Distinct molecular subtype of prostate cancer identified

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A collaborative expedition into the deep genetics of prostate cancer has uncovered a distinct subtype of the disease, one that appears to account for up to 15 percent of all cases, say researchers at Weill Cornell Medical College, the Broad Institute of MIT and Harvard and the Dana-Farber Cancer Institute.

In the study, published online May 20 by the journal *Nature Genetics*, investigators describe how they discovered novel mutations in the SPOP ("S-pop") gene in numerous patient tumors, saying this alteration is thus far unique to prostate cancer and so represents a distinct molecular class that might assist in cancer diagnosis and treatment. Researchers suspect the mutations alter the way cells tag proteins for degradation, leading to an accumulation of dangerous molecules that drive the growth of cancer, perhaps from the beginning.

This finding adds to a string of discovery of other genes linked to prostate cancer over the years by this team of investigators, the totality of which is painting a comprehensive picture of how genetic alterations contribute to prostate cancer -- the most common cancer in men aside from skin cancer, accounting for the second leading cause of cancer deaths.

"These studies constitute a unique, meticulous and intensive look at prostate cancer to see the mechanisms driving this disease," says Dr. Mark A. Rubin, The Homer T. Hirst Professor of Oncology in Pathology and vice chair for experimental pathology at Weill Cornell Medical

College. "This study, and our prior findings, tells us that prostate cancer is not just one disease. So far, we have found two main pathways for prostate cancer to develop and this opens the door to development of specialized diagnostic tools and treatments."

Mutations in SPOP constitute one major pathway, accounting for up to 15 percent of prostate cancer cases. The other is the 50 percent of prostate cancers containing the so-called "ETS" fusion genes, such as TMPRSS2-ERG.

"While there is still a need for increased discovery, it does appear that the overall genetic landscape of prostate cancer is taking shape, and better understanding of the biology and possible therapeutic avenues linked to these alterations has become a very high priority," says Dr. Levi Garraway, a senior associate member of the Broad Institute of MIT and Harvard, and assistant professor at the Dana–Farber Cancer Institute and Harvard Medical School.

Dr. Rubin and Dr. Garraway are co-senior investigators for this study and for others that have preceded it in this unique examination of prostate cancer genes.

In February 2011, the collaborative groups published a study in Nature in which they used whole genome sequencing to discern global changes and patterns of abnormality in seven prostate tumors and compared them to normal tissue samples. They found that areas of the genome had been unexpectedly rearranged -- just as Dr. Rubin and his collaborators at the University of Michigan had in 2005 with the discovery of the common recurrent TMPRSS2-ERG gene rearrangement, created by the fusion of two different genes.

This current study looked at different drivers of cancer, which are mutations in specific genes. It focused on the 1-2 percent of DNA in the

genome that codes for proteins, and, as such, is one of the largest "whole exome" sequencing studies published on prostate cancer to date, according to Dr. Garraway.

The impetus to search for genes in this way came about because of the observation that SPOP appeared to be mutated in some cases of prostate cancer, says Dr. Christopher Barbieri, a fifth year urology resident at Weill Cornell who spent a research year in Dr. Rubin's laboratory in the Department of Pathology and Laboratory Medicine.

Broad Institute researchers, led by Dr. Garraway and Dr. Sylvan Baca, completed an intensive exome sequencing of 112 prostate tumors and normal tissue pairs. The findings were verified in another 400 prostate cancer patient samples from other institutions around the country. Dr. Barbieri of Weill Cornell, Dr. Baca and Dr. Michael Lawrence of the Broad Institute are the study's co-lead investigators.

The teams found three genes significantly altered in the prostate cancers, but not in non-cancerous tissue. In addition to SPOP mutations, which occurred in 6 to 15 percent of tumors across multiple independent cohorts, they found mutations in the FOXA1 and MED12 genes, each of which are found in about 4 percent of patient tumors.

Further examination revealed the interesting nature of SPOP mutations. SPOP belongs to a class of proteins known as ubiquitin ligases, whose role is to mark other proteins in the cell for degradation. The mutations the team discovered all occur where the SPOP protein binds to the other proteins it should tag. "That suggests that there might be an accumulation of proteins in the cell that aren't cleaned out and this might lead to cancer growth, or the mutations could be removing proteins that help prevent unchecked cell growth," says Dr. Rubin. "We are working hard to understand what is happening."

Because they were also found in premalignant lesions, the researchers suspect SPOP mutations occur early in development of the cancer. "This could be one of the switches that turns prostate cancer on," Dr. Rubin says.

They also do not yet know if SPOP mutations define a more aggressive type of prostate cancer.

Dr. Rubin further notes that SPOP mutations and TMPRSS2-ERG fusion genes never occur in the same tumor. They are mutually exclusive, implying two distinct molecular classes of prostate cancer.

"These studies really do provide a comprehensive catalog of the genetic changes occurring in prostate cancer," Dr. Rubin says.

As a urologist who treats men with prostate cancer, Dr. Barbieri says the finding of a SPOP mutation may be one of the breakthroughs oncologists have been seeking. "We have very limited information available to us now on the particular biology of the tumor that prostate cancer patients have, and how best to treat that cancer," he says. "But given the finding that SPOP mutations form a distinct kind of cancer, and if you low ball the incidence at about 10 percent of all tumors, that means, every year, 25,000 men in the U.S. will be diagnosed with tumors that have this mutation. That is a large number. Knowing what these mutations mean may give us huge clues about how the patient's cancer will progress and how they might be best treated in the future," Dr. Barbieri says.

"This prostate cancer subtype appears to contain abnormalities in cellular processes that are quite new to prostate cancer researchers, and should open up many future avenues for enhanced understanding of the disease," says Dr. Garraway. He adds, "our collaboration with the Rubin lab has been crucial to the success of this effort. Our groups bring nicely

complementary expertise in disease biology, genomics and pathology."

"Going forward, we will attempt to define the specific biological roles of several new prostate cancer genes, and we will characterize new prostate cancer genomic alterations that are emerging through ongoing discovery efforts," Dr. Garraway says.

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