TCGA findings provide molecular background for second most common kidney cancer

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Scientists with The Cancer Genome Atlas (TCGA), a National Institutes of Health-funded project, have molecularly characterized two types of the second most common kidney cancer and classified several subtypes of the disease.

Papillary renal cell carcinoma (PRCC) accounts for 15 to 20 percent of kidney cancer cases diagnosed annually. It has long been classified as either Type 1 or Type 2, but until now much of what scientists knew about the underlying genetics of PRCC was based on information garnered from rare, inherited forms of the disease. Little was known about the molecular background of cases that occur without a family history of kidney cancer. Currently, there are no effective therapies for advanced PRCC.

The findings—which describe specific molecular differences between Types 1 and 2, as well as three subtypes of Type 2—were published today in the *New England Journal of Medicine*.

"Papillary renal cell carcinoma presents a particular problem for clinicians—in some patients, the disease remains indolent but widespread in the kidneys. In other cases, individual lesions can be highly aggressive," said Hui Shen, Ph.D., an assistant professor at Van Andel Research Institute (VARI) who performed key bioinformatics work for the study as part of TCGA's Research Network. "These

findings will not only provide doctors with much-needed information upon which to base clinical decisions, but also lay the foundation for the development of targeted therapies to better treat specific subtypes of the disease."

Categorizing cancer

Investigators conducted thorough genomic analyses on tumors from 161 patients and found that Type 1 and Type 2 PRCC are molecularly and genomically distinct, and should be considered two separate diseases. They also found three distinct subtypes of Type 2, each characterized by varying molecular alterations.

One of these Type 2 subtypes is marked by a gain of DNA methylation, or hypermethylation, at thousands of genes across the genome. DNA methylation is a type of modification to the DNA molecule that controls whether genes are switched on or off and, when it goes awry, can contribute to tumorigenesis. This novel subtype of PRCC Type 2—called CpG island methylator phenotype (CIMP)—has the lowest overall survival rates across PRCC types and is tightly associated with alterations in a gene that participates in metabolism. These changes cause CIMP tumor cells to experience a metabolic shift, which supports their rapid growth and survival.

"Samples with CIMP are associated with earlier age of PRCC onset and are the most lethal," Shen said. "The ability to further differentiate between subtypes such as CIMP using molecular markers gives scientists and clinicians a powerful tool for more accurately diagnosing cancer types as well as devising therapeutic strategies that target a patient's specific cancer."

The study also describes alterations of several known cancer-related genetic pathways, including MET/VEGRF and NRF2/ARE. Agents that

target MET/VEGRF are currently in clinical trials for PRCC, and targeted therapies for NRF2/ARE have recently been developed.

A large-scale effort

TCGA is run by NIH's National Cancer Institute (NCI) and National Human Genome Research Institute (NHGRI), and aims to comprehensively characterize cancers that have poor prognoses and a significant impact on public health. The TCGA Research Network is comprised of investigators from research and medical organizations across the U.S, including Shen; Peter Laird, Ph.D., a VARI professor who led the study's methylation data collection as part of the Research Network; and Stephen Baylin, M.D., a professor at VARI and co-head of Cancer Biology at Johns Hopkins University's Sidney Kimmel Comprehensive Cancer Center, who also is an author on the PRCC paper. They joined investigators from a total of 41 organizations who participated in the PRCC work.

Today's publication is one of the most recent in a long series of high-impact papers published as a result of TCGA's efforts. Last month, the group published a comprehensive analysis of invasive lobular breast carcinoma and, also today, a paper describing the genomic background of prostate cancer appeared in the journal *Cell*.

"TCGA's impact on cancer research is immeasurable," Laird said. "It demonstrates how large-scale collaborations between hundreds of scientists can bear fruit and have real, tangible results. TCGA's data is publically available—it benefits everyone in the field as well as patients who will benefit from therapies developed using this information."

Provided by Van Andel Research Institute