MedicalXpress

Team of scientists demonstrate path for tackling rare cancers with no effective treatment

March 23 2017

An international team of scientists led by the Icahn School of Medicine at Mount Sinai and UConn School of Medicine have reported the results of a genome sequencing study for an extremely rare form of cancer. Their findings demonstrate the utility of this approach to open the door for therapy options for rare diseases that are neglected due to scarcity of patients or lack of resources. The paper was published today by *JCI Insight*, a journal of the American Society for Clinical Investigation.

For this project, leading genomic scientists from Mount Sinai, UConn School of Medicine, and other global collaborating institutions performed exome sequencing on tumors and matched normal samples from 17 patients with parathyroid carcinoma, an ultra-rare form of cancer for which there is no effective treatment. When a tumor forms on one of the four small parathyroid glands located behind the thyroid, it can impact the body's control of calcium levels in both blood and bones. Patients with this cancer, if it is not cured early by surgery, typically die from its progressive metabolic complications including very high blood calcium levels, weakened bones, and calcium-induced kidney damage.

The study combined the power of UConn's world-renowned research expertise in parathyroid disease and other endocrine tumors with Mount Sinai's leadership in next-generation genomic sequencing and bioinformatics analysis, along with key contributions from the global consortium they organized.

Researchers found several mutations in known cancer-related genes and pathways, including the CDC73 tumor suppressor, the PI3K/AKT/mTOR pathway, and the Wnt canonical pathway, among others. This in-depth characterization provides a clear view of genetic mechanisms involved in parathyroid carcinoma and could lead to the first therapy options for patients.

"This is the largest genomic sequencing study to date for this rare and deadly cancer, and we believe it serves as important validation for using this approach to uncover clinically relevant information in any number of neglected diseases," said Rong Chen, senior author of the paper and Assistant Professor in the Department of Genetics and Genomic Sciences at Mount Sinai. "Genomic analysis is opening the doors to diseases that could never have been understood through traditional biomedical research because there simply aren't enough patients to observe."

The genetic variants identified in this study have been detected in other cancers and are the subject of ongoing basket trials, or clinical trials focused on specific mutations rather than the tissue where the cancer formed.

Mount Sinai's use of its latest cutting-edge genomics techniques helped build upon the co-senior study author Dr. Andrew Arnold of UConn and his research team's findings published in the *New England Journal of Medicine* in 2003 discovering the first gene in non-familial parathyroid cancer. Dr. Arnold's team has a longstanding history of investigating the molecular genetic underpinnings of endocrine gland tumors, being the first to also discover cyclin D1 (PRAD1), a key regulator in multiple cancers including breast cancer, which turns out in the present study to be altered in parathyroid carcinoma as well.

"I have been involved in the care of patients with advanced parathyroid

carcinoma for well over two decades, and the lack of effective anti-tumor therapy has been terribly frustrating," says Dr. Arnold, the study's co-leader who serves as the Murray-Heilig Chair in Molecular Medicine, Director of the Center for Molecular Medicine, and Chief of Endocrinology at UConn School of Medicine. "Some of the tumor-specific genomic vulnerabilities we found turn out to be shared with much more common cancers, so drugs already being developed for other cancers may prove valuable in parathyroid cancer. This offers new hope for our patients, and serves as a model for approaching other rare and neglected diseases."

"As we generate and analyze large, multi-dimensional data sets from tumors, there is mounting evidence that cancer treatment may be more successful when based on specific genetic markers instead of tissue of origin," said Eric Schadt, PhD, senior author on the paper and the Jean C. and James W. Crystal Professor of Genomics at the Icahn School of Medicine at Mount Sinai, and Founding Director of the Icahn Institute for Genomics and Multiscale Biology. "Conventional wisdom tells us that the only way to treat rare disease is to invest billions of dollars in developing new therapies. This study shows that parathyroid carcinoma may be rare but its genetic mutations are not, indicating that patients may benefit right now from treatments that are already on the market."

More information: Chetanya Pandya et al. Genomic profiling reveals mutational landscape in parathyroid carcinomas, *JCI Insight* (2017). DOI: 10.1172/jci.insight.92061

Provided by The Mount Sinai Hospital