Gene abnormality found to predict childhood leukemia relapse

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Scientists have identified mutations in a gene that predict a high likelihood of relapse in children with acute lymphoblastic leukemia (ALL). Although the researchers caution that further research is needed to determine how changes in the gene, called IKZF1 or IKAROS, lead to leukemia relapse, the findings are likely to provide the basis for future diagnostic tests to assess the risk of treatment failure. By using a molecular test to identify this genetic marker in ALL patients, physicians should be better able to assign patients to appropriate therapies.

The findings of the Children's Oncology Group (COG) study, led by scientists from St. Jude Children's Research Hospital, Memphis, Tenn., the University of New Mexico Cancer Research and Treatment Center, Albuquerque, N.M., and the National Cancer Institute (NCI), part of the National Institutes of Health, appear online Jan.7, 2009, in the *New England Journal of Medicine*, and in print on Jan. 29, 2009.

ALL, a cancer of the white blood cells, is the most common childhood cancer, in that it affects about one in 29,000 children annually. Using currently available therapies, cure rates for ALL are now upwards of 80 percent. However, those therapies carry with them substantial side effects, and even with treatment, only 30 percent of children who experience a relapse of ALL will survive five years. Determining the risk of relapse faced by an individual patient would help physicians tailor treatment intensity appropriately, but until now there has been no good marker for predicting outcome.

"Great progress has been made in recent years in improving the cure rate of childhood ALL," said Stephen Hunger, M.D., chairman of the COG ALL committee and the lead COG investigator on this study. "The findings of this study help us further subdivide those patients who are unlikely to be cured, and identify patients in whom different therapies should be tested."

In the study, researchers analyzed genetic data on leukemia cells obtained at diagnosis from 221 children with high-risk leukemia (i.e. a high chance of relapse) who had been treated in an existing COG study. They conducted their analysis using microarrays and DNA sequencing - technologies which allow researchers to quickly and efficiently identify and analyze multiple genes simultaneously in the same cell. Using these technologies to identify genetic abnormalities in leukemia cells, the investigators examined the DNA of the leukemia cells at the time of diagnosis and then determined if any of the identified genetic changes predicted relapse. To confirm that specific genetic changes were associated with relapse, the scientists also examined a second group of 258 children with ALL who were treated at St. Jude.

"We looked across the genome in an unbiased fashion in an attempt to pull out any genes that were significantly associated with outcome," said Charles Mullighan, M.D., Ph.D., assistant member in the St. Jude Department of Pathology and the paper's first author. "From these findings, we identified a group of genetic abnormalities that together predicted poor outcome."

The most significant association was with the deletions or changes in the IKAROS gene. Mutations of IKAROS were shown to identify a subgroup of patients who were treated in the COG study that had a very poor prognosis. The prognostic significance of these genetic alterations was validated in the independent St. Jude patient group, a finding of particular importance since different types of therapies were used in

these two groups of patients.

Previous research has shown that the IKAROS gene serves as the blueprint for the production of the IKAROS protein, which regulates the activity of many other genes. The IKAROS protein plays an essential role in the development of lymphocytes, the white blood cells that, when changed, give rise to pediatric ALL. The way in which IKAROS abnormalities contribute to the development of relapse remains to be determined.

The study also examined gene expression in the leukemia cells using microarray chips, and found that leukemia cells from patients with IKAROS alterations expressed primitive, stem cell-like genes, suggesting that the cells are less mature and possibly more resistant to the effects of drugs used to treat ALL. "These findings show how detailed analysis of leukemic cells using complementary techniques can enhance our understanding of the genetic basis of leukemia," said co-author Cheryl Willman, director and CEO, University of New Mexico Cancer Research and Treatment Center.

The researchers also tested whether the presence of IKAROS alterations was associated with levels of minimal residual disease, another measure of treatment response in ALL.

"Measurement of levels of minimal residual disease is widely used to monitor treatment responsiveness and also to alter patients' therapy if they have a very poor response to treatment," said James Downing, M.D., St. Jude scientific director and the paper's senior author. "An important analysis we conducted was to see whether identifying the association of IKAROS alterations with poor outcome added anything to just measuring levels of minimal residual disease. And, indeed, it did."

The researchers' analysis indicated that identifying IKAROS alterations

may be clinically useful and will complement existing diagnostic tests and measurement of minimal residual disease levels.

While a clinical test for alterations of IKAROS could prove valuable for predicting poor outcomes in children with ALL, complexities remain. There are different types of deletions in the gene, some that involve the entire IKAROS gene and others that involve only parts of the gene. Because the genetic alterations in IKAROS in ALL are not uniform or limited to a single mutation or deletion, it may be necessary to develop a panel of different tests to detect IKAROS lesions and identify which patients are at highest risk for relapse.

This research was done as part of the NCI Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative, which seeks to utilize the study of genomics to identify therapeutic targets in order to develop more effective treatments for childhood cancers. The first two cancers being studied in the program are ALL and neuroblastoma, a cancer that arises in immature nerve cells and affects mostly infants and children. Combined, these two cancers account for 3,000 new cases each year, and in both cancers, there are some children who have a very favorable prognosis and others who are at high risk for treatment failure. By determining the genetic factors that distinguish these groups, the hope is that researchers can use this information to improve patient outcomes and develop better treatments, particularly for those in the high-risk group.

"In the long term, our goal is to develop effective therapeutic interventions, directed toward vulnerabilities that leukemia cells acquire as a result of the genomic abnormalities identified through the TARGET initiative," said Malcolm Smith, M.D., Ph.D., of NCI's Cancer Therapy Evaluation Program. These are the first results to come out of this initiative. For more information about TARGET, please visit target.cancer.gov

Source: NIH/National Cancer Institute