New chromosomal abnormality identified in leukemia associated with Down syndrome

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Researchers identified a new chromosomal abnormality in acute lymphoblastic leukemia (ALL) that appears to work in concert with another mutation to give rise to cancer. This latest anomaly is particularly common in children with Down syndrome.

The findings have already resulted in new diagnostic tests and potential tools for tracking a patient's response to treatment. The research, led by scientists from St. Jude Children's Research Hospital, also highlights a new potential ALL treatment. Clinicians are already planning trials of an experimental medication targeting one of the altered genes.

This study is published in the October 18 online edition of Nature Genetics.

"A substantial proportion of children with ALL lack one of the previously identified, common chromosomal abnormalities. Also, children with Down syndrome have an increased risk of ALL, but the reasons why are unclear," said Charles Mullighan, M.D., Ph.D., assistant member in the St. Jude Department of Pathology. Mullighan is senior author of the study, which involved scientists from 10 institutions in the U.S. and Italy. "Our results have provided important data regarding the mechanisms contributing to leukemia in these cases," he said.

Instead of the normal pairs of 23 chromosomes, individuals with Down syndrome inherit an extra copy of one chromosome, in this case chromosome 21. Chromosomes are made of DNA and carry the genes

that serve as the assembly and operations manual for life. Down syndrome is associated with a variety of medical and developmental problems, including a 10- to-20-fold increased risk of ALL. But patients with Down syndrome rarely have the genetic and chromosomal alterations commonly associated with childhood ALL. Until recently the genetic basis of the elevated risk for these patients was unknown.

The new gene alteration was identified by St. Jude scientists following up on an earlier observation. They had previously found a recurring deletion in a region of DNA duplicated on the X and Y chromosomes. The region is known as pseudoautosomal region 1 or PAR1.

The PAR1 deletion was found only in patients with a subtype of ALL known as B-progenitor ALL. It was most common in children with both B-progenitor ALL and Down syndrome. In this study, investigators screened almost 400 children with ALL, including 75 patients with Down syndrome. The deletion was present in 7 percent of patients with B-progenitor ALL, but in more than half of the patients with both B progenitor and Down syndrome.

The deletion results in a fusion of two genes, P2RY8 and CRLF2. The fusion puts CRLF2 expression under the control of the P2RY8 promoter. As a result, CRLF2 expression jumps as much as 10 fold.

"CRLF2 over-expression identifies a group of ALL cases which were not previously well characterized, and suggests some novel treatment approaches that may improve patient survival. Patients with Down syndrome are particularly vulnerable to complications from standard chemotherapy, and could therefore benefit from novel therapies," said Karen Rabin, M.D., of Texas Children's Cancer Center and a study co-author. She is a Baylor College of Medicine assistant professor of pediatric hematology/oncology.

The CRLF2 protein normally forms part of a receptor where a small growth factor known as a cytokine binds to white blood cells known as lymphocytes. Both the cytokine, thymic stromal lymphopoietin (TSLP), and CRLF2 are known to play important roles in the development of immune cells known as T lymphocytes as well as in inflammation and allergic disease. They had not previously been linked to leukemia.

CRFL2 is the second gene implicated in development of B-progenitor ALL in patients with Down syndrome. The first, a gene called JAK2, was identified in 2008. JAK2 belongs to a family of genes that produce enzymes called kinases. If permanently switched on, kinases can trigger the uncontrolled cell growth that is a hallmark of cancer.

JAK mutations have also been linked to other cancers. Drugs targeting JAK kinases are already in clinical trials against a variety of blood disorders in adults. Additional trials are being planned against other subtypes of childhood ALL.

In this study, researchers reported a significant association between alterations in both the CRFL2 and JAK2 genes. Almost all JAK mutations were observed in patients with CRLF2 alterations. Almost 28 percent of children with Down syndrome and ALL had changes in both the CRFL2 and JAK genes.

"It has been a mystery as to why the JAK mutations in Down syndrome ALL are different from those seen in other cancers," Mullighan said. "Here we show that the JAK mutations in ALL are almost always observed together with a chromosomal alteration that results in over-expression of CRLF2."

When both the JAK mutation and increased CRLF2 production were introduced into white blood cells growing in the laboratory, those cells were transformed and no longer needed cytokines to grow. Neither

genetic alteration on its own produced the same effect. Researchers also reported their impact could be weakened by the addition of drugs that target JAK mutations.

"We showed that the two proteins, CRLF2 and mutant JAK2, physically interact, and together transform white blood cells. This work has identified a new pathway contributing to the development of leukemia," Mullighan said. A next step is to determine if these mutations also interact in mouse models of ALL.

Source: St. Jude Children's Research Hospital