Tumor genome sequencing shows the most frequently altered gene in bladder cancer

April 20 2015, by Garth Sundem

Dan Theodorescu, MD, PhD, director of the CU Cancer Center shows the gene TERT is the most common alteration in bladder cancer Credit: CU Cancer Center

In results presented today at the American Association for Cancer Research (AACR) Annual Meeting 2015, a collaborative study by the University of Colorado Cancer Center and the National Cancer Institute (NCI) reports that the TERT gene promoter was altered in 69 percent of

54 cases of bladder cancer due to variants that occur after birth (called "somatic") and in 56 percent of bladder cancers due to inherited variants (called "germline"). The study shows these TERT alterations frequently co-occur with alterations in recently identified bladder cancer genes such as the stromal antigen 2 (STAG2), and the lysine-specific demethylase 6A (KDM6A).

"We expect these TERT alterations happen early in the development of bladder cancer as a sort of precursor to the disease itself and so it may be possible to develop a genetic test that examines urine as a way to screen for the disease," says Dan Theodorescu, MD, PhD, director of the CU Cancer Center and the paper's senior author.

The TERT gene encodes the enzyme telomerase, the concentration of which helps to determine the length of telomeres, protective genetic material attached to the ends of chromosomes. Specifically, the alterations so frequently seen in these samples of bladder cancer were in regions of DNA just upstream from the TERT gene, called "promoter" regions, which help to determine how often a gene is manufactured into a protein. Unpublished data show that TERT alterations lead to shorter telomere length in human samples of bladder tumor tissue when compared with telomere length in surrounding healthy tissue from the same patient. Likewise a 2011 meta-analysis of telomere length and cancer showed that shorter telomeres are associated with the development of many types of cancer.

Somatic alterations were also observed in 15 percent of tumors in the BRCA1-associated protein-1 (BAP1) gene, a gene that has recently been characterized in the development of bladder cancer. The BAP1 alterations co-occurred with KDM6A mutations and contributed to a high frequency of BRCA pathway defects due to germline and somatic alteration of BRCA1, BRCA2, ATM, and PALB2.

Prior studies have shown that BRCA1- and BRCA2-mutant breast, ovarian, and prostate cancers are responsive to the class of drugs known as poly(ADP-ribose) polymerase (PARP) inhibitors.

"We are hopeful that FDA-approved drugs such as PARP inhibitors that are currently being developed to treat BRCA-mutant cancers may be effective in treating the potentially large number of bladder cancer patients with BRCA DNA repair pathway defects, as indicated by our current results," says Michael Nickerson, PhD, staff scientist and lead author from the National Cancer Institute.

Finally, somatic STAG2 alterations were observed in 17 percent of tumors and were associated with a poor prognosis, implying it may be a marker for an especially aggressive form of the disease. The STAG2 and KDM6A genes are located on the X chromosome, which may explain why men, with only one copy of these cancer genes, are more likely to develop bladder cancer.

"We hope the study offers a more complete picture of the genetic landscape of bladder cancer," Theodorescu says. "Now that we and many other groups have defined the extent of the genetic alterations in bladder cancer, we can start to pick apart the biology of how these alterations cause cancer and how we can intervene to better manage or stop the disease."

Provided by University of Colorado Denver