Solution to medical mystery may help some children avoid bone marrow transplantation

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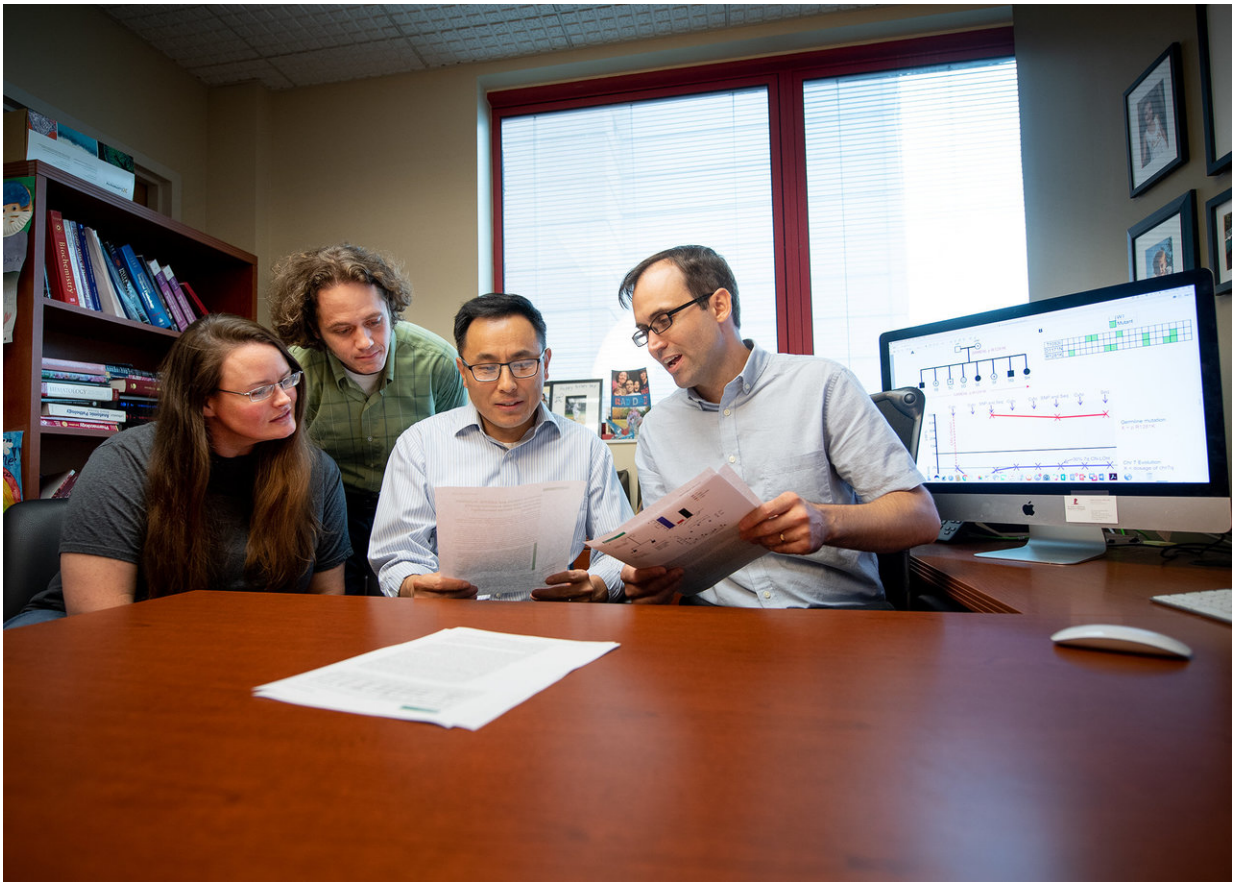

The study authors are Tamara Lamprecht, Jason Schwartz, M.D., Jing Ma, Ph.D., and Jeffrey Klco, M.D., Ph.D.. Credit: St. Jude Children's Research Hospital / Justin Veneman

Researchers have helped solve a decades-old mystery about which mutations are responsible for an inherited bone marrow disorder. The answer may allow some children to avoid the risk and expense of bone marrow transplantation, a common treatment for leukemia and bone marrow disorders.

Investigators at St. Jude Children's Research Hospital and UCSF, led the study, which appears today in the scientific journal *JCI Insight*.

Researchers analyzed blood samples from 16 siblings in five families affected by a rare bone marrow disorder and found they all carried germline mutations in the genes SAMD9 or SAMD9L. The disorder is myelodysplasia and leukemia syndrome with monosomy 7, which is also called familial monosomy 7 syndrome. In three of the five families, an apparently healthy parent also carried the mutation. Germline mutations are found in the DNA of every cell and are usually inherited.

"Surprisingly, the health consequences of these mutations varied tremendously for reasons that must still be determined, but the findings are already affecting how we may choose to manage these patients," said Jeffery Klco, M.D., Ph.D., assistant member of the St. Jude Department of Pathology. Klco is co-corresponding author of the study.

Five families, two genes

Three of the 16 siblings developed acute myeloid leukemia (AML) and died of the disease or related complications. Two other siblings were diagnosed with myelodysplastic syndrome (MDS), a disorder characterized by below-average numbers of normal blood cells. The symptoms include anemia, infections, bleeding and an increased risk of AML.

But 11 children with the mutations were apparently healthy, although

several had been treated for anemia and other conditions associated with low blood counts. Some of these patients had a previous history of bone marrow monosomy 7, which spontaneously corrected over time. These patients, despite no therapy, now appeared to have normal bone marrow function.

"This was an even greater surprise," Klco said. "The spontaneous recovery experienced by some children with the germline mutations suggests some patients with SAMD9 and SAMD9L mutations who were previously considered candidates for bone marrow transplantation may recover hematologic function on their own."

The findings also identified SAMD9 and SAMD9L as cancer predisposition genes that should be included in genetic counseling and screening offered to at-risk patients and families. These families include those affected by myelodysplasia and related blood abnormalities like AML. St. Jude is establishing a clinic to develop clinical trials and new treatments for children with bone marrow failure disorders, including MDS. The clinic will be led by Marcin Wlodarski, M.D., Ph.D., an assistant member of the St. Jude Department of Hematology.

Gathering evidence

The findings resolve a mystery dating to the 1980s. That is when Kevin Shannon, M.D., of the University of California, San Francisco, and his colleagues reported several families with children and adolescents who developed myelodysplasia or AML. They also had one, rather than the usual two, copies of chromosome 7, a condition known as monosomy 7. Efforts to identify the mutation or mutations involved were unsuccessful at the time, but Shannon and his colleagues started collecting and banking blood samples from other families with a similar medical history.

A key clue to solving the puzzle came in 2016 when scientists in Japan showed that germline SAMD9 mutations cause MIRAGE syndrome, a complex developmental disorder in which some children develop MDS with monosomy 7. Researchers at the University of Washington School of Medicine then identified SAMD9L mutations in children with a rare neurological syndrome associated with myelodysplasia and monosomy 7. Mutations in SAMD9 and SAMD9L were quickly identified in children with other rare neurologic and developmental disorders. Remarkably, the SAMD9 and SAMD9L genes are located on chromosome 7 and the mutant copy is invariably lost from the bone marrow cells of children with monosomy 7.

In 2017, Klco and his colleague reported that eight of 46 St. Jude patients with MDS, or 17 percent, had germline mutations in SAMD9 and SAMD9L. "Together with the current study, this research suggests mutations in these genes cause a diverse spectrum of disorders that disrupt the same growth-control pathway in different tissues," Shannon said. He is a co-corresponding author of the current study.

Mysteries remain

Researchers have proposed how and why the mutant genes sometimes disappear.

SAMD9 and SAMD9L are activated in response to viral infections. While the normal function of both proteins is poorly understood, abnormally activated SAMD9 and SAMD9L are known to inhibit cell growth.

In this study, intensive sequencing of mutant cells, a process known as deep sequencing, showed that selective pressure on developing blood cells, including blood stem cells, favors cells without the SAMD9 or SAMD9L mutations. That may increase pressure for cells to selectively

jettison chromosome 7 with the gene alteration or take other molecular measures to counteract the mutant protein.

This research also showed that in patients who developed AML, loss of chromosome 7 was associated with the development of mutations in additional genes, including ETV6, KRAS, SETBP1, and RUNX1. These same mutations are broadly associated with monosomy 7 in AML, which suggests that understanding how SAMD9 and SAMD9L mutations contribute to leukemia has implications beyond familial cases.

The presence of secondary mutations may also help clinicians identify which patients will benefit from immediate treatment, including chemotherapy or bone marrow transplantation to prevent or treat AML or myelodysplasia, Klco said. For patients without the mutations or significant symptoms due to low blood cell numbers, watchful waiting with careful follow-up may sometimes be an option.

"Now that we know this disease can resolve without treatment in some patients, we need to focus on developing screening and treatment guidelines," Klco said. "We want to reserve hematopoietic bone marrow transplantation for those who truly need the procedure. These findings will help to point the way.

"So little is known about SAMD9 and SAMD9L that we need to continue working in the lab to better understand how these mutations impact blood cell development and how they are activated in response to infections and other types of stress," he said.

Provided by St. Jude Children's Research Hospital

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