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Whole genome sequencing of rare olfactory neuroblastoma

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The Translational Genomics Research Institute (TGen) and the Virginia G. Piper Cancer Center at Scottsdale Healthcare have conducted whole genome sequencing (WGS) of a rare nasal tract cancer called olfactory neuroblastoma (ONB).

Analysis of the billions of molecules that make up the patient's normal DNA, and cancerous DNA, discovered genetic mutations that could be future targets of advanced precision-medicine drug development.

Results of the study appeared today in the on-line journal *PLoS One*.

"Currently, physicians have few choices when formulating a treatment plan for a patient with advanced cancer, especially in cases of rare cancers," said Dr. Glen Weiss, the paper's lead author. He holds joint appointments at TGen and at the Virginia G. Piper Cancer Center Clinical Trials, a partnership between Scottsdale Healthcare and TGen that treats cancer patients with promising new drugs.

"There has been no comprehensive genomic sequencing study to identify mutation profiles of these rare ONB cancers in order to identify therapeutic targets for treating these patients," said Dr. Weiss, Director of Thoracic Oncology at the Virginia G. Piper Cancer Center, and a Clinical Associate Professor in TGen's Cancer and Cell Biology Division.

Personalized medicine involves precise drugs aimed at specific genetic

targets intended to shrink, and even eliminate, tumors without the debilitating toxic side effects of conventional chemotherapies.

The study involved a 29-year-old man who presented at the Virginia G. Piper Cancer Center at Scottsdale Healthcare following years of standard-of-care treatment involving surgery, radiation and conventional chemotherapy. His metastatic ONB had continued to mutate and return, resulting in deforming lesions and extensive surgeries that required plastic reconstruction.

His biopsied tumor and blood were analyzed at TGen, which spelled out the billions of individual molecular bases in the DNA of the patient's tumor, and in his normal DNA. A comparison identified several significant gene mutations, including: MAP4K2, SIN3B, TAOK2, KDR, TP53, MYC, and NLRC4. These were selected based on clinical relevance and previously published literature on the target genes and their association with carcinogenesis, or the creation and evolution of cancer.

"The mutated target genes implicate aberrations in DNA repair mechanisms and apoptosis," said Dr. John Carpten, the paper's senior author. He is a Professor and Director of TGen's Integrated Cancer Genomics Division and Deputy Director of Research for TGen. "This work provides novel insights into the underpinnings of a rare but terrible form of cancer. Hopefully we can translate these findings into tools for improved clinical management of rare tumors such as this."

The paper cites the need for additional study of how the ONB cancer mutates and progresses, and how whole genome sequencing can play an important role in future analysis.

"With the reduction in cost, improvement in speed of analysis and with more complete understanding of complex genetic alterations, we

anticipate that WGS will be applied in the clinic more frequently to common and rare cancers and will pave the way to personalized medicine," Dr. David Craig, another of the paper's senior authors. He is an Associate Professor and Associate Director of TGen's Neurogenomics Division.

The paper, "Paired tumor and normal whole genome sequencing of metastatic olfactory neuroblastoma," was part of a pilot study entitled, "An Ancillary Pilot Trial Using Whole Genome Tumor Sequencing in Patients with Advanced Refractory Cancer."

The National Foundation for Cancer Research, and the TGen Foundation, funded the study.

"This study represents a milestone in cancer research, and is about better treatments — and even cures — for cancer through genomics-based personalized medicine," said Franklin C. Salisbury Jr., President of the National Foundation for Cancer Research. "Whole genome sequencing is giving scientists a better understanding of the genetic basis of many cancers. Based on mutations uncovered by sequencing, doctors will be able to identify both existing anti-cancer drugs, or new anti-cancer drugs, designed to target those very mutations. This is Research for a Cure."

Provided by The Translational Genomics Research Institute