Tumor suppressor mutations alone don't explain deadly cancer

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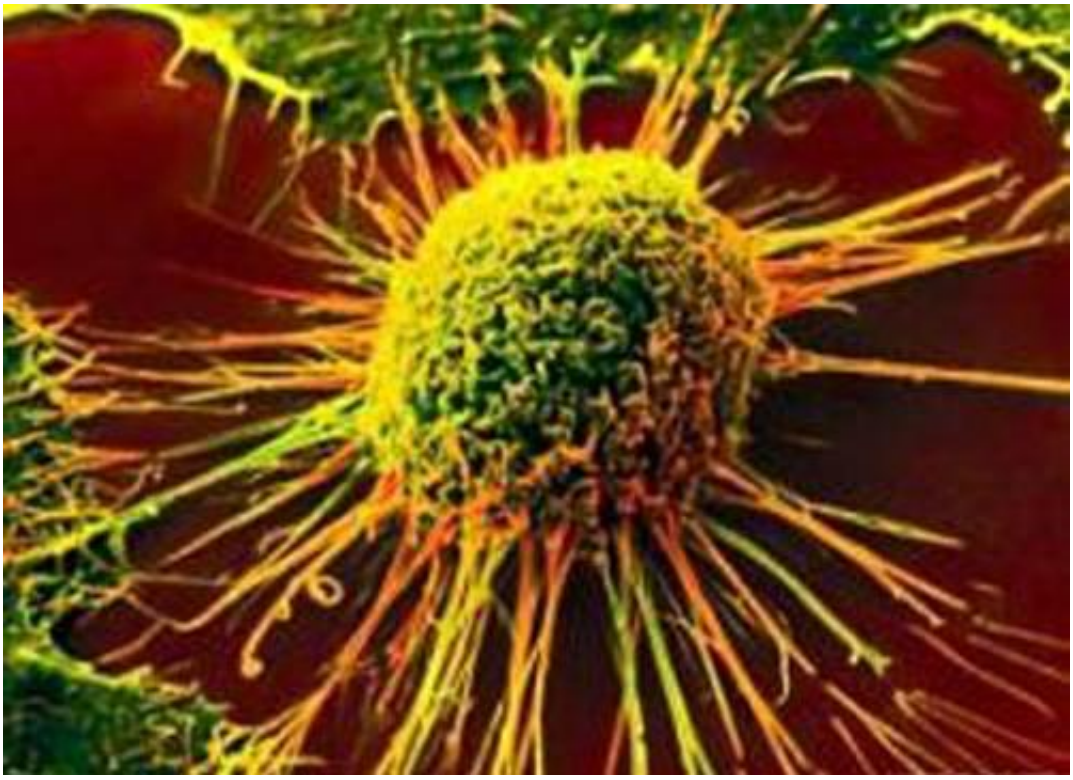

Although mutations in a gene dubbed "the guardian of the genome" are widely recognized as being associated with more aggressive forms of cancer, researchers at the University of California, San Diego School of Medicine have found evidence suggesting that the deleterious health effects of the mutated gene may in large part be due to other genetic

abnormalities, at least in squamous cell head and neck cancers.

The study, published online August 3 in the journal *Nature Genetics*, shows that high mortality rates among head and neck cancer patients tend to occur only when mutations in the tumor suppressor gene coincide with missing segments of genetic material on the cancer genome's third chromosome.

The link between the two had not been observed before because the mutations co-occur in about 70 percent of head and neck tumors and because full genetic fingerprints of large numbers of cancer tumors have become available only recently.

"These two genetic malfunctions are not two separate stab wounds to the body," said co-senior author Trey Ideker, PhD, chief of the Division of Genetics. "One exposes the Achilles tendon and the other is a direct blow to it."

To patients with these cancers, the study's results mean that there may be therapeutic value in testing tumors for the two genetic identifiers, known as a TP53 mutation (short for tumor protein 53) and a 3p deletion (short for deletions of genetic information on the short arm "p" of the third chromosome).

TP53 plays a key role in regulating cell growth, detecting and fixing DNA, and directing cell apoptosis (death) if the DNA damage is irreparable. Because of this, the TP53 protein is sometimes called the "guardian of the genome."

The study's findings suggest that if both markers are present, treatment should be intensified. If only one mutation is present, treatment might be de-intensified because the TP53 mutation alone is less deadly than previously thought. The latter would have immediate benefits in

reducing deaths caused by complications related to medical care.

"We are in the early stages of being able to personalize head and neck cancer treatments based on the tumor's actual biology, the same as what's done with breast cancers," said co-senior author Quyen Nguyen, MD, PhD, associate professor of Otolaryngology-Head and Neck Surgery. "In the past, treatments have been based largely on the size and location of the tumor. Now, we know that some large tumors may respond to less aggressive treatment while some small tumors may need intensified treatment. This will have a huge impact for patients."

The study analyzed the complete genomic signatures of 250 cases of squamous cell head and neck cancer extracted from The Cancer Genome Atlas, a repository of sequenced cancer genomes for more than 20 different types of human cancers maintained by the National Institutes of Cancer. All of the tumors were from patients younger than 85 years of age.

Of these, 179 had both mutations; 50 had one of the two mutations; and 22 had neither mutation. Comparisons with patient outcome data showed that half of patients with both mutations would likely die of cancer within 2 years, while 66 percent of patients with one or neither mutation would be expected to live five years or more. These survival statistics were independent of the patients' clinical cancer stage.

Besides causing cervical cancer, the human papilloma virus (HPV) is implicated in the growing epidemic of head and neck cancers in otherwise healthy adults. It is believed that the virus can co-opt the activity of TP53, affecting cells in much the same way as a TP53 mutation but without causing a mutation. For this reason, the analysis examined HPV-positive and HPV-negative tumors separately.

One of the study's more compelling discoveries is that among HPV-

positive tumors, the most aggressive cancer cases were also highly linked to the presence of 3p deletions.

"Our findings raise fundamental questions about the role of TP53 in cancer and suggest that some of the deleterious health effects of TP53 mutations might actually be due to something else going on in the third chromosome," said lead author Andrew Gross, a graduate student in the Bioinformatics and Systems Biology Program.

More information: Multi-tiered genomic analysis of head and neck cancer ties TP53 mutation to 3p loss, *Nature Genetics*, dx.doi.org/10.1038/ng.3051

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