# Study finds more than 100 gene variations linked with response to leukemia treatment

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Scientists from St. Jude Children's Research Hospital and the Children's Oncology Group (COG) have discovered in children with acute lymphoblastic leukemia (ALL) scores of inherited genetic variations that clinicians might be able to use as guideposts for designing more effective chemotherapy for this cancer.

The findings are important because although cure rates for ALL exceed 80 percent, patient responses vary significantly to the same drugs. Much of this variance has been unexplained. The newly discovered genetic variations, however, will likely give scientists a clearer understanding of why treatments fail in some patients with ALL, and how to predict early in treatment which children could be successfully treated with less aggressive treatment.

"This study differs from most previous investigations of gene variations linked to chemotherapy outcome because those studies focused only on the genes of the leukemic cells themselves," said Mary Relling, Pharm.D., St. Jude Pharmaceutical Sciences chair. "We focused on genomic variation that is inherited and affects all cells in the body, not just the leukemic cells." Relling is the senior author of a report on the team's study that appears in the January 28, 2009, issue of the *Journal of the American Medical Association*.

In their research, St. Jude scientists collaborated with a team from COG, a worldwide group of medical institutions that cooperate in laboratory research studies and clinical trials of cancer treatments for children.

Instead of studying genetic variations acquired by leukemia cells, scientists identified small genetic variations the children inherited from their parents.

The researchers then determined which of those small, inherited variations, called single-nucleotide polymorphisms (SNPs), were associated with minimal residual disease (MRD). MRD is the small number of leukemic cells that survive after remission induction therapy—the initial treatment. This measurement helps clinicians identify patients whose disease is highly responsive to chemotherapy and therefore might be cured with milder and less-toxic treatment; and also shows if remission induction therapy will likely fail.

The researchers performed a search of 476,796 inherited SNPs from two independent groups of children with newly diagnosed ALL: 318 patients on clinical trials at St. Jude and 169 patients on COG clinical trials.

The study discovered 102 of the inherited genetic variations that affected the level of residual leukemia or MRD. A high proportion (21 of 102) of these MRD-linked SNPs also predicted leukemic relapse; moreover, 21 SNPs linked eradication of MRD with greater exposure of the leukemic cells to the chemotherapy drugs.

For example, the researchers discovered five SNPs that are located in and around a gene called IL15, which codes for a protein called interleukin 15 that stimulates multiplication of leukemic cells. The finding was significant because previous studies showed that IL15 protects tumors from certain chemotherapy drugs; and that it is linked to both invasion of the central nervous system by leukemic cells and an increased risk of recurrence in that area following treatment. In the current study, the team found a link between the IL15 SNPs, increased levels of IL15 in leukemia cells, and an increased risk of high MRD at the end of induction therapy.

"Our finding that IL15 plays such an important role in the failure of chemotherapy suggests that this gene may be a marker we could use to predict outcome of therapy," Relling said. "IL15 might also represent a new target for novel drugs that knock out its activity and improve the outcome of patients with high levels of this interleukin."

In addition, 21 of the 102 SNPs that predicted MRD also significantly associated with the pharmacokinetics of two antileukemic drugs, etoposide and methotrexate, which are representative of the array of antileukemic medications used to treat lymphoblastic leukemia. Pharmacokinetics comprises the various biochemical fates of a drug in the body—absorption, distribution throughout the body, breakdown and excretion. In almost all cases, gene variation predicting faster elimination of the drugs from the body was associated with higher levels of MRD, suggesting that higher drug doses may be able to overcome the problem of low drug exposure related to an inherited tendency for fast drug elimination, Relling said.

Overall, 63 of the 102 SNPs were associated with early response to therapy, with relapse or with pharmacokinetics of drugs.

Few of the 102 SNPs the team identified in this study had previously been suggested by other investigators to be likely to affect the outcome of ALL chemotherapy. This suggests the need for further research using whole-genome approaches to identify SNPs that affect how individual patients will respond to chemotherapy, Relling said.

"Our results show the importance of surveying variations in the entire human genome in normal cells from patients, since many such variations can determine the effectiveness of chemotherapy," said Jun Yang, Ph.D., a fellow in the St. Jude Department of Pharmaceutical Sciences and the paper's first author. "It also showed that our genome-wide approach to identifying such SNPs is useful for identifying genetic

variations that can be used to predict treatment outcomes. In the future, such information might help clinicians use drugs more effectively to overcome the patient's own genetic variation and reduce the chance of treatment failure."

Source: St. Jude Children's Research Hospital