

# Mouse cancer genome unveils genetic errors in human cancers

March 23 2011

---

Scientists who pioneered sequencing the genomes of cancer patients to find novel genetic changes at the root of the disease now have turned their attention to a laboratory workhorse -- a mouse.

By sequencing the genome of a mouse with cancer, researchers at Washington University School of Medicine in St. Louis have uncovered mutations that also drive cancer in humans. The investigators are the first to sequence a mouse cancer genome, and their research is reported online March 23 in the [Journal of Clinical Investigation](#).

"This approach gives us a way to rapidly evaluate whether mutations in human tumors are likely to be important," says senior author Timothy Ley, MD, the Lewis T. and Rosalind B. Apple Professor of Oncology. "If we find mutations that occur in mouse models and we see those same mutations, however rare, in human cancers, they are highly likely to be relevant."

Ley and his colleagues at Washington University's Genome Institute have sequenced the genomes of nearly 250 cancer patients and their tumors. By comparing the [DNA sequences](#) of tumor and healthy cells from each patient, they have uncovered a number of novel mutations underlying cancer.

But the endeavor is time consuming. Human tumor cells typically acquire several hundred mutations; the vast majority are background alterations that occur naturally throughout the course of a person's life.

The challenge is to sift through the genetic "noise" to find the handful of mutations in each tumor that drive cancer development.

Ley and his colleagues theorized that their work could be simplified if they looked for mutations in mouse models of cancer. These mice are inbred, which suggests they have fewer background mutations.

The current study involved a mouse model for acute promyelocytic leukemia (APL) that was developed in Ley's lab more than a decade ago by Peter Westervelt, MD, PhD, now director of the [Bone Marrow Transplant/Leukemia Section](#) in the Division of Oncology. The disease is a subtype of [acute myeloid](#) leukemia, a cancer of the blood and bone marrow.

APL is a cancer success story: once the most deadly form of leukemia, today APL is highly treatable. However, about 20 percent of patients experience a recurrence after standard treatment, pointing to the need for more effective therapy.

For the current study, the investigators inserted into the mouse genome a mutated human gene, called PML-RARA, which is known to initiate APL in patients. Then, they waited a year for full-blown leukemia to develop.

During that waiting period, bone marrow cells in the mouse are thought to acquire additional mutations that transform cells into full-blown leukemia. The purpose of the study was to find those cooperating mutations and determine whether they also occur in leukemia patients.

Unlike sequencing studies that focus only on genes, which make up just 1 percent of the entire genome, whole genome sequencing captures the full breadth of genetic alterations in DNA, including large insertions, deletions and other structural changes.

When co-authors Richard Wilson, PhD, and Elaine Mardis, PhD, director and co-director of The Genome Institute, respectively, and their colleagues sequenced the genome of the mouse tumor cells, they found genetic mutations in three genes, each of which alter a single letter in the DNA sequence and disrupt the instructions for making proteins.

One of these mutations, in the Jak1 gene, also occurred in six of 89 other APL mouse tumors they studied. Moreover, the mutation was identical to one that other research teams recently identified in one patient with APL and in other patients with acute lymphoblastic leukemia (ALL).

"By establishing that the mutation occurs in other mouse tumor samples and in patients with leukemia, that tells us this mutation is a driver; it almost certainly is relevant for the progression of cancer," Ley says.

A further analysis by lead author Lukas Wartman, MD, a fourth-year fellow in the Division of Medical Oncology, found that JAK1 cooperates with the initiating mutation in APL to cause a rapidly fatal leukemia in the mice. Mice with APL who expressed the mutant human JAK1 gene developed leukemia in just a month rather than a year.

"We also evaluated a JAK inhibitor in 10 mouse APL tumors and all of them responded, even those without a mutation in the gene," Wartman says. "This suggests that JAK1 is part of a crucial cancer pathway for this disease. Interestingly, JAK inhibitors are already in clinical trials for a number of cancers."

For Wartman, the research is personal. During his fourth year of medical school at Washington University, he was diagnosed with ALL. Chemotherapy put his cancer into remission, but five years later, it returned. Wartman then was treated with a stem cell transplant from his younger brother. He has now been cancer-free for two and a half years.

"This work is really important for me but also for so many other [cancer patients](#) and cancer survivors who want to know why they got cancer in the first place," Wartman says. "We think studies like this can help answer that question."

The researchers also found a large deletion in the Kdm6a (also known as Utx) gene in the mouse tumor genome. A similar deletion was found in another three of 14 mouse APL genomes they studied and in one human AML sample. Deletions in the same gene also have been associated with human cancers, including kidney and esophageal tumors and multiple myeloma, another blood cancer.

Ley says the new research also highlights the value of mouse models of cancer to find important mutations in patients.

"There's been an ongoing debate for 15 years about whether mouse models of cancer are relevant to cancer that develops in people," he explains. "By sequencing this genome, I think the answer is clear: this mouse model is remarkably similar to the human disease. This gives us a new way to use whole-genome sequencing to rapidly identify the most relevant mutations in human cancers."

Looking ahead, the researchers say they will complement their efforts to sequence human cancer genomes with their mouse [genome](#) counterparts, when good mouse models are available.

"We expect this to expedite our ability to determine whether mutations in patients are important for disease progression," Wilson says. "If we find the same mutations in human cancers and in a [mouse model](#) of the disease, then we know they are likely to be relevant, even if we've only seen the mutations in a small fraction of patients."

**More information:** Wartman LD, Larson DE, Mardis, ER, Wilson

RK, Ley TJ et al. Sequencing a mouse acute promyelocytic leukemia genome reveals genetic events relevant for disease progression. *Journal of Clinical Investigation*, March 23, 2011.

Provided by Washington University School of Medicine

Citation: Mouse cancer genome unveils genetic errors in human cancers (2011, March 23)  
retrieved 3 May 2024 from

<https://medicalxpress.com/news/2011-03-mouse-cancer-genome-unveils-genetic.html>

<p>This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.</p>
--