BRIEF UPDATE

Gene Variants Offer Clues to High-Risk Childhood ALL

By Susan Jenks

Researchers have identified a new genetic fingerprint in pediatric acute lymphoblastic leukemia (ALL) that may predict which children already at high risk for relapse will have the worst survival. The finding, which adds to the growing knowledge about the molecular makeup of these high-risk cancers, also casts light on the ethnic disparities in childhood leukemia.

Survival in pediatric ALL, the most common childhood cancer, exceeds 80% with current treatments. But among children who relapse, only 30% survive, according to Cheryl Willman, M.D., who heads the University of New Mexico Cancer Research and Treatment Center in Albuquerque.

Willman and colleagues found that a few children with high-risk ALL acquired abnormalities in the cytokine receptor–like factor 2 (CRLF2) gene. The abnormalities were associated with the poorest outcomes, despite intensive therapy. Most of the children also had mutations in at least two of three Janus kinase (JAK) genes, which play a key role in cell signaling and often become altered as cancer develops. Willman presented the group’s findings at a meeting of the American Association for Cancer Research on the science of health disparities, held Sept. 28-Oct. 3.

The study also found that Hispanic children, who have the highest incidence of pediatric ALL in the United States, were disproportionately represented in the group with the worst outcomes. “The science shows there’s a biologic reason for this outcome, not a social or cultural one,” Willman said. The study, part of the National Cancer Institute’s Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative, was published online in Blood in August. TARGET researchers at NCI, the Children’s Oncology Group, and St. Jude’s Children’s Research Hospital in Memphis, as well as the University of New Mexico, have identified other molecular abnormalities characteristic of relapsed childhood ALL, including IKZF1 deletions and JAK mutations (see JNCI News, May 20, 2009).

“We believe that multiple genetic lesions cooperate to produce any full leukemia, and CRLF2 and JAK... cooperate in this way,” Willman said.

Among the lesions identified so far, the genetic reshuffling of CRLF2 is an important initiating event in leukemogenesis and a focus of increasing research interest. Although its function is not fully understood, Willman said, the gene is a cell surface receptor for TSLP, the thymic stromal lymphopoietin gene. TSLP regulates development of several blood cell lines, including lymphoid cells, and is thought to signal through kinase proteins. But “there is still controversy on this issue,” she added.

Eight Distinctive Gene Patterns

Working with other TARGET investigators, Willman’s team initially looked at a cohort of 207 uniformly treated children with high-risk, B-precursor ALL. Within this group, they identified eight distinctive genetic patterns or clusters illustrating a “striking degree of genetic heterogeneity” even in the tissues of so few children, Willman said.

The 207 children all shared high-risk ALL characteristics, such as older age, male sex, high white blood cell counts, and high rates of residual disease at the end of induction therapy. Roughly 25% self-reported their ethnicity as Hispanic, and most showed no evidence of the recurring chromosomal abnormalities associated with poor outcomes in this disease.

Within the high-risk group, the researchers eventually focused on a group of 50 children who fared far worse than their peers. Only 20% had 4-year, relapse-free survival, compared with 94.7% in a second group with the best outcomes and 63.5% for the cohort as a whole. The children in the worst-outcome category also were disproportionately Hispanic. In addition, they had the highest frequency of residual disease at the end of induction therapy—81%–89% of cases compared with 35% for the cohort as a whole. Five-year survival among the Hispanic children in this group, Willman said, was near zero.

JAK2 was often mutated, and mutations occurred in JAK1 as well. And although almost all 50 children had CRLF2 gene rearrangements, only half had the JAK mutations, and these differed from the classic mutations seen in myeloproliferative disorders. The mutations appear in another region of the gene. “We don’t understand yet why this happens, but it’s an important finding,” Willman said, because it suggests different molecular pathways in the formation of lymphoid versus myeloid leukemia.

Altogether, the investigators identified six or seven highly overexpressed genes associated with mutations in tyrosine kinases in the leukemic cells of children with high-risk ALL. Willman said they decided to concentrate on CRLF2 not only because it was overexpressed in these cells but also because studies of DNA copy number
variations showed deletions of CRLF2 gene copies in some of the children.

In the worst-outcome category, only two of the 50 children had Down syndrome, a known high-risk group for developing leukemia. But although more than half of Down syndrome children carry genetic CRLF2 rearrangements, as well as JAK mutations, Willman said, they tend to be more responsive to therapy than other children with high-risk ALL, for reasons that are not yet clear. The investigators theorize that this occurs because of something on the extra chromosome these children carry, which requires further research, Willman said.

**Genetic Ancestry Surprises**

Investigators also examined ethnicity in the children. Genetic analysis revealed a surprising gap between self-reported ethnic identity and genetic heritage, Willman said, especially in the children with the worst outcomes. Sixty percent of children in this group self-reported Hispanic descent, but 78% had a significant degree—greater than 20%—of American Indian ancestry, which was associated with an increase in relapse rates. Even non-Hispanic white children with more than 20% American Indian ancestry saw an increase in relapse frequency, she said.

"The deeper you go into genetic ancestry, the more complex it becomes," Willman said. "But understanding these factors is very important even in diseases, like pediatric ALL, which we think of as relatively simple" compared with other cancers. The future of cancer research lies in similar genetic heritage studies, she said.

Willman said investigators already have confirmed the biologic and clinical significance of CRLF2 in a larger cohort of 800 high-risk ALL children enrolled in the Children's Oncology Group. Drugs targeting CRLF2 are in development now, she added, and researchers continue to test other kinase inhibitors in animal models.

In animal studies, the researchers also tested three existing JAK inhibitors as treatments for ALL. All three failed. "We thought we had it in the bag, but it’s more complicated than that," Willman said.