteins might also help protect cells from other sources of radiation, and could be a way to reduce radiation risks to individuals such as astronauts who are exposed to radiation, Cheung added.

Cheung, who is a physician-scientist, was interested in how ionizing radiation induces damage in DNA. She said she was "surprised that so little is known

about why people differ in the amount of damage they sustain” when exposed to radiation.

Experiments comparing these effects in humans would be unacceptable, she said, so Cheung and her colleagues used human cell lines as proxies – exposing them to a standard radiation dose and noting which cells survived and which were killed. The cell lines had been previously developed from cells collected from 15 families in Utah, and represented about 150 individuals with well-documented pedigrees.

The scientists used microarrays designed to analyze the activity of more than 10,000 genes to take snapshots of gene expression in the cells prior to radiation exposure, and at two and six hours after exposure. After those studies, the researchers narrowed their focus to 3,280 genes whose expression went up or down by at least 50 percent.

Among those genes, some were already known to have roles in repairing DNA damage, regulating the cell cycle, or apoptosis – the programmed death of unneeded or damaged cells.

Each pattern of gene expression change in an individual’s cells represented an inborn “phenotype,” indicating sensitivity to radiation. In Cheung’s experiments, sensitivity was a function of whether the cells survived or were killed by the dose of radiation.

The radiation-response genes the team identified had been catalogued in the Human Genome Project, so their locations within the genome were known. But the activity of each gene was controlled by a switch-like bit of regulatory DNA. Variations in these regulatory sequences accounted for the differences in radiation response from one person to another. The locations of these regulators were not known. Cheung and her colleagues knew that some of the sequences might be within the genes themselves, whereas others could be nearby or even on another chromosome.

Using computational analysis, the scientists identified more than 1,250 phenotypes that segregated in certain families. They mapped the regulatory sequences that were responsible for this variation to specific locations in the human genome. In many cases, however, the locations were not pinpoints but long stretches of genetic material. To narrow down the search further, the researchers employed “text mining,” a computer tool that searches written material for patterns that reveal hidden information. In this case, the scientists searched for clues to the locations of the regulatory DNA by text mining journal articles that included the names of the genes of interest.

In addition, the team also used RNA interference technology to turn down the gene regulators. These experiments showed that turning down the activity of the regulatory DNA altered the expression of the corresponding genes identified in their large-scale search of the scientific literature.

What emerged from this painstaking research – which Cheung says was carried out “by two people at the lab bench and one at the computer” -- was a set of 18 radiation-response genes, five of which were regulated by DNA sequences within or in neighboring the genes (so-called *cis* regulators), and 13 that were controlled by distant DNA sequences (*trans* regulators).

As the researchers expected, a number of the regulatory sequences proved to be transcription factors, which bind to genes and turn their activity up or down. But to their surprise, the majority turned out not to be transcription factors. “And yet they still influence gene expression,” Cheung said. “So we are now trying to find out how they regulate gene expression levels.”

Cheung said she hopes her team’s findings will “open up the doors” to a future in which biomarker tests will reveal a patient’s susceptibility to radiation damage, leading to a personalized prescription for therapy.

Beyond this kind of application, she added, the successful – if laborious – series of analyses that turned up the regulatory sequences and their locations “seems to be a good way to identify a large set of genetic variations that contribute to sensitivity to environmental agents.”