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Evolution of human genome's 'guardian' gives people unique protections from DNA damage

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Human evolution has created enhancements in key genes connected to the p53 regulatory network – the so-called guardian of the genome – by creating additional safeguards in human genes to boost the network's ability to guard against DNA damage that could cause cancer or a variety of genetic diseases, an international team of scientists led by Cincinnati Children's Hospital Medical Center writes in the Jan. 22 *Proceedings of the National Academy of Sciences*.

Because genetically engineered mouse models are increasingly powerful tools in understanding the risks and mechanisms of human diseases – and rodents do not have the same evolution-based safeguards in p53 function as humans – the study also underscores the need for additional considerations in the interpretation of research using rodent models.

"Our findings are especially important because rodents are often used as model organisms to investigate the genetic origins of diseases that affect humans, such as cancer investigators evaluating the impact of DNA-damaging agents," said Anil Jegga, DVM, a researcher in the Division of Biomedical Informatics at Cincinnati Children's. "Rodent models remain important to our understanding of disease processes, although our study suggests the need to address experimentally the differences in p53 regulatory pathways between humans and rodent models."

In the study, Jegga and his colleagues used comparative functional

genomics to look systematically at small DNA sequences associated with the promoters, or enhancers, of specific genes that carry out orders from p53. These promoter elements act like antennae – responding to activated p53 by boosting target gene expression and function inside a cell's nucleus.

By comparing these response elements across nearly 50 different binding sites of genes in the p53 network, and looking specifically at genes that repair DNA damage in 14 species (from zebra fish to humans), researchers were able to reveal critical evolutionary changes in their function. The 14 species represented an estimated 500 million years of evolutionary separation, helping investigators determine how the function of p53 response elements was conserved or changed as different species developed.

Dr. Jegga said researchers were surprised to find the acquisition of functional response for certain genes involved in DNA metabolism or repair to be mostly unique in humans. While the functional ability of some genes is shared with chimpanzees and rhesus monkeys, researchers said DNA metabolism and repair function it is not shared at all with rodents.

In humans, when DNA damage is detected, the p53 network seems to have gained additional capabilities that allow it to slow cell growth, initiate repairs or, if needed, apoptotic cell death. Apoptotic, or programmed cell death capability in the p53 network, is thought to be evolutionarily conserved throughout the development of vertebrate species and was probably established after the divergence of vertebrates and non-vertebrates. DNA metabolism and repair capabilities controlled by p53 may have emerged more recently in evolutionary history to create primate-specific response characteristics, the researchers explained.

"The fact that DNA metabolism and repair genes have undergone this

kind of evolution in humans may reflect an increased need for coordinated control of molecular repair activities during DNA replication to allow for the maintenance of genomic integrity during complex differentiation, growth, and aging," said Bruce Aronow, Ph.D., co-director of Computational Medicine at Cincinnati Children's and a study co-author.

"That different strategies to guard our chromosome structures and DNA sequences against damage are subject to evolutionary adaptation is also suggested by other knowledge we have," Dr. Aronow explained. "For example, compared to rodents humans have much shorter telomeres, which are regions of highly repetitive DNA at the end of chromosomes that help shield against damage. Shorter telomeres can make people more susceptible to chromosomal damage and increase our risk of developing malignant tumors. When genes replicate, the process does not copy the very ends of the gene, so telomeres act like caps on the ends of shoelaces, helping preserve DNA structure and preventing genetic unraveling and loss of genetic information."

A clue to p53 functional differences may be found in sunlight. Exposure to the ultra-violet rays in sunlight activates the DNA-damage responses of the repair gene (Ddb2) in humans, but the same gene does not function in rodents. Some studies have suggested that rodents may have a reduced need for genetic protection from sunlight because they are nocturnal and have a fur shield.

"Although the full implications of these evolutionary points remain far from clear, our work demonstrates that there has been both refinement and evolution of gene networks controlled by p53," Dr. Aronow said. "Exciting work is underway by research groups within the National Cancer Institute's Mouse Models of Human Cancer Consortium to develop mice that are genetically engineered to test the combined effects of altering p53 and telomerase, the enzyme that controls the length and

stability of repeating DNA sequences in the telomere region. Mouse models will continue to become progressively more powerful tools for studying human cancer and additional information about the p53 network will help us refine our interpretation of pre-clinical research that may lead to improved cancer prevention for at-risk and normal individuals."

In conducting their analysis of p53 target genes, the international research team used comparative DNA sequence analysis and functional tests of highly engineered yeast and mouse cell culture assays to examine 47 established p53 response elements in 14 vertebrate and non-vertebrate species. The study included researchers from the National Institute for Cancer Research (Molecular Mutagenesis Unit, Department of Translational Oncology) in Genoa, Italy, and the Laboratory of Molecular Genetics Chromosome Stability Group of the National Institute of Environmental Health Sciences (National Institutes of Health).

Source: Cincinnati Children's Hospital Medical Center