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Rare childhood leukemia reveals surprising genetic secrets

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A coalition of leukemia researchers led by scientists from UC San Francisco has discovered surprising genetic diversity in juvenile myelomonocytic leukemia (JMML), a rare but aggressive childhood blood cancer.

Using comprehensive genomic sequencing, the team identified new gene mutations and epigenetic DNA modifications responsible for many cases of the disease, some of which could be targeted with off-the-shelf drugs. The study—published Oct. 12 in the journal *Nature Genetics*—also revealed genetic predictors of which patients are less likely to respond to existing treatments, which could help physicians quickly identify children who should be candidates for experimental therapies.

"We've created the most comprehensive portrait yet of how this cancer evolves from first diagnosis through remission or relapse," said study senior author Mignon Loh, MD, chair of pediatric molecular oncology at UCSF Benioff Children's Hospital San Francisco. "What we found helps make sense of why patients' outcomes have been so wildly different."

JMML is an aggressive, chronic leukemia that mainly affects children under the age of four, and strikes one or two per million children in the United States each year. Currently, the only known treatment for JMML is a bone marrow transplant. This intensive approach, which has long-term side effects, only works in about 50 percent of patients, with relapse being the most common cause of treatment failure, said Loh, who is also a member of the UCSF Helen Diller Family Comprehensive

Cancer Center.

"The goal of this study," she said, "was to identify genetic alterations that we hope can identify targeted medications that can more effectively kill leukemia cells."

The course of JMML is also highly variable: very rare children spontaneously go into remission with minimal treatment, while fully half of JMML patients suffer from a highly aggressive form of the disease that fails to respond to bone marrow transplant. Not having any way to identify which children would respond well to treatment and which would not has been a major challenge for physicians, according to Elliot Stieglitz, MD, an assistant professor of pediatrics at UCSF who trained in Loh's laboratory during his fellowship is co-first author of the new study.

"We have personally treated patients with JMML at UCSF with identical 'driver' mutations, some of whom survived, while others died," Stieglitz said. "Our frustration was the main impetus that led us to carry out this study."

Diverse genomics suggest new treatment options

In the new study, the researchers used comprehensive whole-exome gene sequencing, assisted by novel computational algorithms, to compare the genomes of healthy blood cells to those of cancer cells at diagnosis and relapse in 27 JMML patients ranging from one month to three years of age. Based on the findings from these patients, they then performed targeted sequencing of suspected mutation hot spots in another 71 patients.

Previously, just five defects in the Ras oncogene pathway had been associated with JMML. The new analysis added 10 new mutations of

known oncogenes and tumor suppressors to the list of potential causes, including two additional Ras pathway genes. These new disease-associated mutations occurred in genes coding for proteins that function as signaling molecules, transcription factors, epigenetic regulators and elements of the spliceosome complex, a component of cells' DNA transcription machinery.

Several of these newly discovered mutations raise the possibility of targeting subpopulations of JMML cases with existing drugs: Janus kinase (JAK) inhibitors, currently used to treat certain other bone marrow and blood cancers such as polycythemia vera, might inhibit signaling through a hyperactive JAK-STAT pathway identified in some patients, while other agents such as 5-azacytidine, most commonly used as a treatment for a blood disorder known as myelodysplastic syndrome, could be used to reduce excessive epigenetic DNA methylation seen in others.

Mutation quantity, not type, predicts outcomes

The team also performed a ten-year survival study with the same participants and found that patients' prognosis depended more on the number of mutations they had than on the specific mutations involved. Patients with more than one mutation at the time of diagnosis had a significantly worse long-term prognosis: Of the 34 patients who had at least two mutations, only 29 percent survived for ten years, compared to a 65 percent survival rate for patients who had one or fewer detectable mutations.

"We have now shown that while 'driver' mutations in the Ras pathway likely cause the leukemia to develop in the first place, it is the presence of these additional mutations that contribute to poor outcome," Loh said, noting that therapies will likely require targeting multiple pathways at once. "Precisely how these secondary mutations will interact with the

Ras pathway is the focus of our ongoing work."

For Loh and Stieglitz, the findings are more than academic.

"At the beginning of my fellowship, we treated a delightfully precocious 2-year-old boy who eventually succumbed to JMML, despite world-class care," Stieglitz said. "His family originally donated leukemia samples to us for research, and it was this patient's sample that led to the first major breakthrough in our study and will possibly impact the way certain patients are treated going forward."

As a result of these breakthroughs, Stieglitz said, their clinical team now offers CLIA-approved testing for the most common mutations seen in the new study, which can be ordered by any physician around the world.

More information: Elliot Stieglitz et al. "The genomic landscape of juvenile myelomonocytic leukemia," *Nature Genetics* (2015). DOI: 10.1038/ng.3400

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