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Team finds new avenues of precision medicine for treating cancer

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An international team of scientists, including those at the Translational Genomic Research Institute (TGen), have discovered new avenues of potential treatments for a rare and deadly cancer known as Adrenocortical Carcinoma, or ACC.

In a study published today in the scientific journal *Cancer Cell*, researchers conducted an extensive genomic profile of ACC, a cancer of the adrenal glands, which are located above the kidneys. Current treatment options for ACC have not changed in decades and are not curative.

"This is one of the most comprehensive genomic characterizations ever done of this rare tumor type," said Dr. Timothy Whitsett, an Assistant Professor in TGen's Cancer and Cell Biology Division, and one of the study's authors. "This study should provide rationale and validation for new therapeutic strategies and clinical studies, providing potentially better treatments for ACC patients."

The study is part of The Cancer Genome Atlas (TCGA), a program overseen by the National Institutes of Health (NIH) that aims to generate comprehensive, multi-dimensional maps of the key molecular changes in major types of cancer.

"This data has implications for diagnosing and predicting outcomes of adrenal cancer. It also allows us to probe deep into the biology of the disease to understand how these new gene mutations contribute to

adrenal cancer progression and formation," said senior author Dr. Gary D. Hammer, the Millie Schembechler Professor of Adrenal Cancer at the University of Michigan Comprehensive Cancer Center.

The ACC study examined 91 tumor samples from six countries across four continents, providing a global look at this disease.

One of the major findings of this study is the identification of a third class, or subtype, of ACC. The study showed that the three subtypes of ACC hold significantly different outcomes for patients, and—based on their distinct molecular biomarkers—could help determine the best course of treatment for each patient.

"Clinical implementation of this three-class grading system would represent a true advance for patient care," the report said.

Another key finding was that many adrenal tumors undergo whole genome doubling—a phenomenon in which each chromosome in the gene replicates and creates a second copy. This reflects instability of the cancer genome, which is particularly prominent in adrenal cancer.

The study also identified additional genes that may drive the formation and progression of ACC tumors. And based on a review of clinical trials and FDA-approved cancer drugs, the study identified 51 genetic alterations that could provide targets for new therapeutics.

"We hope these results illustrate how integrating molecular and clinico-pathologic data can inform more precise therapeutic decision making for ACC patients," said Dr. Whitsett, who along with TGen colleagues provided analyses of ACC's cellular pathways, clinical pathology data and overall disease expertise.

Other than surgery and radiation, a standard treatment for ACC is the

use of a compound called mitotane, a chemical relative of DDT, which the U.S. banned as an insecticide in 1972. The adrenal glands are responsible for making several critical hormones, including those needed to respond to stress and maintain normal blood sugar levels. While use of mitotane in ACC patients reduces tumors, it does not provide a cure and has significant side effects. New and better therapies are needed for these patients.

The study published in *Cancer Cell*, titled Comprehensive Pan-Genomic Characterization of Adrenocortical Carcinoma, was coordinated by the National Cancer Institute and the National Human Genome Research Institute, and funded by the NIH.

Another TGen study finds how genes are expressed in ACC

In another study of ACC published March 10 in the journal *PLOS ONE*, TGen researchers used a new method of investigating DNA methylation—one of many mechanisms that cells use to control how genes are expressed—to identify new genes and cellular pathways associated with cancer of the adrenal glands.

"Using the 'discretization method,' which groups samples according to the DNA methylation levels, we were able to more precisely learn which DNA methylation changes result in aberrant gene and cellular-pathway expression in ACC," said Dr. Bodour Salhia, an Assistant Professor of TGen's Integrated Cancer Genomics Division, and the study's senior author. "This analysis of our data revealed new information about how genes are modulated and specifically how important tumor-suppressor genes can be turned off and allow the cancer to grow."

This study in *PLOS ONE* was able to use data unearthed during the

Cancer Cell study to further understanding of the potential drivers of ACC, Dr. Salhia said.

The study in *PLOS ONE*, titled Pathway Implications of Aberrant Global Methylation in Adrenocortical Cancer, was funded in part by the TGen Foundation through its ATAC Research Fund, the Kirsten's Legacy Fund, and contributions by the Virginia G. Piper Charitable Trust and an individual contributor, Mr. Ray Thurston.

More information: Siyuan Zheng et al. Comprehensive Pan-Genomic Characterization of Adrenocortical Carcinoma, *Cancer Cell* (2016). DOI: 10.1016/j.ccell.2016.04.002

Christophe R. Legendre et al. Pathway Implications of Aberrant Global Methylation in Adrenocortical Cancer, *PLOS ONE* (2016). DOI: 10.1371/journal.pone.0150629

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